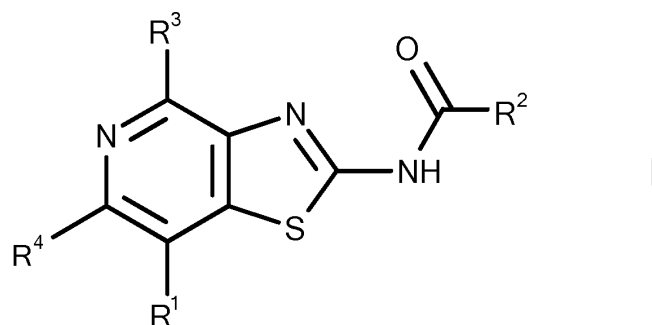


Thiazolopyridine derivatives as adenosine receptor antagonists

The invention relates to thiazolopyridine derivatives which fall under the general formula I,

5

10



15

and the use of the compounds of the present invention for the treatment and/or prevention of hyperproliferative or infectious diseases and disorders in mammals, especially humans, and pharmaceutical compositions containing such compounds.

Background of the invention

20

25

Adenosine is an ubiquitous modulator of numerous physiological activities, particularly within the cardiovascular, nervous and immune systems. Adenosine is related both structurally and metabolically to the bioactive nucleotides adenosine triphosphate (ATP), adenosine diphosphate (ADP), adenosine monophosphate (AMP) and cyclic adenosine monophosphate (cAMP), to the biochemical methylating agent S-adenosyl-L-methione (SAM) and structurally to the coenzymes NAD, FAD and coenzyme A and to RNA.

30

Via cell surface receptors, adenosine modulates diverse physiological functions including induction of sedation, vasodilatation, suppression of cardiac rate and contractility, inhibition of platelet aggregability, stimulation of gluconeogenesis and inhibition of lipolysis. Studies show that adenosine is able to activate adenylate cyclases, open potassium channels, reduce flux through calcium channels, and inhibit or stimulate phosphoinositide turnover through receptor-mediated

mechanisms (Muller C. E. and Stein B., *Current Pharmaceutical Design*, 2: 501, 1996; Muller C. E., *Exp. Opin. Ther. Patents*, 7(5): 419, 1997).

Adenosine receptors belong to the superfamily of G-protein-coupled receptors (GPCRs). Four major subtypes of adenosine receptors have been
5 pharmacologically, structurally and functionally characterized (Fredholm et al., *Pharm. Rev.*, 46: 143-156, 1994) and referred to as A₁, A_{2A}, A_{2B} and A₃. Though the same adenosine receptor can couple to different G-proteins, adenosine A₁ and A₃ receptors usually couple to inhibitory G-proteins referred to as G_i and G_o which inhibit adenylyate cyclase and down-regulate cellular cAMP levels. In contrast, the
10 adenosine A_{2A} and A_{2B} receptors couple to stimulatory G-proteins referred to as G_s that activate adenylyate cyclase and increase intracellular levels of cAMP (Linden J., *Annu. Rev. Pharmacol. Toxicol.*, 41: 775-87 2001).

According to the invention, "adenosine-receptor-selective ligands" are substances
15 which bind selectively to one or more subtypes of the adenosine receptors, thus either mimicking the action of adenosine (adenosine agonists) or blocking its action (adenosine antagonists). According to their receptor selectivity, adenosine-receptor-selective ligands can be divided into different categories, for example ligands which bind selectively to the A₁ or A₂ receptors and in the case of the latter also, for example, those which bind selectively to the A_{2A} or the A_{2B} receptors. Also possible
20 are adenosine receptor ligands which bind selectively to a plurality of subtypes of the adenosine receptors, for example ligands which bind selectively to the A₁ and the A₂, but not to the A₃ receptors. The abovementioned receptor selectivity can be determined by the effect of the substances on cell lines which, after stable transfection with the corresponding cDNA, express the receptor subtypes in
25 question (Olah, M. E. et al., *J. Biol. Chem.*, 267: 10764-10770, 1992). The effect of the substances on such cell lines can be monitored by biochemical measurement of the intracellular messenger cAMP (Klotz, K. N. et al., *Naunyn Schmiedeberg's Arch. Pharmacol.* 357: 1-9, 1998).

It is known that the A₁ receptor system include the activation of phospholipase C and modulation of both potassium and calcium ion channels. The A₃ subtype, in
30 addition to its association with adenylyate cyclase, also stimulates phospholipase C and so activates calcium ion channels.

5 The A₁ receptor (326-328 amino acids) was cloned from various species (canine, human, rat, dog, chick, bovine, guinea-pig) with 90-95 % sequence identify among the mammalian species. The A_{2A} receptor (409-412 amino acids) was cloned from canine, rat, human, guinea pig and mouse. The A_{2B} receptor (332 amino acids) was cloned from human and mouse with 45 % homology of human A_{2B} with human A₁ and A_{2A} receptors. The A₃ receptor (317-320 amino acids) was cloned from human, rat, dog, rabbit and sheep.

10 The A₁ and A_{2A} receptor subtypes are proposed to play complementary roles in adenosine's regulation of the energy supply. Adenosine, which is a metabolic product of ATP, diffuses from the cell and acts locally to activate adenosine receptors to decrease the oxygen demand (A₁ and A₃) or increase the oxygen supply (A_{2A}) and so reinstate the balance of energy supply / demand within the tissue. The actions of both subtypes are to increase the amount of available oxygen
15 to tissue and to protect cells against damage caused by a short-term imbalance of oxygen. One of the important functions of endogenous adenosine is preventing damage during traumas such as hypoxia, ischaemia, hypotension and seizure activity. Furthermore, it is known that the binding of the adenosine receptor agonist to mast cells expressing the rat A₃ receptor resulted in increased inositol triphosphate and intracellular calcium concentrations, which potentiated antigen
20 induced secretion of inflammatory mediators. Therefore, the A₃ receptor plays a role in mediating asthmatic attacks and other allergic responses.

25 These adenosine receptors are encoded by distinct genes and are classified according to their affinities for adenosine analogues and methylxanthine antagonists (Klinger et al., Cell Signal., 14 (2): 99-108, 2002).

30 Concerning the role of adenosine on the nervous system, the first observations were made on the effects of the most widely used of all psychoactive drugs being caffeine. Actually, caffeine is a well-known adenosine receptor antagonist that is able to enhance the awareness and learning abilities of mammals. The adenosine A_{2A} receptor pathway is responsible for these effects (Fredholm et al., Pharmacol. Rev., 51 (1): 83-133, 1999; Huang et al., Nat Neurosci., 8 (7): 858-9, 2005), and the

effects of caffeine on the adenosine A_{2A} receptor signaling pathway encouraged the research of highly specific and potent adenosine A_{2A} antagonists.

5 In mammals, adenosine A_{2A} receptors have a limited distribution in the brain and are found in the striatum, olfactory tubercle and nucleus acumbens (Dixon et al., Br. J. Pharmacol., 118 (6): 1461-8, 1996). High and intermediate levels of expression can be observed in immune cells, heart, lung and blood vessels. In the peripheral system, G₃ seems to be the major G-protein associated with adenosine A_{2A} receptor but in the striatum, it has been shown that striatal adenosine A_{2A} receptors mediate their effects through activation of a G-protein referred to as G_{oif} (Kull et al., Mol. Pharmacol., 58 (4): 772-7, 2000), which is similar to G₃ and also couples to adenylate cyclase.

To date, studies on genetically modified mice and pharmacological analysis suggest that A_{2A} receptor is a promising therapeutic target for the treatment of central nervous system (CNS) disorders and diseases such as Parkinson's disease, Huntington's disease, attention deficit hyperactivity disorders (ADHD), stroke (ischemic brain injury), and Alzheimer's disease (Fredholm et al., Annu. Rev. Pharmacol. Toxicol., 45: 385-412, 2005; Higgins et al.; Behav. Brain Res. 185: 32-42, 2007; Dall' Igna et al., Exp. Neurol., 203 (1): 241-5, 2007; Arendash et al., Neuroscience, 142 (4): 941-52, 2006; Trends in Neurosci., 29 (11), 647-654, 2006; Expert Opinion Ther. Patents, 17, 979-991, 2007; Exp. Neurol., 184 (1), 285-284, 2003; Prog. Brain Res, 183, 183-208, 2010; J. Alzheimer Dis., Suppl 1, 1 17-126, 2010; J. Neurosci., 29 (47), 14741-14751, 2009; Neuroscience, 166 (2), 590-603, 2010; J. Pharmacol. Exp. Ther., 330 (1), 294-303, 2009; Frontiers Biosci., 13, 2614-2632, 2008) but also for various psychoses of organic origin (Weiss et al., Neurology, 61 (11 Suppl 6): 88-93, 2003).

The use of adenosine A_{2A} receptor knockout mice has shown that adenosine A_{2A} receptor inactivation protects against neuronal cell death induced by ischemia (Chen et al., J. Neurosci., 19 (21): 9192-200, 1999 and Monopoli et al., Neuroreport, 9 (17): 3955-9, 1998) and the mitochondrial toxin 3-NP (Blum et al., J. Neurosci., 23 (12): 5361-9, 2003). Those results provided a basis for treating ischasmia and Huntington's disease with adenosine A_{2A} antagonists. The blockade of adenosine A_{2A} receptors has also an antidepressant effect (El Yacoubi et al.,

Neuropharmacology, 40 (3): 424-32, 2001). Finally, this blockade prevents memory dysfunction (Cunha et al., Exp. Neurol., 210 (2): 776-81, 2008; Takahashi et al., Front. Biosci., 13: 2614-32, 2008) and this could be a promising therapeutic route for the treatment and/or prevention of Alzheimer's disease.

5

For reviews concerning A_{2A} adenosine receptors see e.g. Moreau et al. (Brain Res. Reviews 31: 65-82, 1999) and Svenningsson et al. (Progress in Neurobiology 59: 355-396, 1999).

10

To date, several adenosine A_{2A} receptor antagonists have shown promising potential for treatment of Parkinson's disease. As an example, KW-6002 (Istradefylline) completed a phase III clinical trial in the USA after studies demonstrated its efficacy in alleviation of symptoms of the disease (Bara-Himenez et al., Neurology, 61 (3): 293-6, 2003 and Hauser et al., Neurology, 61 (3): 297-303, 2003). SCH420814 (Preladenant), which is now in phase II clinical trial in the USA and produces an improvement in motor function in animal models of Parkinson's disease (Neustadt et al., Bioorg. Med. Chem. Lett., 17 (5): 1376-80, 2001) and also in human patients (Hunter J. C, poster Boston 2006 - <http://www.a2apd.org/Speaker/abstracts/Hunter.pdf>).

15

20

Besides the welcome utility of A_{2A} receptor antagonists to treat neurodegenerative diseases, those compounds have been considered for complementary symptomatic indications. These are based on the evidence that A_{2A} receptor activation may contribute to the pathophysiology of a range of neuropsychiatric disorders and dysfunctions such as depression, excessive daytime sleepiness, restless legs syndrome, attention deficit hyperactivity disorder, and cognitive fatigue (Neurology, 61 (Suppl 6), 82-87, 2003; Behav. Pharmacol., 20 (2), 134-145, 2009; CNS Drug Discov., 2 (1), 1-21, 2007).

25

30

Some authors suggest the application of A_{2A} antagonists for the treatment of diabetes (WO1999035147; WO2001002400). Other studies suggest the involvement of A_{2A} adenosine receptors in wound healing or atrial fibrillation (Am. J. Path., 6, 1774- 1778, 2007; Arthritis & Rheumatism, 54 (8), 2632-2642, 2006).

Some of the potent adenosine A_{2A} antagonists discovered in the past by the pharmaceutical companies, have advanced into clinical trials showing positive results and demonstrating the potential of this compound class for the treatment of neurodegenerative disorders like Parkinson's, Huntington's or Alzheimer's disease, but also in other CNS related diseases like depression, restless syndrome, sleep and anxiety disorders (Clin. Neuropharmacol., 33, 55-60, 2010; J. Neurosci., 30 (48), 2010), 16284-16292; Parkinson Relat. Disord., 16 (6), 423-426, 2010; Expert Opinion Ther. Patents, 20(8), 987-1005, 2010; Current Opinion in Drug Discovery & Development, 13 (4), 466-480, 2010 and references therein; Mov. Disorders, 25 (2), S305, 2010).

Known A_{2A} inhibitors are Istradefylline (KW-6002), Preladenant (SCH420814), SCH58261, CGS15943, Tozadenant, Vipadenant (V-2006), V-81444 (CPI-444, HTL-1071, PBF-509, Medi-9447, PNQ-370, ZM-241385, ASO-5854, ST-1535, ST-4206, DT1133 and DT-0926, which are in most cases developed for Parkinson's disease.

Adenosine A_{2B} receptors were cloned from rat hypothalamus (Rivkees and Reppert, 1992), human hippocampus (Pierce et al., 1992), and mouse mast cells (Marquardt et al., 1994), employing standard polymerase chain reaction techniques with degenerate oligonucleotide primers designed to recognize conserved regions of most G protein-coupled receptors. The human A_{2B} receptor shares 86 to 87% amino acid sequence homology with the rat and mouse A_{2B} receptors (Rivkees and Reppert, 1992; Pierce et al., 1992; Marquardt et al., 1994) and 45% amino acid sequence homology with human A₁ and A_{2A} receptors. As expected for closely related species, the rat and mouse A_{2B} receptors share 96% amino acid sequence homology. By comparison, the overall amino acid identity between A₁ receptors from various species is 87% (Palmer and Stiles, 1995). A_{2A} receptors share 90% of homology between species (Ongini and Fredholm, 1996), with most differences occurring in the 2nd extracellular loop and the long C-terminal domain (Palmer and Stiles, 1995). The lowest (72%) degree of identity between species is observed for A₃ receptor sequences (Palmer and Stiles, 1995).

The adenosine analog NECA remains the most potent A_{2B} agonist (Bruns, 1981; Feoktistov and Biaggioni, 1993, 1997; Brackett and Daly, 1994), with a

concentration producing a half-maximal effect (EC_{50}) for stimulation of adenylyl cyclase of approximately 2 μ M. It is, however, nonselective and activates other adenosine receptors with even greater affinity, with an EC_{50} in the low nanomolar (A_1 and A_{2A}) or high nanomolar (A_3) range. The characterization of A_{2B} receptors, therefore, often relies on the lack of effectiveness of compounds that are potent and selective agonists of other receptor types. A_{2B} receptors have been characterized by a method of exclusion, i.e., by the lack of efficacy of agonists that are specific for other receptors. The A_{2A} selective agonist CGS-21680 (Webb et al., 1992), for example, has been useful in differentiating between A_{2A} and A_{2B} adenosine receptors (Hide et al., 1992; Chern et al., 1993; Feoktistov and Biaggioni, 1995; van der Ploeg et al., 1996). Both receptors are positively coupled to adenylyl cyclase and are activated by the nonselective agonist NECA. CGS-21680 is virtually ineffective on A_{2B} receptors but is as potent as NECA in activating A_{2A} receptors, with an EC_{50} in the low nanomolar range for both agonists (Jarvis et al., 1989; Nakane and Chiba, 1990; Webb et al., 1992; Hide et al., 1992; Feoktistov and Biaggioni, 1993; Alexander et al., 1996). A_{2B} receptors have also a very low affinity for the A_1 selective agonist R-PIA (Feoktistov and Biaggioni, 1993; Brackett and Daly, 1994) as well as for the A_3 selective agonist N^6 -(3-iodobenzyl)-N-methyl-5'-carbamoyl-adenosine (IB-MECA) (Feoktistov and Biaggioni, 1997). The agonist profile $NECA > R-PIA = IB-MECA > CGS-21680$ was determined in human erythroleukemia (HEL) cells for A_{2B} -mediated cAMP accumulation. The difference between EC_{50} for NECA and the rest of the agonists is approximately 2 orders of magnitude. Therefore, responses elicited by NECA at concentrations in the low micromolar range (1–10 μ M), but not by R-PIA, IB-MECA or CGS-21680, are characteristic of A_{2B} receptors.

Whereas A_{2B} receptors have, in general, a lower affinity for agonists compared to other receptor subtypes, this is not true for antagonists. The structure activity relationship of adenosine antagonists on A_{2B} receptors has not been fully characterized, but at least some xanthines are as or more potent antagonists of A_{2B} receptor subtypes than of other subtypes. In particular, DPSPX (1,3-dipropyl-8-sulphophenylxanthine), DPCPX (1,3-dipropyl-8c-yclopentylxanthine), DPX (1,3-diethylphenylxanthine), the antiasthmatic drug enprofylline (3-n-propylxanthine) and the non-xanthine compound 2,4-dioxobenzopteridine (alloxazine) have affinities in

the mid to high nM range.

Other known A_{2B} inhibitors are ATL801, PSB-605, PSB-1115, ISAM-140, GS6201, MRS1706 and MRS1754.

5 It is disclosed herein that adenosine receptors play a non-redundant role in down-regulation of inflammation in vivo by acting as a physiological "STOP" (a termination mechanism) that can limit the immune response and thereby protect normal tissues from excessive immune damage during pathogenesis of different diseases.

10 A_{2A} receptor antagonists provide long term enhancement of immune responses by reducing T-cell mediated tolerance to antigenic stimuli, enhancing the induction of memory T cells and enhancing the efficacy of passive antibody administration for the treatment of cancer and infectious diseases while A_{2A} receptor agonists provide long term reduction of immune responses by enhancing T-cell mediated tolerance
15 to antigenic stimuli, in particular to reduce use of immunosuppressive agents in certain conditions.

Immune modulation is a critical aspect of the treatment of a number of diseases and disorders. T cells in particular play a vital role in fighting infections and have the capability to recognize and destroy cancer cells. Enhancing T cell mediated
20 responses is a key component to enhancing responses to therapeutic agents. However, it is critical in immune modulation that any enhancement of an immune response is balanced against the need to prevent autoimmunity as well as chronic inflammation. Chronic inflammation and self-recognition by T cells is a major cause for the pathogenesis of systemic disorders such as rheumatoid arthritis, multiple
25 sclerosis and systemic lupus erythematosus. Furthermore, long term immunosuppression is required in preventing rejection of transplanted organs or grafts.

Tumor-induced immunosuppression is a major hurdle to the efficacy of current cancer therapies. Because of their remarkable clinical efficacy against a broader
30 range of cancers, recent successes with immune checkpoint blockade inhibitors such as anti-CTLA-4 and anti-PD-1/PDL1 are revolutionizing cancer treatment.

Adenosine is one of the new promising immunosuppressive targets revealed in preclinical studies. This metabolite is produced by the ectoenzyme CD73 expressed on host suppressor cells and tumor cells. Increased expression of CD73 correlates with poor prognosis in patients with a number of cancers, including colorectal cancer (Liu et al, J. Surgical Oncol, 2012), gastric cancer (Lu et al., World J. Gastroenterol., 2013), gallbladder cancer (Xiong et al., Cell and Tissue Res., 2014). Preclinical studies demonstrated that protumor effects of CD73 can be driven (at least in part) by adenosine-mediated immunosuppression. As disclosed above, adenosine binds to four known receptors A₁, A_{2A}, A_{2B}, and A₃, with the activation of A_{2A} and A_{2B} receptors known to suppress the effector functions of many immune cells, i.e. A_{2A} and A_{2B} receptors induce adenylate-cyclase-dependent accumulation of cAMP leading to immunosuppression. Since antagonizing A₁ and A₃ would counteract the desired effect and A₁ and A₃ agonists serve as potential cardioprotective agents, selectivity towards A₁ and A₃ needs to be achieved (Antonioli et al., Nat. rev. Cancer, 2013, Thiel et al., Microbes and Infection, 2003). In the microenvironment of the tumor, both A_{2A} and A_{2B} receptor activation has been demonstrated to suppress antitumor immunity and increase the spread of CD73 tumors. In addition, either A_{2A} or A_{2B} blockade with small molecule antagonists can reduce tumor metastasis. It has been found that blocking of A_{2A} receptor can overcome tumor escape mechanisms including both anergy and regulatory T cell induction caused by tumor cells and cause long-term tumor susceptibility to treatment. Ohta et al. demonstrated rejection of approximately 60% of established CL8-1 melanoma tumors in A_{2A} receptor-deficient mice compared to no rejection in normal mice (Ohta, et al.; PNAS 103 (35): 13132-7, 2006). In agreement, the investigators also showed improved inhibition of tumor growth, destruction of metastases and prevention of neovascularization by anti-tumor T cells after treatment with an A_{2A} receptor antagonist.

Tumors have been shown to evade immune destruction by impeding T cell activation through inhibition of co-stimulatory factors in the B7-CD28 and TNF families, as well as by attracting regulatory T cells, which inhibit anti-tumor T cell responses (Wang, Cancer. Semin. Cancer. Biol. 16: 73-79, 2006; Greenwald, et al., Ann. Rev. Immunol. 23: 515-48, 2005; Watts, Ann. Rev. Immunol. 23: 23-68, 2005; Sadum et al., Clin. Cane. Res. 13 (13): 4016-4025, 2007). Because A_{2A} receptor expression is increased in lymphocytes following activation, therapies that liberate

lymphocyte effector responses, such as anti-CTLA-4 and anti-PD-1, may also increase the effects of A_{2A}-mediated immunosuppression. Immune checkpoint blockade in combination with A_{2A} or dual A_{2A/2B} antagonists increase the magnitude of immune responses to tumors and metastasis. Accordingly, combination of A_{2A} inhibition with anti-PD-1 therapy enhances IFN- γ production by T-cells in a co-culture with MC38 tumor cells, improves mouse survival in 4T1 mammary tumor model and decreases tumor growth in AT-3ova^{dim} CD73⁺ tumors (Beavis et al., 5 Cancer Immunol. Res., 2015; Mittal et al., Cancer Res., 2014).

Furthermore, preclinical studies demonstrated that A_{2B} inhibition leads to decreased tumor growth and extended survival of mice in Lewis lung carcinoma, MB49 bladder carcinoma, ortho 4T1 mammary carcinoma models (Ryzhov et al., 2009, Cekic et al., 2012) and the combination of A_{2B} inhibition with anti-PD-1 therapy reduces lung metastases of B16-F10 melanoma tumors and improves mouse survival in the 4T1 mammary tumor model.

15 WO 03/050241 describes the methods to increase an immune response to an antigen, increasing vaccine efficacy or increasing an immune response to a tumor antigen or immune cell-mediated tumor destruction by administering an agent that inhibits extracellular adenosine or inhibits adenosine receptors.

20 WO 2004/089942, WO 2005/000842 and WO 2006/008041 disclose benzothiazole derivatives, including Tozadenant, as A_{2A} inhibitors for the treatment of Parkinson's disease. WO 2004/092171 and WO 2005/028484 disclose similar thiazolopyridine and pyrazolopyrimidine derivatives also as A_{2A} inhibitors for the treatment of Parkinson's disease. However, these compounds do not show significant A_{2B} inhibitory activity and do only show good pharmacokinetic properties in the rat, the Parkinson's disease animal model but not in the mouse, the cancer animal model. Furthermore, the compounds do not show that they are able to prevent immunosuppression and thus are able to support anti-tumor T cell induced inhibition of tumor growth, reduction or destruction of metastases and prevention of neovascularization.

30 Thus, there remains a need for therapies that provide long term enhancement of immune responses to specific antigens, particularly for the treatment and prevention

of hyperproliferative and infectious diseases and disorders and thus the object of the present invention was to provide methods of treatment that allow simplified treatment protocols and enhance immune responses against certain antigens. It was a specific object of the invention to provide improved methods of preventing or treating hyperproliferative and infectious diseases and disorders in a host, especially to provide effective A_{2A} or dual $A_{2A/2B}$ antagonists for the treatment and prevention of such diseases.

Summary of the invention

Surprisingly, it has been found that the compounds according to the invention are highly effective inhibitors of the A_{2A} adenosine receptor or both the A_{2A} and A_{2B} adenosine receptors and at the same time have high selectivity over the A_1 and A_3 adenosine receptors, and thus the compounds of the present invention can be used for the treatment of hyperproliferative diseases and disorders such as cancer and infectious diseases and disorders.

Particularly, in contrast to the known adenosine A_{2A} receptor antagonist Tozadenant and similar benzothiazole derivatives, the compounds of the present invention surprisingly show an A_{2A}/A_{2B} dual activity which is preferred for the treatment and/or prevention of hyperproliferative and infectious diseases and disorders as it is disclosed above or the compounds of the present invention show at least a high A_{2A} inhibitory activity together with the other surprising advantages disclosed herein leading to a high efficacy in the treatment and/or prevention of hyperproliferative and infectious diseases and disorders.

Additionally, in comparison with the known adenosine A_{2A} receptor antagonist Tozadenant and similar benzothiazole derivatives, the compounds of the present invention surprisingly show better pharmacokinetic properties in mouse as the animal model relevant for cancer, which is preferred for the treatment and/or prevention of hyperproliferative and infectious diseases and disorders as it is disclosed above.

Furthermore, as discussed above, adenosine in tumor microenvironment can inhibit T cell activity by signaling through A_{2A} receptors and suppress cytokine secretion by T cells. A_{2A} specific agonists like CGS-21680 or NECA, similar to adenosine, inhibit T cell cytokine secretion in vitro and in vivo. In contrast, potential A_{2A} antagonists or A_{2A}/A_{2B} dual antagonists can rescue T cells from this inhibition. In contrast to the known adenosine A_{2A} receptor antagonist Tozadenant, the compounds of the present invention show that they are able to rescue T cells from inhibition and are able to prevent the suppression of cytokine secretion as induced by adenosine or A_{2A} specific agonists like CGS-2168, CGS-21680 or NECA, which is preferred for the treatment and/or prevention of hyperproliferative and infectious diseases and disorders as it is disclosed above. Therefore, the compounds of the present invention surprisingly are able to prevent immunosuppression and thus are able to support anti-tumor T cell induced inhibition of tumor growth, reduction or destruction of metastases and prevention of neovascularization.

The invention relates to a compound selected from the group consisting of:

1	(R)-3-Aminomethyl-pyrrolidine-1-carboxylic acid (4-methoxy-7-phenyl-thiazolo[4,5-c]pyridin-2-yl)-amide
2	N-{4-methoxy-7-[4-(oxan-4-yloxy)phenyl]-[1,3]thiazolo[4,5-c]pyridin-2-yl}-8-oxa-2-azaspiro[4.5]decane-2-carboxamide
3	(S)-3-Aminomethyl-pyrrolidine-1-carboxylic acid (4-methoxy-7-phenyl-thiazolo[4,5-c]pyridin-2-yl)-amide
4	Cyclopropanecarboxylic acid (6-fluoro-4-methoxy-7-morpholin-4-yl-thiazolo[4,5-c]pyridin-2-yl)-amide
5	4-Methoxy-7-(tetrahydro-pyran-4-yl)-thiazolo[4,5-c]pyridin-2-ylamine
6	N-(6-Fluoro-4-methoxy-7-morpholin-4-yl-thiazolo[4,5-c]pyridin-2-yl)-4-(1H-tetrazol-5-yl)-benzamide
7	7-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid (6-fluoro-4-methoxy-7-morpholin-4-yl-thiazolo[4,5-c]pyridin-2-yl)-amide
8	7-(3,6-Dihydro-2H-pyran-4-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-ylamine
9	N-[7-(1H-indol-6-yl)-4-methoxy-[1,3]thiazolo[4,5-c]pyridin-2-yl]-8-oxa-2-azaspiro[4.5]decane-2-carboxamide

5	10	(R)-7-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid (6-fluoro-4-methoxy-7-morpholin-4-yl-thiazolo[4,5-c]pyridin-2-yl)-amide
	11	(5S)-N-[6-fluoro-4-methoxy-7-(morpholin-4-yl)-[1,3]thiazolo[4,5-c]pyridin-2-yl]-7-oxa-2-azaspiro[4.5]decane-2-carboxamide
	12	(R)-7-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid (6-fluoro-4-methoxy-7-phenyl-thiazolo[4,5-c]pyridin-2-yl)-amide
	13	(5S)-N-{6-fluoro-4-methoxy-7-phenyl-[1,3]thiazolo[4,5-c]pyridin-2-yl}-7-oxa-2-azaspiro[4.5]decane-2-carboxamide
10	14	3-Dimethylaminomethyl-bicyclo[1.1.1]pentane-1-carboxylic acid (4-methoxy-7-morpholin-4-yl-thiazolo[4,5-c]pyridin-2-yl)-amide
	15	7-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide
15	16	N-[6-fluoro-4-methoxy-7-(morpholin-4-yl)-[1,3]thiazolo[4,5-c]pyridin-2-yl]-2-oxa-7-azaspiro[4.4]nonane-7-carboxamide
	17	N-[4-methoxy-7-(oxan-4-yl)-[1,3]thiazolo[4,5-c]pyridin-2-yl]-2-[(2-methoxyethyl)amino]-1,3-thiazole-5-carboxamide
	18	(R)-2-Oxa-7-aza-spiro[4.4]nonane-7-carboxylic acid (6-fluoro-4-methoxy-7-morpholin-4-yl-thiazolo[4,5-c]pyridin-2-yl)-amide
20	19	(5S)-N-[6-fluoro-4-methoxy-7-(morpholin-4-yl)-[1,3]thiazolo[4,5-c]pyridin-2-yl]-2-oxa-7-azaspiro[4.4]nonane-7-carboxamide
	20	N-[6-Fluoro-4-methoxy-7-(tetrahydro-pyran-4-yl)-thiazolo[4,5-c]pyridin-2-yl]-N',N'-dimethyl-terephthalamide
	21	1-Imidazol-1-ylmethyl-cyclopropanecarboxylic acid [6-fluoro-4-methoxy-7-(tetrahydro-pyran-4-yl)-thiazolo[4,5-c]pyridin-2-yl]-amide
25	22	N-[6-fluoro-4-methoxy-7-(oxan-4-yl)-[1,3]thiazolo[4,5-c]pyridin-2-yl]-1-(2-methoxyethyl)-1H-pyrazole-4-carboxamide
	23	N-[6-fluoro-4-methoxy-7-(oxan-4-yl)-[1,3]thiazolo[4,5-c]pyridin-2-yl]-1-methyl-1H-pyrazole-4-carboxamide
30	24	(R)-7-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide
	25	(S)-7-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide
	26	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [6-fluoro-4-methoxy-7-(tetrahydro-pyran-4-yl)-thiazolo[4,5-c]pyridin-2-yl]-amide

5	27	4-Hydroxy-4-methyl-piperidine-1-carboxylic acid [6-fluoro-7-(4-fluoro-phenyl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide
	28	Cyclopropanecarboxylic acid [6-fluoro-4-methoxy-7-(tetrahydro-pyran-4-yl)-thiazolo[4,5-c]pyridin-2-yl]-amide
	29	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [6-fluoro-7-(4-fluoro-phenyl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide
	30	Cyclopropanecarboxylic acid [7-(3-ethylaminomethyl-phenyl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide
10	31	7-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [6-fluoro-4-methoxy-7-(tetrahydro-pyran-4-yl)-thiazolo[4,5-c]pyridin-2-yl]-amide
	32	1H-Imidazole-4-carboxylic acid (6-fluoro-4-methoxy-7-phenyl-thiazolo[4,5-c]pyridin-2-yl)-amide
	33	N-[6-fluoro-4-methoxy-7-(oxan-4-yl)-[1,3]thiazolo[4,5-c]pyridin-2-yl]-2-oxa-7-azaspiro[4.4]nonane-7-carboxamide
15	34	(R)-7-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [6-fluoro-4-methoxy-7-(tetrahydro-pyran-4-yl)-thiazolo[4,5-c]pyridin-2-yl]-amide
	35	(5S)-N-[6-fluoro-4-methoxy-7-(oxan-4-yl)-[1,3]thiazolo[4,5-c]pyridin-2-yl]-7-oxa-2-azaspiro[4.5]decane-2-carboxamide
	36	1-Methyl-1H-pyrazole-4-carboxylic acid [4-methoxy-7-(2,2,2-trifluoro-ethoxy)-thiazolo[4,5-c]pyridin-2-yl]-amide
20	37	(R)-2-Oxa-7-aza-spiro[4.4]nonane-7-carboxylic acid [6-fluoro-4-methoxy-7-(tetrahydro-pyran-4-yl)-thiazolo[4,5-c]pyridin-2-yl]-amide
	38	(5S)-N-[6-fluoro-4-methoxy-7-(oxan-4-yl)-[1,3]thiazolo[4,5-c]pyridin-2-yl]-2-oxa-7-azaspiro[4.4]nonane-7-carboxamide
	39	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [7-(3-amino-phenyl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide
25	40	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [4-methoxy-7-(3-oxo-cyclopent-1-enyl)-thiazolo[4,5-c]pyridin-2-yl]-amide
	41	Bicyclo[1.1.1]pentane-1,3-dicarboxylic acid [6-fluoro-4-methoxy-7-(tetrahydro-pyran-4-yl)-thiazolo[4,5-c]pyridin-2-yl]-amide (2-hydroxy-ethyl)-methyl-amide
	42	N-[7-(2,5-dihydrofuran-3-yl)-4-methoxy-[1,3]thiazolo[4,5-c]pyridin-2-yl]cyclopropanecarboxamide
30		

5	43	N-[7-(2,5-dihydrofuran-3-yl)-4-methoxy-[1,3]thiazolo[4,5-c]pyridin-2-yl]-1H-imidazole-4-carboxamide
	44	N-[7-(2,5-dihydrofuran-3-yl)-4-methoxy-[1,3]thiazolo[4,5-c]pyridin-2-yl]-8-oxa-2-azaspiro[4.5]decane-2-carboxamide
	45	N-[7-(2,5-dihydrofuran-3-yl)-4-methoxy-[1,3]thiazolo[4,5-c]pyridin-2-yl]-7-oxa-2-azaspiro[4.5]decane-2-carboxamide
	46	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [7-(1-acetyl-1,2,3,6-tetrahydro-pyridin-4-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide
10	47	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid (4-methoxy-7-thiophen-2-yl-thiazolo[4,5-c]pyridin-2-yl)-amide
	48	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid (7-furan-2-yl-4-methoxy-thiazolo[4,5-c]pyridin-2-yl)-amide
	49	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [7-(3-ethylaminomethyl-phenyl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide
15	50	N-[6-Fluoro-4-methoxy-7-(tetrahydro-pyran-4-yl)-thiazolo[4,5-c]pyridin-2-yl]-N'-(2-hydroxy-ethyl)-N'-methyl-terephthalamide
	51	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid (4-methoxy-7-piperidin-1-yl-thiazolo[4,5-c]pyridin-2-yl)-amide
20	52	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid (7-furan-3-yl-4-methoxy-thiazolo[4,5-c]pyridin-2-yl)-amide
	53	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [4-methoxy-7-(4-methyl-piperazin-1-yl)-thiazolo[4,5-c]pyridin-2-yl]-amide
	54	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [4-methoxy-7-(3-methoxy-phenyl)-thiazolo[4,5-c]pyridin-2-yl]-amide
25	55	N-{6-cyano-4-methoxy-[1,3]thiazolo[4,5-c]pyridin-2-yl}-1-(2-methoxyethyl)-1H-pyrazole-4-carboxamide
	56	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [4-methoxy-7-(6-methyl-pyridazin-3-yl)-thiazolo[4,5-c]pyridin-2-yl]-amide
30	57	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid (7-azetidin-1-yl-4-methoxy-thiazolo[4,5-c]pyridin-2-yl)-amide
	58	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [7-(3-hydroxy-azetidin-1-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide

5	59	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid (7-cyclohex-1-enyl-4-methoxy-thiazolo[4,5-c]pyridin-2-yl)-amide
	60	1H-Imidazole-4-carboxylic acid (4-methoxy-7-phenyl-thiazolo[4,5-c]pyridin-2-yl)-amide
	61	N4-[7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-[1,3]thiazolo[4,5-c]pyridin-2-yl]-N1,N1-dimethylbenzene-1,4-dicarboxamide
	62	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid (7-cyclohexyl-4-methoxy-thiazolo[4,5-c]pyridin-2-yl)-amide
10	63	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [7-(4,4-difluorocyclohex-1-enyl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide
	64	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [7-(3,6-dihydro-2H-thiopyran-4-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide
	65	1H-Imidazole-4-carboxylic acid [7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide
15	66	N-[4-methoxy-7-(4-methoxycyclohex-1-en-1-yl)-[1,3]thiazolo[4,5-c]pyridin-2-yl]-8-oxa-2-azaspiro[4.5]decane-2-carboxamide
	67	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [4-methoxy-7-(2-methyl-thiazol-4-yl)-thiazolo[4,5-c]pyridin-2-yl]-amide
	68	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [4-methoxy-7-(1-pyridin-3-ylmethyl-1H-pyrazol-4-yl)-thiazolo[4,5-c]pyridin-2-yl]-amide
20	69	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [4-methoxy-7-(1-pyridin-2-ylmethyl-1H-pyrazol-4-yl)-thiazolo[4,5-c]pyridin-2-yl]-amide
	70	(5R)-N-[4-methoxy-7-(4-methoxycyclohex-1-en-1-yl)-[1,3]thiazolo[4,5-c]pyridin-2-yl]-7-oxa-2-azaspiro[4.5]decane-2-carboxamide
25	71	N-[7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-[1,3]thiazolo[4,5-c]pyridin-2-yl]-4-(1H-1,2,3-triazol-1-yl)benzamide
	72	4-{[7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-[1,3]thiazolo[4,5-c]pyridin-2-yl]carbonyl}benzoic acid
30	73	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid (7-[1,4]dioxan-2-yl-4-methoxy-thiazolo[4,5-c]pyridin-2-yl)-amide

5	74	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid {7-[1-(2,2-difluoroethyl)-1H-pyrazol-4-yl]-4-methoxy-thiazolo[4,5-c]pyridin-2-yl}-amide
	75	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [4-methoxy-7-(1-pyridin-4-ylmethyl)-1H-pyrazol-4-yl]-thiazolo[4,5-c]pyridin-2-yl]-amide
	76	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [7-(1-benzyl-1H-pyrazol-4-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide
10	77	(5S)-N-[4-methoxy-7-(4-methoxycyclohex-1-en-1-yl)-[1,3]thiazolo[4,5-c]pyridin-2-yl]-7-oxa-2-azaspiro[4.5]decane-2-carboxamide
	78	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [4-methoxy-7-(6-oxo-1,6-dihydro-pyridin-3-yl)-thiazolo[4,5-c]pyridin-2-yl]-amide
15	79	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [7-(1-difluoromethyl-1H-pyrazol-4-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide
	80	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid (4-difluoromethoxy-7-phenyl-thiazolo[4,5-c]pyridin-2-yl)-amide
	81	N-[7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-[1,3]thiazolo[4,5-c]pyridin-2-yl]-2-[(2-methoxyethyl)amino]-1,3-thiazole-5-carboxamide
20	82	N-[7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-[1,3]thiazolo[4,5-c]pyridin-2-yl]-4-[(1H-imidazol-1-yl)methyl]benzamide
	83	N-[7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-[1,3]thiazolo[4,5-c]pyridin-2-yl]-4-[(1R)-1-acetamidoethyl]benzamide
25	84	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid {4-methoxy-7-[1-(tetrahydro-pyran-2-ylmethyl)-1H-pyrazol-4-yl]-thiazolo[4,5-c]pyridin-2-yl}-amide
	85	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid {4-methoxy-7-[1-(tetrahydro-pyran-4-ylmethyl)-1H-pyrazol-4-yl]-thiazolo[4,5-c]pyridin-2-yl}-amide
30	86	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [7-(1,1-dioxo-hexahydro-1H-thiopyran-4-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide

5	87	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid {4-methoxy-7-[1-(tetrahydro-pyran-3-ylmethyl)-1H-pyrazol-4-yl]-thiazolo[4,5-c]pyridin-2-yl}-amide
	88	N-[7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-[1,3]thiazolo[4,5-c]pyridin-2-yl]-4-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)piperidine-1-carboxamide
	89	3-[7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-[1,3]thiazolo[4,5-c]pyridin-2-yl]-1-[4-(2-oxopyrrolidin-1-yl)phenyl]urea
10	90	N-[4-({[7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-[1,3]thiazolo[4,5-c]pyridin-2-yl]carbamoyl}amino)phenyl]-2-(dimethylamino)acetamide
	91	N-[7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-[1,3]thiazolo[4,5-c]pyridin-2-yl]-4-(2,4-dioxo-1,3-thiazolidin-3-yl)piperidine-1-carboxamide
	92	N-[4-({[7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-[1,3]thiazolo[4,5-c]pyridin-2-yl]carbamoyl}amino)-2-methylphenyl]acetamide
15	93	N4-[7-(3,6-dihydro-2H-pyran-4-yl)-4-hydroxy-[1,3]thiazolo[4,5-c]pyridin-2-yl]-N1-(2-hydroxyethyl)-N1-methylbenzene-1,4-dicarboxamide
	94	3-[7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-[1,3]thiazolo[4,5-c]pyridin-2-yl]-1-[4-(3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-1-yl)phenyl]urea
20	95	3-[7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-[1,3]thiazolo[4,5-c]pyridin-2-yl]-1-[4-(2-oxo-1,3-oxazolidin-3-yl)phenyl]urea
	96	N1-[7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-[1,3]thiazolo[4,5-c]pyridin-2-yl]-N4,N4-dimethylpiperidine-1,4-dicarboxamide
25	97	[4-(4-Methoxy-7-phenyl-thiazolo[4,5-c]pyridin-2-ylcarbamoyl)-benzyl]-methyl-carbamic acid methyl ester
	98	2,8-Diaza-spiro[4.5]decane-2-carboxylic acid [7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide
30	99	4-(2,5-Dioxo-pyrrolidin-1-yl)-piperidine-1-carboxylic acid (4-methoxy-7-phenyl-thiazolo[4,5-c]pyridin-2-yl)-amide

5	100	4-(2,5-Dioxo-pyrrolidin-1-yl)-piperidine-1-carboxylic acid [7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide
	101	Bicyclo[1.1.1]pentane-1,3-dicarboxylic acid (6-fluoro-4-methoxy-7-phenyl-thiazolo[4,5-c]pyridin-2-yl)-amide (2-hydroxy-ethyl)-methylamide
	102	2,7-Diaza-spiro[4.5]decane-2-carboxylic acid [7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide
10	103	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid (4-methoxy-7-{1-[2-(2-methoxy-ethoxy)-ethyl]-1H-pyrazol-4-yl}-thiazolo[4,5-c]pyridin-2-yl)-amide
	104	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid (4-methoxy-7-{1-[(R)-1-(tetrahydro-pyran-3-yl)methyl]-1H-pyrazol-4-yl}-thiazolo[4,5-c]pyridin-2-yl)-amide
15	105	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid (4-methoxy-7-{1-[(S)-1-(tetrahydro-pyran-3-yl)methyl]-1H-pyrazol-4-yl}-thiazolo[4,5-c]pyridin-2-yl)-amide
	106	N1-[7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-[1,3]thiazolo[4,5-c]pyridin-2-yl]piperidine-1,4-dicarboxamide
20	107	N-[7-(3,6-dihydro-2H-pyran-4-yl)-4-hydroxy-[1,3]thiazolo[4,5-c]pyridin-2-yl]-2-oxa-7-azaspiro[4.4]nonane-7-carboxamide
	108	N-[7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-[1,3]thiazolo[4,5-c]pyridin-2-yl]-2-oxa-7-azaspiro[4.4]nonane-7-carboxamide
25	109	4-({4-methoxy-7-phenyl-[1,3]thiazolo[4,5-c]pyridin-2-yl}carbonyl)benzoic acid
	110	N-{4-methoxy-7-phenyl-[1,3]thiazolo[4,5-c]pyridin-2-yl}-4-(1H-1,2,3,4-tetrazol-5-yl)benzamide
30	111	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [7-(4,4-difluorocyclohexyl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide
	112	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [4-methoxy-7-(3-methylamino-phenyl)-thiazolo[4,5-c]pyridin-2-yl]-amide

5	113	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [4-methoxy-7-(5-methyl-thiophen-2-yl)-thiazolo[4,5-c]pyridin-2-yl]-amide
	114	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [4-methoxy-7-(5-methyl-furan-2-yl)-thiazolo[4,5-c]pyridin-2-yl]-amide
	115	4-[(4-methoxy-7-{1-[(pyridin-3-yl)methyl]-1H-pyrazol-4-yl}-[1,3]thiazolo[4,5-c]pyridin-2-yl)carbonyl]benzoic acid
	116	N-[7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-[1,3]thiazolo[4,5-c]pyridin-2-yl]-1H-pyrazole-4-carboxamide
	117	N-{4-methoxy-7-phenyl-[1,3]thiazolo[4,5-c]pyridin-2-yl}-1H-pyrazole-4-carboxamide
10	118	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid (4-methoxy-7-{1-[(S)-1-(tetrahydro-pyran-2-yl)methyl]-1H-pyrazol-4-yl}-thiazolo[4,5-c]pyridin-2-yl)-amide
	119	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid (4-methoxy-7-{1-[(R)-1-(tetrahydro-pyran-2-yl)methyl]-1H-pyrazol-4-yl}-thiazolo[4,5-c]pyridin-2-yl)-amide
	120	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [7-(3-methanesulfonylamino-phenyl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide
15	121	(R)-2,7-Diaza-spiro[4.5]decane-2-carboxylic acid [7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide
	122	(S)-2,7-Diaza-spiro[4.5]decane-2-carboxylic acid [7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide
	123	Piperidine-1,4-dicarboxylic acid 4-dimethylamide 1-[(4-methoxy-7-phenyl-thiazolo[4,5-c]pyridin-2-yl)-amide]
20	124	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [7-(2-amino-pyridin-4-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide
	125	N-[7-(3,6-Dihydro-2H-pyran-4-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-4-(4-methyl-piperazine-1-carbonyl)-benzamide
	126	N-[7-(3,6-Dihydro-2H-pyran-4-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-N'-(2-piperidin-1-yl-ethyl)-terephthalamide
25	127	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [4-methoxy-7-(2-methylamino-pyridin-4-yl)-thiazolo[4,5-c]pyridin-2-yl]-amide
	128	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [4-methoxy-7-(5-methyl-cyclohex-1-enyl)-thiazolo[4,5-c]pyridin-2-yl]-amide
30		

5	129	N-[7-(3,6-Dihydro-2H-pyran-4-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-4-(4-hydroxy-4-methyl-piperidine-1-carbonyl)-benzamide
	130	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [7-(3-fluoro-5-methanesulfonylamino-phenyl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide
	131	4-(2,5-Dioxo-imidazolidin-1-yl)-piperidine-1-carboxylic acid [7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide
	132	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [4-methoxy-7-(3-methyl-3,6-dihydro-2H-pyran-4-yl)-thiazolo[4,5-c]pyridin-2-yl]-amide
10	133	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [4-methoxy-7-(3-trifluoromethyl-piperidin-1-yl)-thiazolo[4,5-c]pyridin-2-yl]-amide
	134	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [4-methoxy-7-(3-methoxy-piperidin-1-yl)-thiazolo[4,5-c]pyridin-2-yl]-amide
	135	Imidazo[1,2-a]pyridine-3-carboxylic acid [7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide
15	136	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [4-methoxy-7-(5-oxo-2,5-dihydro-1H-pyrrol-3-yl)-thiazolo[4,5-c]pyridin-2-yl]-amide
	137	4-(2,5-Dioxo-imidazolidin-1-yl)-piperidine-1-carboxylic acid (4-methoxy-7-phenyl-thiazolo[4,5-c]pyridin-2-yl)-amide
	138	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [7-(5-amino-2-fluoro-pyridin-3-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide
20	139	N-(2-Azetidin-1-yl-ethyl)-N'-[7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-terephthalamide
	140	2-Pyridin-3-yl-1H-imidazole-4-carboxylic acid [7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide
25	141	N-{4-methoxy-7-[3-(trifluoromethyl)phenyl]-[1,3]thiazolo[4,5-c]pyridin-2-yl}-8-oxa-2-azaspiro[4.5]decane-2-carboxamide
	142	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [7-(5-amino-6-fluoro-pyridin-3-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide
	143	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [7-(5-amino-pyridin-3-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide
30	144	{4-[7-(3,6-Dihydro-2H-pyran-4-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]carbamoyl}-phenyl}-acetic acid

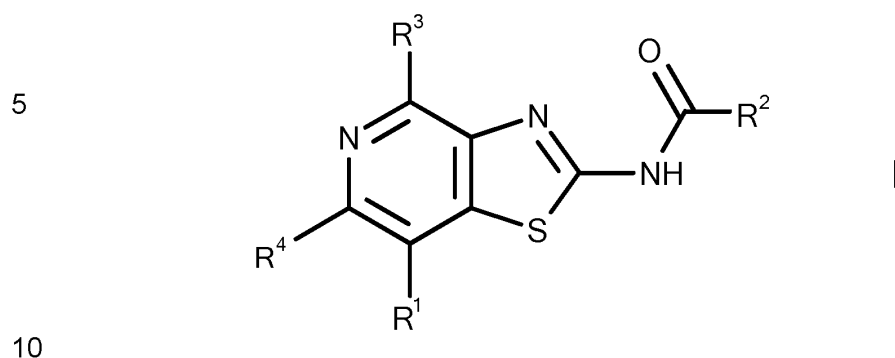
5	145	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [4-methoxy-7-((S)-3-methyl-cyclohex-1-enyl)-thiazolo[4,5-c]pyridin-2-yl]-amide
	146	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [4-methoxy-7-((R)-3-methyl-cyclohex-1-enyl)-thiazolo[4,5-c]pyridin-2-yl]-amide
	147	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid {4-methoxy-7-[3-(1-methyl-1H-pyrazol-4-yloxy)-phenyl]-thiazolo[4,5-c]pyridin-2-yl}-amide
	148	4-[7-(3,6-Dihydro-2H-pyran-4-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-ylcarbamoyl]-thiazole-2-carboxylic acid
10	149	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [7-(4-fluoro-3-hydroxy-phenyl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide
	150	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [7-(2-fluoro-5-hydroxy-phenyl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide
	151	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid ((R)-7-[1,4]dioxan-2-yl-4-methoxy-thiazolo[4,5-c]pyridin-2-yl)-amide
15	152	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid ((S)-7-[1,4]dioxan-2-yl-4-methoxy-thiazolo[4,5-c]pyridin-2-yl)-amide
	153	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [7-(3-hydroxy-phenyl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide
	154	{4-[7-(3,6-Dihydro-2H-pyran-4-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-ylcarbamoyl]-thiazol-2-yl}-acetic acid
20	155	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [7-(6-aminomethyl-2-methyl-pyrimidin-4-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide
	156	1-Phenyl-1H-pyrazole-4-carboxylic acid [7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide
	157	1-Pyridin-4-yl-1H-pyrazole-4-carboxylic acid [7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide
25	158	1-(1H-Imidazol-2-ylmethyl)-1H-pyrazole-4-carboxylic acid [7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide
	159	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid {4-methoxy-7-[3-(3,3,3-trifluoro-propylamino)-phenyl]-thiazolo[4,5-c]pyridin-2-yl}-amide
	160	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid {4-methoxy-7-[3-(pyridin-3-yloxy)-phenyl]-thiazolo[4,5-c]pyridin-2-yl}-amide
30		

5	161	N-(7-[1,4]Dioxan-2-yl-4-methoxy-thiazolo[4,5-c]pyridin-2-yl)-terephthalamic acid
	162	2-Pyridin-2-yl-1H-imidazole-4-carboxylic acid [7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide
	163	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid {4-methoxy-7-[1-(1-methyl-1-phenyl-ethyl)-1H-pyrazol-4-yl]-thiazolo[4,5-c]pyridin-2-yl}-amide
	164	N-(7-[1,4]Dioxan-2-yl-4-methoxy-thiazolo[4,5-c]pyridin-2-yl)-4-(1H-tetrazol-5-yl)-benzamide
10	165	2-Pyridin-4-yl-1H-imidazole-4-carboxylic acid [7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide
	166	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid (4-methoxy-7-{3-[(oxazol-4-ylmethyl)-amino]-phenyl}-thiazolo[4,5-c]pyridin-2-yl)-amide
	167	{4-[7-(3,6-Dihydro-2H-pyran-4-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-ylcarbamoyl]-benzyl}-methyl-carbamic acid methyl ester
15	168	5-[7-(3,6-Dihydro-2H-pyran-4-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-ylcarbamoyl]-1H-imidazole-2-carboxylic acid
	169	N-((R)-7-[1,4]Dioxan-2-yl-4-methoxy-thiazolo[4,5-c]pyridin-2-yl)-terephthalamic acid
	170	N-((S)-7-[1,4]Dioxan-2-yl-4-methoxy-thiazolo[4,5-c]pyridin-2-yl)-terephthalamic acid
20	171	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid (7-iodo-4-methoxy-thiazolo[4,5-c]pyridin-2-yl)-amide
	172	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [7-(2-cyano-pyridin-4-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide
	173	(5R)-N-[7-(3,6-dihydro-2H-pyran-4-yl)-4-(2H3)methoxy-[1,3]thiazolo[4,5-c]pyridin-2-yl]-7-oxa-2-azaspiro[4.5]decane-2-carboxamide
	174	(5S)-N-[7-(3,6-dihydro-2H-pyran-4-yl)-4-(2H3)methoxy-[1,3]thiazolo[4,5-c]pyridin-2-yl]-7-oxa-2-azaspiro[4.5]decane-2-carboxamide

30

and physiologically acceptable salts, derivatives, solvates, prodrugs and stereoisomers thereof, including mixtures thereof in all ratios.

The compounds of the present invention fall under the general formula I,



wherein

- 15
- R^1 is linear or branched alkyl having 1-10 C atoms which is unsubstituted or mono-, di- or trisubstituted by R^5 and in which 1-4 C atoms may be replaced, independently of one another, by O, S, SO, SO₂, NH, NCH₃, –OCO–, –NHCONH–, –NHCO–, –NR⁶SO₂R⁷–, –COO–, –CONH–, –NCH₃CO–, –CONCH₃–, –C≡C– groups and/or –CH=CH– groups, and/or, in addition, 1-10 H atoms may be replaced by F and/or Cl, or mono- or bicyclic cyclic alkyl having 3-7 C atoms which is unsubstituted or mono-, di- or trisubstituted by R^5 and in which 1-4 C atoms may be replaced, independently of one another, by O, S, SO, SO₂, NH, NCH₃, –OCO–, –NHCONH–, –NHCO–, –NR⁶SO₂R⁷–, –COO–, –CONH–, –NCH₃CO–, –CONCH₃–, –C≡C– groups and/or by –CH=CH– groups and/or, in addition, 1-10 H atoms may be replaced by F and/or Cl, or mono- or bicyclic heteroaryl, heterocyclyl, aryl or cyclic alkylaryl, containing 3 to 14 carbon atoms and 0-4 heteroatoms, independently selected from N, O and S, which is unsubstituted or mono-, di- or trisubstituted by R^5 ,
- 20
- R^2 is linear or branched alkyl having 1-10 C atoms which is unsubstituted or mono-, di- or trisubstituted by R^5 and in which 1-4 C atoms may be replaced, independently of one another, by O, S, SO, SO₂, NH, NCH₃, –OCO–, –NHCONH–, –NHCO–, –NR⁶SO₂R⁷–, –COO–, –CONH–, –NCH₃CO–, –CONCH₃–, –C≡C– groups and/or –CH=CH– groups, and/or, in addition, 1-10 H atoms may be replaced by F and/or Cl, or cyclic alkyl having 3-7 C atoms which is unsubstituted or mono-, di- or trisubstituted
- 25
- 30

by by R⁵ and in which 1-4 C atoms may be replaced, independently of one another, by O, S, SO, SO₂, NH, NCH₃, -OCO-, -NHCONH-, -NHCO-, -NR⁶SO₂R⁷-, -COO-, -CONH-, -NCH₃CO-, -CONCH₃-, -C≡C- groups and/or by -CH=CH- groups and/or, in addition, 1-11 H atoms may be replaced by F and/or Cl, or mono- or bicyclic heteroaryl, heterocyclyl, aryl or cyclic alkylaryl, containing 3 to 14 carbon atoms and 0-4 heteroatoms, independently selected from N, O and S, which is unsubstituted or mono-, di- or trisubstituted by R⁵,

5 R³ is linear or branched alkyl or O-alkyl having 1-6 C atoms or cyclic alkyl having 3-6 C atoms, which is unsubstituted or mono-, di- or trisubstituted by H, =S, =NH, =O, OH, cyclic alkyl having 3-6 C atoms, COOH, Hal, NH₂, SO₂CH₃, SO₂NH₂, CN, CONH₂, NHCOCH₃, NHCONH₂ or NO₂,

10 R⁴ is H, D, linear or branched alkyl having 1-6 C atoms, CN or Hal,

R⁵ is H, R⁶, =S, =NR⁶, =O, OH, COOH, Hal, NH₂, SO₂CH₃, SO₂NH₂, CN, CONH₂, NHCOCH₃, NHCONH₂, NO₂, or linear or branched alkyl having 1-10 C atoms which is unsubstituted or mono-, di- or trisubstituted by R⁶ and in which 1-4 C atoms may be replaced, independently of one another, by O, S, SO, SO₂, NH, NCH₃, -OCO-, -NHCONH-, -NHCO-, -NR⁶SO₂R⁷-, -COO-, -CONH-, -NCH₃CO-, -CONCH₃-, -C≡C- groups and/or -CH=CH- groups, and/or, in addition, 1-10 H atoms may be replaced by F and/or Cl, or mono- or bicyclic cyclic alkyl having 3-7 C atoms which is unsubstituted or mono-, di- or trisubstituted by by R⁶ and in which 1-4 C atoms may be replaced, independently of one another, by O, S, SO, SO₂, NH, NCH₃, -OCO-, -NHCONH-, -NHCO-, -NR⁶SO₂R⁷-, -COO-, -CONH-, -NCH₃CO-, -CONCH₃-, -C≡C- groups and/or by -CH=CH- groups and/or, in addition, 1-10 H atoms may be replaced by F and/or Cl, or mono- or bicyclic heteroaryl, heterocyclyl, aryl or cyclic alkylaryl, containing 3 to 14 carbon atoms and 0-4 heteroatoms, independently selected from N, O and S, which is unsubstituted or mono-, di- or trisubstituted by R⁶,

20 R⁶, R⁷ are independently of one another selected from the group consisting of H, =S, =NH, =O, OH, COOH, Hal, NH₂, SO₂CH₃, SO₂NH₂, CN, CONH₂, NHCOCH₃, NHCONH₂, NO₂ and linear or branched alkyl having 1-10 C atoms in which 1-4 C atoms may be replaced, independently of one another, by O, S, SO, SO₂, NH, NCH₃, -OCO-, -NHCONH-, -NHCO-, -

25
 30

COO–, –CONH–, –NCH₃CO–, –CONCH₃–, –C≡C– groups and/or –
CH=CH– groups, and/or, in addition, 1-10 H atoms may be replaced by F
and/or Cl,

Hal is F, Cl, Br, or I,

D is deuterium

5

and physiologically acceptable salts, derivatives, solvates, prodrugs and
stereoisomers thereof, including mixtures thereof in all ratios.

Furthermore, the abbreviations below have the following meanings:

Boc ter-butoxycarbonyl

10

CBZ benzyloxycarbonyl

DNP 2,4-dinitrophenyl

Fmoc 9-fluorenylmethoxycarbonyl

imi-DNP 2,4-dinitrophenyl in the 1-position of the imidazole ring

OMe methyl ester

15

POA phenoxyacetyl

DCCldicyclohexylcarbodiimide

HOBt1-hydroxybenzotriazole

The invention further relates to a pharmaceutical preparation comprising the
compound according to the present invention and/or one of its physiologically
acceptable salts, derivatives, solvates, prodrugs and stereoisomers, including
mixtures thereof in all ratios.

20

The invention also relates to a pharmaceutical preparation according to the
invention of this type, comprising further excipients and/or adjuvants.

25

In addition, the invention relates to an above pharmaceutical preparation according
to the invention, comprising at least one further medicament active compound.

Pharmaceutically or physiologically acceptable derivatives are taken to mean, for
example, salts of the compounds of the present invention, and also so-called pro-
drug compounds. Prodrug compounds are taken to mean derivatives of the
compounds of the present invention which have been modified by means of, for
example, alkyl or acyl groups (see also amino- and hydroxyl-protecting groups

30

below), sugars or oligopeptides and which are rapidly cleaved or liberated in the organism to form the effective molecules. These also include biodegradable polymer derivatives of the compound of the present invention, as described, for example, in Int. J. Pharm. 115 (1995), 61-67.

5 The compound of the present invention can be used in its final non-salt form. On the other hand, the present invention also encompasses the use of pepstatin in the form of its pharmaceutically acceptable salts, which can be derived from various organic and inorganic bases by procedures known in the art. Pharmaceutically acceptable salt forms of pepstatin are for the most part prepared by conventional
10 methods. If the compound of the present invention contains a carboxyl group, one of its suitable salts can be formed by reacting the compound of the present invention with a suitable base to give the corresponding base-addition salt. Such bases are, for example, alkali metal hydroxides, including potassium hydroxide, sodium hydroxide and lithium hydroxide; alkaline-earth metal hydroxides, such as barium hydroxide and calcium hydroxide; alkali metal alkoxides, for example potassium ethoxide and sodium propoxide; and various organic bases, such as
15 piperidine, diethanolamine and N-methylglutamine. The aluminium salts of pepstatin are likewise included.

20 Furthermore, the base salts of the compounds of the present invention include aluminium, ammonium, calcium, copper, iron(III), iron(II), lithium, magnesium, manganese(III), manganese(II), potassium, sodium and zinc salts, but this is not intended to represent a restriction.

25 Of the above-mentioned salts, preference is given to ammonium; the alkali metal salts sodium and potassium, and the alkaline-earth metal salts calcium and magnesium. Salts of the compounds of the present invention which are derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary and tertiary amines, substituted amines, also including naturally occurring substituted amines, cyclic amines, and basic ion exchanger resins, for example arginine, betaine, caffeine, chloroprocaine, choline, N,N'-dibenzylethylenediamine (benzathine), dicyclohexylamine, diethanolamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine,
30 N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine,

5 hydrabamine, isopropylamine, lidocaine, lysine, meglumine, N-methyl-D-glucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethanolamine, triethylamine, trimethylamine, tripropylamine and tris-(hydroxymethyl)methylamine (tromethamine), but this is not intended to represent a restriction.

As mentioned, the pharmaceutically acceptable base-addition salts of pepstatin are formed with metals or amines, such as alkali metals and alkaline-earth metals or organic amines. Preferred metals are sodium, potassium, magnesium and calcium. Preferred organic amines are N,N'-dibenzylethylenediamine, chlorprocaine,
10 choline, diethanolamine, ethylenediamine, N-methyl-D-glucamine and procaine.

The base-addition salts of the compounds of the present invention are prepared by bringing the free acid form into contact with a sufficient amount of the desired base, causing the formation of the salt in a conventional manner. The free acid can be regenerated by bringing the salt form into contact with an acid and isolating the free
15 acid in a conventional manner. The free acid forms differ in a certain respect from the corresponding salt forms thereof with respect to certain physical properties, such as solubility in polar solvents; for the purposes of the invention, however, the salts otherwise correspond to the respective free acid forms thereof.

20 In view of that stated above, it can be seen that the term "pharmaceutically acceptable salt" in the present connection is taken to mean an active compound which comprises the compound of the present invention in the form of one of its salts, in particular if this salt form imparts improved pharmacokinetic properties on the active compound compared with the free form of the active compound or any
25 other salt form of the active compound used earlier. The pharmaceutically acceptable salt form of the active compound can also provide this active compound for the first time with a desired pharmacokinetic property which it did not have earlier and can even have a positive influence on the pharmacodynamics of this active compound with respect to its therapeutic efficacy in the body.

30 Solvates of the compound of the present invention are taken to mean adductions of inert solvent molecules pepstatin which form owing to their mutual attractive force. Solvates are, for example, hydrates, such as monohydrates or dihydrates, or alco-

holates, i.e. addition compounds with alcohols, such as, for example, with methanol or ethanol.

5 All physiologically acceptable salts, derivatives, solvates and stereoisomers of these compounds, including mixtures thereof in all ratios, are also in accordance with the invention.

10 Compounds of the present invention may contain one or more centres of chirality, so that all stereoisomers, enantiomers, diastereomers, etc., of the compounds of the present invention are also claimed in the present invention.

The invention also relates to the optically active forms (stereoisomers), the enantiomers, the racemates, the diastereomers and hydrates and solvates of these compounds.

15 Compounds of the present invention according to the invention may be chiral owing to their molecular structure and may accordingly occur in various enantiomeric forms. They may therefore be in racemic or optically active form. Since the pharmaceutical efficacy of the racemates or stereoisomers of the compounds according to the invention may differ, it may be desirable to use the enantiomers. In these cases, the end product, but also even the intermediates, may be separated
20 into enantiomeric compounds by chemical or physical measures known to the person skilled in the art or already employed as such in the synthesis.

25 Pharmaceutically or physiologically acceptable derivatives are taken to mean, for example, salts of the compounds according to the invention and also so-called prodrug compounds. Prodrug compounds are taken to mean compounds of the present invention which have been modified with, for example, alkyl or acyl groups (see also amino- and hydroxyl-protecting groups below), sugars or oligopeptides and which are rapidly cleaved or liberated in the organism to form the effective compounds according to the invention. These also include biodegradable polymer derivatives of the compounds according to the invention, as described, for example,
30 in Int. J. Pharm. 115 (1995), 61-67.

Suitable acid-addition salts are inorganic or organic salts of all physiologically or pharmacologically acceptable acids, for example halides, in particular hydrochlorides or hydrobromides, lactates, sulfates, citrates, tartrates, maleates, fumarates, oxalates, acetates, phosphates, methylsulfonates or p-toluenesulfonates.

Very particular preference is given to the hydrochlorides, the trifluoroacetates or the bistrifluoroacetates of the compounds according to the invention.

Solvates of the compounds of the present invention are taken to mean adductions of inert solvent molecules onto the compounds of the present invention which form owing to their mutual attractive force. Solvates are, for example, hydrates, such as monohydrates or dihydrates, or alcoholates, i.e. addition compounds with alcohols, such as, for example, with methanol or ethanol.

It is furthermore intended that a compound of the present invention includes isotope-labelled forms thereof. An isotope-labelled form of a compound of the present invention is identical to this compound apart from the fact that one or more atoms of the compound have been replaced by an atom or atoms having an atomic mass or mass number which differs from the atomic mass or mass number of the atom which usually occurs naturally. Examples of isotopes which are readily commercially available and which can be incorporated into a compound of the present invention by well-known methods include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, fluorine and chlorine, for example ^2H , ^3H , ^{13}C , ^{14}C , ^{15}N , ^{18}O , ^{17}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F and ^{36}Cl , respectively. A compound of the present invention, a prodrug thereof or a pharmaceutically acceptable salt of either which contains one or more of the above-mentioned isotopes and/or other isotopes of other atoms is intended to be part of the present invention. An isotope-labelled compound of the present invention can be used in a number of beneficial ways. For example, an isotope-labelled compound of the present invention into which, for example, a radioisotope, such as ^3H or ^{14}C , has been incorporated is suitable for medicament and/or substrate tissue distribution assays. These radioisotopes, i.e. tritium (^3H) and carbon-14 (^{14}C), are particularly preferred owing to their simple preparation and excellent detectability. Incorporation of heavier isotopes, for example deuterium (^2H), into a compound of the present invention has therapeutic

advantages owing to the higher metabolic stability of this isotope-labelled compound. Higher metabolic stability translates directly into an increased in-vivo half-life or lower dosages, which under most circumstances would represent a preferred embodiment of the present invention. An isotope-labelled compound of the present invention can usually be prepared by carrying out the procedures disclosed in the synthesis schemes and the related description, in the example part and in the preparation part in the present text, replacing a non-isotope-labelled reactant with a readily available isotope-labelled reactant.

In order to manipulate the oxidative metabolism of the compound by way of the primary kinetic isotope effect, deuterium (^2H) can also be incorporated into a compound of the present invention. The primary kinetic isotope effect is a change in the rate of a chemical reaction that results from exchange of isotopic nuclei, which in turn is caused by the change in ground state energies necessary for covalent bond formation after this isotopic exchange. Exchange of a heavier isotope usually results in a lowering of the ground state energy for a chemical bond and thus causes a reduction in the rate in rate-limiting bond breakage. If the bond breakage occurs in or in the vicinity of a saddle-point region along the coordinate of a multi-product reaction, the product distribution ratios can be altered substantially. For explanation: if deuterium is bonded to a carbon atom in a non-exchangeable position, rate differences of $k_M/k_D = 2-7$ are typical. If this rate difference is successfully applied to a compound of the present invention that is susceptible to oxidation, the profile of this compound in vivo can thereby be drastically modified and result in improved pharmacokinetic properties.

When discovering and developing therapeutic agents, the person skilled in the art attempts to optimise pharmacokinetic parameters while retaining desirable in-vitro properties. It is reasonable to assume that many compounds with poor pharmacokinetic profiles are susceptible to oxidative metabolism. In-vitro liver microsomal assays currently available provide valuable information on the course of oxidative metabolism of this type, which in turn permits the rational design of deuterated compounds of the present invention with improved stability through resistance to such oxidative metabolism. Significant improvements in the pharmacokinetic profiles of the compounds of the present invention are thereby obtained and can be expressed quantitatively in terms of increases in the in-vivo half-life ($T/2$), concen-

tration at maximum therapeutic effect (C_{max}), area under the dose response curve (AUC), and F ; and in terms of reduced clearance, dose and costs of materials.

5 The following is intended to illustrate the above: a compound of the present invention which has multiple potential sites of attack for oxidative metabolism, for example benzylic hydrogen atoms and hydrogen atoms bonded to a nitrogen atom, is prepared as a series of analogues in which various combinations of hydrogen atoms are replaced by deuterium atoms, so that some, most or all of these hydrogen atoms have been replaced by deuterium atoms. Half-life determinations enable favourable and accurate determination of the extent to which the improve-
10 ment in resistance to oxidative metabolism has improved. In this way, it is determined that the half-life of the parent compound can be extended by up to 100% as the result of deuterium-hydrogen exchange of this type.

15 The replacement of hydrogen by deuterium in a compound of the present invention can also be used to achieve a favourable modification of the metabolite spectrum of the starting compound in order to diminish or eliminate undesired toxic metabolites. For example, if a toxic metabolite arises through oxidative carbon-hydrogen (C-H) bond cleavage, it can reasonably be assumed that the deuterated analogue will greatly diminish or eliminate production of the undesired metabolite, even if the particular oxidation is not a rate-determining step. Further information on
20 the state of the art with respect to deuterium-hydrogen exchange is given, for example in Hanzlik et al., J. Org. Chem. 55, 3992-3997, 1990, Reider et al., J. Org. Chem. 52, 3326-3334, 1987, Foster, Adv. Drug Res. 14, 1-40, 1985, Gillette et al., Biochemistry 33(10), 2927-2937, 1994, and Jarman et al., Carcinogenesis 16(4), 683-688, 1993.

25 The invention also relates to mixtures of the compounds of the present invention according to the invention, for example mixtures of two diastereomers, for example in the ratio 1:1, 1:2, 1:3, 1:4, 1:5, 1:10, 1:100 or 1:1000. These are particularly preferably mixtures of two stereoisomeric compounds. However, preference is also given to mixtures of two or more compounds of the present invention.
30

In addition, the invention relates to a process for the preparation of the compounds of the present invention, characterized in that

a) a compound of the formula II undergoes a reduction to give a compound of formula III, a compound of formula III is reacted with a compound of formula IV at elevated temperature to give a compound of formula V, a compound of formula V is converted to a compound of the formula VI employing the use of catalyst and base, a compound of formula VI is converted to a compound of the formula VII by bromination, a compound of the formula VII is converted to a compound of the formula VIII under essentially basic conditions and a compound of the formula VIII is reacted with a compound of the formula IX under standard amidation or carbamide formation conditions to give a compound of the formula I,

5

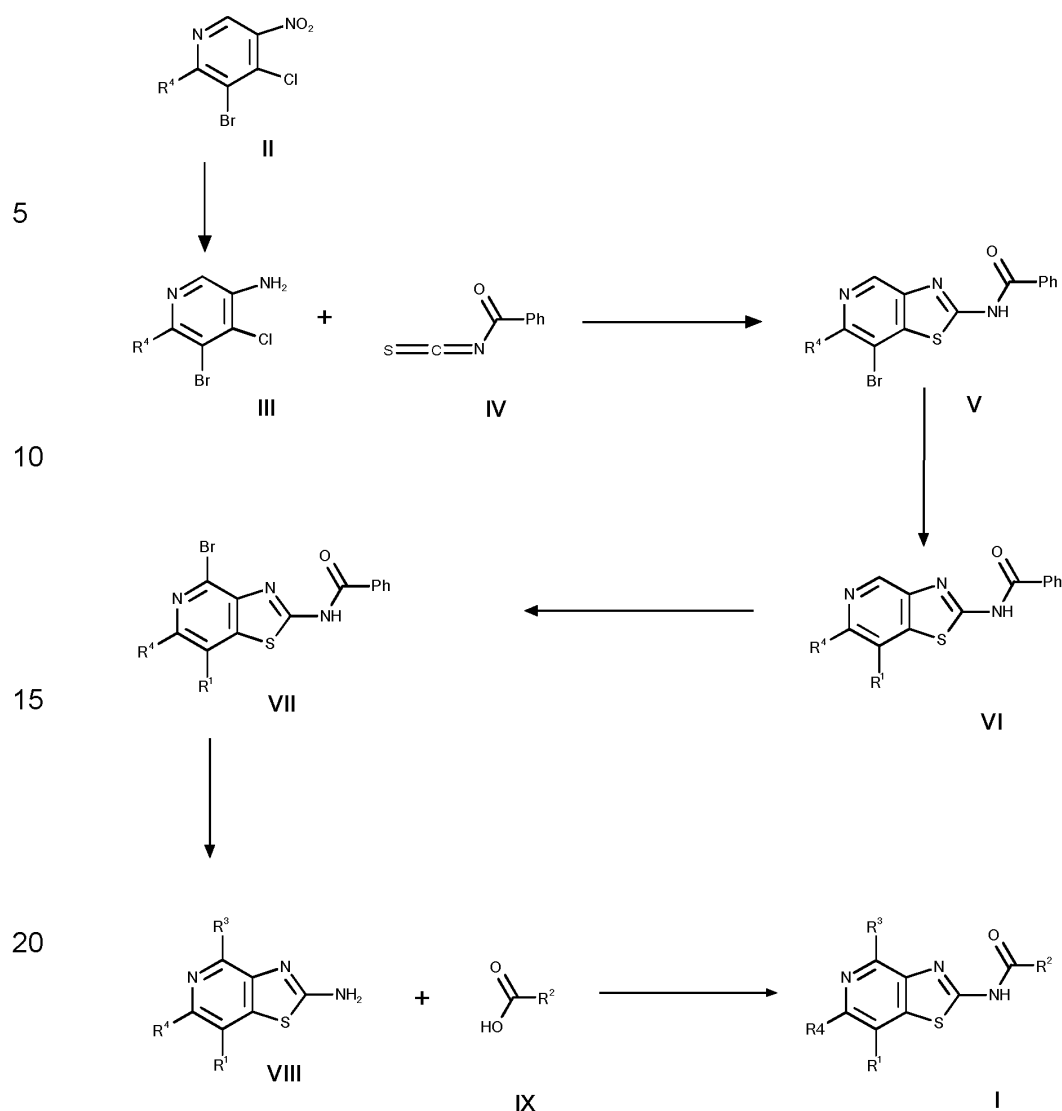
10

15

20

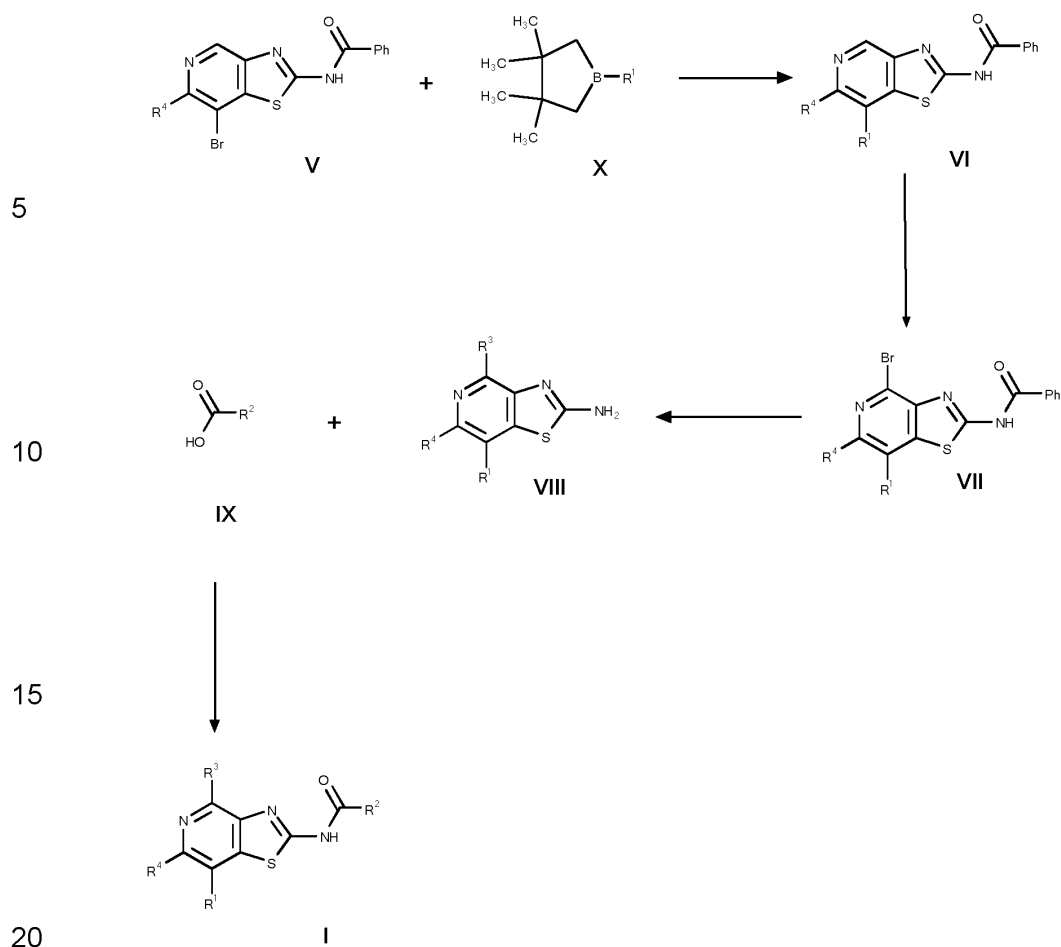
25

30

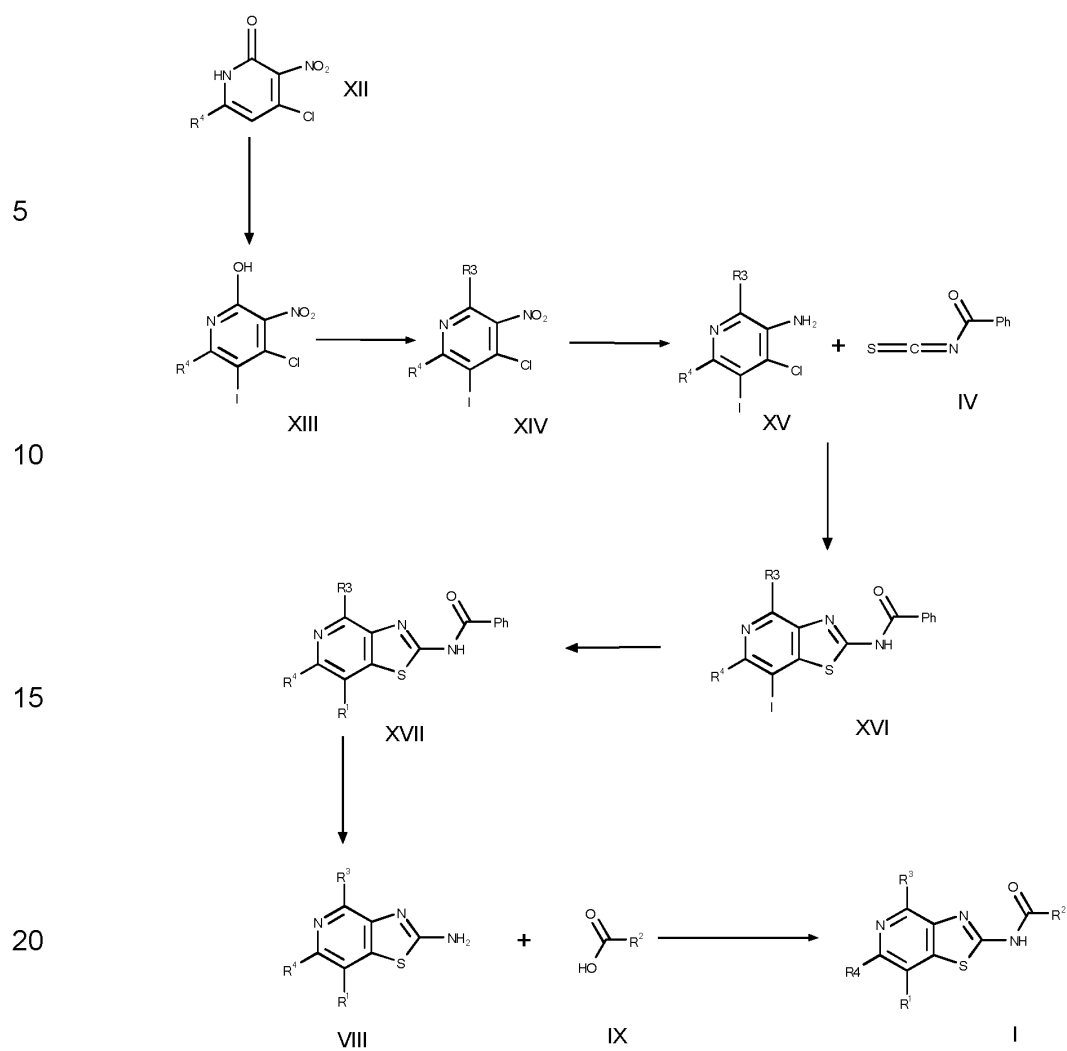


- b) a compound of the formula V is reacted with a compound of the formula X under Suzuki-type reaction conditions to give a compound of the formula VI, a compound of formula VI is converted to a compound of the formula VII by bromination, a compound of formula VII is converted to a compound of the formula VIII under essentially basic conditions and a compound of the formula VIII is reacted with a compound of the formula IX under standard amidation or carbamide formation conditions to give a compound of the formula I,

35



c) a compound of the formula XII is iodinated to give a compound of the formula XIII, a compound of formula XIII is converted to a compound of the formula XIV by treatment with base and an electrophile, a compound of formula XIV is converted to a compound of the formula XV by reduction, a compound of formula XV is reacted with a compound of formula IV at elevated temperature to give a compound of the formula XVI, a compound of formula XVI is converted under catalytic conditions to a compound of the formula XVII, a compound of the formula XVII is converted to a compound of the formula VIII under basic conditions and a compound of the formula VIII is reacted with a compound of the formula IX under standard amidation or carbamide formation conditions to give a compound of the formula I,



25

- d) the base of a compound of the present invention is converted into one of its salts by treatment with an acid, or
- e) an acid of a compound of the present invention is converted into one of its salts by treatment with a base.

30

It is also possible to carry out the reactions stepwise in each case and to modify the sequence of the linking reactions of the building blocks with adaptation of the protecting-group concept.

5 The starting materials or starting compounds are generally known. If they are novel, they can be prepared by methods known per se.

If desired, the starting materials can also be formed in situ by not isolating them from the reaction mixture, but instead immediately converting them further into the compounds of the present invention.

10 The compounds of the present invention are preferably obtained by liberating them from their functional derivatives by solvolysis, in particular by hydrolysis, or by hydrogenolysis. Preferred starting materials for the solvolysis or hydrogenolysis are those which contain correspondingly protected amino, carboxyl and/or hydroxyl groups instead of one or more free amino, carboxyl and/or hydroxyl groups,
15 preferably those which carry an amino-protecting group instead of an H atom which is connected to an N atom. Preference is furthermore given to starting materials which carry a hydroxyl-protecting group instead of the H atom of a hydroxyl group. Preference is also given to starting materials which carry a protected carboxyl group instead of a free carboxyl group. It is also possible for a plurality of identical or
20 different protected amino, carboxyl and/or hydroxyl groups to be present in the molecule of the starting material. If the protecting groups present are different from one another, they can in many cases be cleaved off selectively.

25 The term "amino-protecting group" is generally known and relates to groups which are suitable for protecting (blocking) an amino group against chemical reactions, but which can easily be removed after the desired chemical reaction has been carried out elsewhere in the molecule. Typical of such groups are, in particular, unsubstituted or substituted acyl groups, furthermore unsubstituted or substituted aryl (for example 2,4-dinitrophenyl) or aralkyl groups (for example benzyl, 4-nitrobenzyl, triphenylmethyl). Since the amino-protecting groups are removed after
30 the desired reaction or reaction sequence, their type and size is, in addition, not crucial, but preference is given to those having 1-20, in particular 1-8, C atoms. The term "acyl group" is to be understood in the broadest sense in connection with the

present process. It encompasses acyl groups derived from aliphatic, araliphatic, aromatic or heterocyclic carboxylic acids or sulfonic acids and, in particular, alkoxy-carbonyl, aryloxy-carbonyl and especially aralkoxy-carbonyl groups. Examples of such acyl groups are alkanoyl, such as acetyl, propionyl, butyryl, aralkanoyl, such as phenylacetyl, aroyl, such as benzoyl or toluyl, aryoxylalkanoyl, such as phenoxyacetyl, alkoxy-carbonyl, such as methoxycarbonyl, ethoxycarbonyl, 2,2,2-trichloroethoxycarbonyl, BOC, 2-iodoethoxycarbonyl, aralkoxy-carbonyl, such as CBZ, 4-methoxybenzyloxycarbonyl or Fmoc. Preferred acyl groups are CBZ, Fmoc, benzyl and acetyl.

The term "acid-protecting group" or "carboxyl-protecting group" is likewise generally known and relates to groups which are suitable for protecting a -COOH group against chemical reactions, but which can easily be removed after the desired chemical reaction has been carried out elsewhere in the molecule. The use of esters instead of the free acids, for example of substituted and unsubstituted alkyl esters (such as methyl, ethyl, tert-butyl and substituted derivatives thereof), of substituted and unsubstituted benzyl esters or silyl esters, is typical. The type and size of the acid-protecting groups is not crucial, but preference is given to those having 1-20, in particular 1-10, C atoms.

The term "hydroxyl-protecting group" is likewise generally known and relates to groups which are suitable for protecting a hydroxyl group against chemical reactions, but which can easily be removed after the desired chemical reaction has been carried out elsewhere in the molecule. Typical of such groups are the above-mentioned unsubstituted or substituted aryl, aralkyl or acyl groups, furthermore also alkyl groups. Their type and size of the hydroxyl-protecting groups is not crucial, but preference is given to those having 1-20, in particular 1-10, C atoms. Examples of hydroxyl-protecting groups are, inter alia, benzyl, p-nitrobenzoyl, p-toluenesulfonyl and acetyl, where benzyl and acetyl are preferred.

Further typical examples of amino-, acid- and hydroxyl-protecting groups are found, for example, in "Greene's Protective Groups in Organic Synthesis", fourth edition, Wiley-Interscience, 2007.

The functional derivatives of the compounds of the present invention to be used as starting materials can be prepared by known methods of amino-acid and peptide synthesis, as described, for example, in the said standard works and patent applications.

5 The compounds of the present invention are liberated from their functional derivatives, depending on the protecting group used, for example, with the aid of strong acids, advantageously using trifluoroacetic acid or perchloric acid, but also using other strong inorganic acids, such as hydrochloric acid or sulfuric acid, strong
10 organic acids, such as trichloroacetic acid, or sulfonic acids, such as benzoyl- or p-toluenesulfonic acid. The presence of an additional inert solvent and/or a catalyst is possible but is not always necessary.

Depending on the respective synthetic route, the starting materials can optionally be reacted in the presence of an inert solvent.

15 Suitable inert solvents are, for example, heptane, hexane, petroleum ether, DMSO, benzene, toluene, xylene, trichloroethylene-, 1,2-dichloroethanecarbon tetrachloride, chloroform or dichloromethane; alcohols, such as methanol, ethanol, isopropanol, n-propanol, n-butanol or tert-butanol; ethers, such as diethyl ether,
20 diisopropyl ether (preferably for substitution on the indole nitrogen), tetrahydrofuran (THF) or dioxane; glycol ethers, such as ethylene glycol monomethyl or monoethyl ether, ethylene glycol dimethyl ether (diglyme); ketones, such as acetone or butanone; amides, such as acetamide, dimethylacetamide, N-methylpyrrolidone (NMP) or dimethylformamide (DMF); nitriles, such as acetonitrile; esters, such as ethyl acetate, carboxylic acids or acid anhydrides, such as, for example, such as
25 acetic acid or acetic anhydride, nitro compounds, such as nitromethane or nitrobenzene, optionally also mixtures of the said solvents with one another or mixtures with water.

The amount of solvent is not crucial; 10 g to 500 g of solvent can preferably be
30 added per g of the compound of the present invention to be reacted.

It may be advantageous to add an acid-binding agent, for example an alkali metal or alkaline-earth metal hydroxide, carbonate or bicarbonate or other alkali or

alkaline-earth metal salts of weak acids, preferably a potassium, sodium or calcium salt, or to add an organic base, such as, for example, on triethylamine, dimethylamine, pyridine or quinoline, or an excess of the amine component.

5 The resultant compounds according to the invention can be separated from the corresponding solution in which they are prepared (for example by centrifugation and washing) and can be stored in another composition after separation, or they can remain directly in the preparation solution. The resultant compounds according to the invention can also be taken up in desired solvents for the particular use.

10 The reaction duration depends on the reaction conditions selected. In general, the reaction duration is 0.5 hour to 10 days, preferably 1 to 24 hours. On use of a microwave, the reaction time can be reduced to values of 1 to 60 minutes.

15 The compounds of the present invention and also the starting materials for their preparation are, in addition, prepared by known methods, as described in the literature (for example in standard works, such as Houben-Weyl, Methoden der organischen Chemie [Methods of Organic Chemistry], Georg-Thieme-Verlag, Stuttgart), for example under reaction conditions which are known and suitable for the said reactions. Use can also be made here of variants known per se, which are not described here in greater detail.

20 Conventional work-up steps, such as, for example, addition of water to the reaction mixture and extraction, enable the compounds to be obtained after removal of the solvent. It may be advantageous, for further purification of the product, to follow this with a distillation or crystallisation or to carry out a chromatographic purification.

25 An acid of the present invention can be converted into the associated addition salt using a base, for example by reaction of equivalent amounts of the acid and base in an inert solvent, such as ethanol, and inclusive evaporation. Suitable bases for this reaction are, in particular, those which give physiologically acceptable salts. Thus, the acid of the present invention can be converted into the corresponding metal salt, in particular alkali or alkaline-earth metal salt, using a base (for example sodium
30 hydroxide, potassium hydroxide, sodium carbonate or potassium carbonate) or into the corresponding ammonium salt. Organic bases which give physiologically

acceptable salts, such as, for example, ethanolamine, are also suitable for this reaction.

5 On the other hand, a base of the present invention can be converted into the associated acid-addition salt using an acid, for example by reaction of equivalent amounts of the base and acid in an inert solvent, such as ethanol, with subsequent evaporation. Suitable acids for this reaction are, in particular, those which give physiologically acceptable salts. Thus, it is possible to use inorganic acids, for example sulfuric acid, nitric acid, hydrohalic acids, such as hydrochloric acid or hydrobromic acid, phosphoric acids, such as orthophosphoric acid, sulfamic acid, 10 furthermore organic acids, in particular aliphatic, alicyclic, araliphatic, aromatic or heterocyclic, mono- or polybasic carboxylic, sulfonic or sulfuric acids, for example formic acid, acetic acid, propionic acid, pivalic acid, diethylacetic acid, malonic acid, succinic acid, pimelic acid, fumaric acid, maleic acid, lactic acid, tartaric acid, malic acid, citric acid, gluconic acid, ascorbic acid, nicotinic acid, isonicotinic acid, 15 methane- or ethanesulfonic acid, ethanedisulfonic acid, 2-hydroxysulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, naphthalenemom- and disulfonic acids or laurylsulfuric acid. Salts with physiologically unacceptable acids, for example picrates, can be used for the isolation and/or purification of the compounds of the present invention.

20 It has been found that the compounds of the present invention are well tolerated and have valuable pharmacological properties.

Since adenosine receptors, such as A_{2A} and A_{2B} , are shown to down-regulate the immune response during inflammation and protect tissues from immune damage, 25 inhibition of signaling through adenosine receptors can be used to intensify and prolong the immune response.

Methods are provided herein to increase an immune response. In one example, the method increases desirable and targeted tissue damage, such as damage of a tumor, for example cancer. Disclosed herein are methods of inhibiting one or more 30 processes conducive to the production of extracellular adenosine and adenosine-triggered signaling through adenosine receptors. For example, enhancement of an immune response, local tissue inflammation, and targeted tissue destruction is

accomplished by: inhibiting or reducing the adenosine-producing local tissue hypoxia; by degrading (or rendering inactive) accumulated extracellular adenosine; by preventing or decreasing expression of adenosine receptors on immune cells; and or by inhibiting/antagonizing signaling by adenosine ligands through adenosine receptors. The results disclosed herein demonstrate that by in vivo administration of agents that disrupt the "hypoxia -> adenosine accumulation -> immunosuppressive adenosine receptor signaling to immune cells" pathway in subjects suffering from various diseases (e.g. cancer and sepsis) can result in in vivo treatment of tumors or improved immunization.

In one example, the method includes administering one or more inhibitors of extracellular adenosine and or adenosine receptor inhibitors, such as an adenosine receptor antagonist. To increase the efficacy of a vaccine, one or more adenosine receptor inhibitors and/or inhibitors of extracellular adenosine can be administered in conjunction with the vaccine. In one example, one or more adenosine receptor inhibitors or inhibitors of extracellular adenosine are administered to increase an immune response/inflammation. In another example, a method is provided to achieve targeted tissue damage, such as for tumor destruction.

The invention therefore furthermore relates to the use of compounds according to the invention for the preparation of a medicament for the treatment and/or prophylaxis of diseases which are caused, promoted and/or propagated by adenosine or other A_{2A} and/or A_{2B} receptor agonists.

The invention thus also relates, in particular, to a medicament comprising at least one compound according to the invention and/or one of its physiologically acceptable salts, derivatives, solvates, prodrugs and stereoisomers, including mixtures thereof in all ratios, for use in the treatment and/or prophylaxis of physiological and/or pathophysiological states.

Particular preference is given, in particular, to physiological and/or pathophysiological states which are connected to adenosine A_{2A} and/or A_{2B} receptors.

Physiological and/or pathophysiological states are taken to mean physiological and/or pathophysiological states which are medically relevant, such as, for

example, diseases or illnesses and medical disorders, complaints, symptoms or complications and the like, in particular diseases.

5 The invention furthermore relates to a medicament comprising at least one compound according to the invention and/or one of its physiologically acceptable salts, derivatives, solvates, prodrugs and stereoisomers, including mixtures thereof in all ratios, for use in the treatment and/or prophylaxis of physiological and/or pathophysiological states selected from the group consisting of hyperproliferative and infectious diseases and disorders.

10 The invention further relates to a medicament comprising at least one compound according to the invention and/or one of its physiologically acceptable salts, derivatives, solvates, prodrugs and stereoisomers, including mixtures thereof in all ratios, for use in the treatment and/or prophylaxis of physiological and/or pathophysiological states selected from the group consisting of hyperproliferative and infectious diseases and disorders, wherein the hyperproliferative disease or
15 disorder is cancer.

The invention thus particularly preferably relates to a medicament comprising at least one compound according to the invention and/or one of its physiologically acceptable salts, derivatives, solvates, prodrugs and stereoisomers, including
20 mixtures thereof in all ratios, wherein the cancer is selected from the group consisting of acute and chronic lymphocytic leukemia, acute granulocytic leukemia, adrenal cortex cancer, bladder cancer, brain cancer, breast cancer, cervical cancer, cervical hyperplasia, cervical cancer, chorio cancer, chronic granulocytic leukemia, chronic lymphocytic leukemia, colon cancer, endometrial cancer, esophageal cancer, essential thrombocytosis, genitourinary carcinoma, glioma, glioblastoma,
25 hairy cell leukemia, head and neck carcinoma, Hodgkin's disease, Kaposi's sarcoma, lung carcinoma, lymphoma, malignant carcinoid carcinoma, malignant hypercalcemia, malignant melanoma, malignant pancreatic insulinoma, medullary thyroid carcinoma, melanoma, multiple myeloma, mycosis fungoides, myeloid and lymphocytic leukemia, neuroblastoma, non-Hodgkin's lymphoma, non-small cell
30 lung cancer, osteogenic sarcoma, ovarian carcinoma, pancreatic carcinoma, polycythemia vera, primary brain carcinoma, primary macroglobulinemia, prostatic cancer, renal cell cancer, rhabdomyosarcoma, skin cancer, small-cell lung cancer,

soft-tissue sarcoma, squamous cell cancer, stomach cancer, testicular cancer, thyroid cancer and Wilms' tumor.

5 The invention further preferably relates to a medicament comprising at least one compound according to the invention and/or one of its physiologically acceptable salts, derivatives, solvates, prodrugs and stereoisomers, including mixtures thereof in all ratios, for use in the treatment and/or prophylaxis of physiological and/or pathophysiological states selected from the group consisting of hyperproliferative and infectious diseases and disorders, wherein the hyperproliferative disease or disorder is selected from the group consisting of age-related macular degeneration, 10 Crohn's disease, cirrhosis, chronic inflammatory-related disorders, proliferative diabetic retinopathy, proliferative vitreoretinopathy, retinopathy of prematurity, granulomatosis, immune hyperproliferation associated with organ or tissue transplantation and an immunoproliferative disease or disorder selected from the group consisting of inflammatory bowel disease, psoriasis, rheumatoid arthritis, 15 systemic lupus erythematosus (SLE), vascular hyperproliferation secondary to retinal hypoxia and vasculitis.

The invention further preferably relates to a medicament comprising at least one compound according to the invention and/or one of its physiologically acceptable salts, derivatives, solvates, prodrugs and stereoisomers, including mixtures thereof 20 in all ratios, for use in the treatment and/or prophylaxis of physiological and/or pathophysiological states selected from the group consisting of hyperproliferative and infectious diseases and disorders, wherein the infectious disease or disorder is selected from the group consisting of

a) virally induced infectious diseases which are caused by retroviruses, 25 hepadnaviruses, herpesviruses, flaviviridae and/or adenoviruses wherein the retroviruses are selected from lentiviruses or oncoretroviruses, wherein the lentivirus is selected from the group consisting of HIV-1, HIV-2, FIV, BIV, SIVs, SHIV, CAEV, VMV and EIAV and the oncoretrovirus is selected from the group consisting of HTLV-I, HTLV-II and BLV, the hepadnavirus is selected from the group consisting of HBV, GSHV and WHV, the herpesvirus is selected from the group 30 from the group consisting of HSV I, HSV II, EBV, VZV, HCMV or HHV 8 and the flaviviridae is selected from the group consisting of HCV, West Nile and Yellow Fever,

- 5 b) bacterial infectious diseases which are caused by Gram-positive bacteria wherein the Gram-positive bacteria are selected from the group consisting of methicillin-susceptible and methicillin-resistant staphylococci (including *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Staphylococcus*
10 *haemolyticus*, *Staphylococcus hominis*, *Staphylococcus saprophyticus*, and coagulase-negative staphylococci), glycopeptides-intermediate susceptible *Staphylococcus aureus* (GISA), penicillin-susceptible and penicillin-resistant streptococci (including *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus avium*, *Streptococcus bovis*,
15 *Streptococcus lactis*, *Streptococcus sanguis* and Streptococci Group C (GCS), Streptococci Group G (GGs) and viridans streptococci), enterococci (including vancomycin-susceptible and vancomycin-resistant strains such as *Enterococcus faecalis* and *Enterococcus faecium*), *Clostridium difficile*, *Listeria monocytogenes*, *Corynebacterium jeikeium*, *Chlamydia* spp (including *C. pneumoniae*) and *Mycobacterium tuberculosis*,
- 20 c) bacterial infectious diseases which are caused by Gram-negative bacteria wherein the Gram-negative bacteria are selected from the group consisting of the Genus Enterobacteriaceae, including *Escherichia* spp. (including *Escherichia coli*), *Klebsiella* spp., *Enterobacter* spp., *Citrobacter* spp., *Serratia* spp., *Proteus* spp., *Providencia* spp., *Salmonella* spp., *Shigella* spp., the genus *Pseudomonas* (including *P. aeruginosa*), *Moraxella* spp. (including *M. catarrhalis*),
25 *Haemophilus* spp. and *Neisseria* spp.,
- d) infectious diseases induced by intracellular active parasites selected from the group consisting of phylum Apicomplexa, or Sarcomastigophora (including *Trypanosoma*, *Plasmodia*, *Leishmania*, *Babesia* or *Theileria*), Cryptosporidia, *Sarcocystida*, *Amoeba*, *Coccidia* and *Trichomonadia*.

25 It is intended that the medicaments disclosed above include a corresponding use of the compounds according to the invention for the preparation of a medicament for the treatment and/or prophylaxis of the above physiological and/or pathophysiological states.

30 It is additionally intended that the medicaments disclosed above include a corresponding method for the treatment and/or prophylaxis of the above

physiological and/or pathophysiological states in which at least one compound according to the invention is administered to a patient in need of such a treatment.

5 The compounds according to the invention preferably exhibit an advantageous biological activity which can easily be demonstrated in enzyme assays and animal experiments, as described in the examples. In such enzyme-based assays, the compounds according to the invention preferably exhibit and cause an inhibiting effect, which is usually documented by IC₅₀ values in a suitable range, preferably in the micromolar range and more preferably in the nanomolar range.

10 The compounds according to the invention can be administered to humans or animals, in particular mammals, such as apes, dogs, cats, rats or mice, and can be used in the therapeutic treatment of the human or animal body and in the combating of the above-mentioned diseases. They can furthermore be used as diagnostic agents or as reagents.

15 Furthermore, compounds according to the invention can be used for the isolation and investigation of the activity or expression of adenosine A_{2A} and/or A_{2B} receptors. In addition, they are particularly suitable for use in diagnostic methods for diseases in connection with disturbed adenosine A_{2A} and/or A_{2B} receptor activity. The invention therefore furthermore relates to the use of the compounds according to the invention for the isolation and investigation of the activity or expression of
20 adenosine A_{2A} and/or A_{2B} receptors or as binders and inhibitors of adenosine A_{2A} and/or A_{2B} receptors.

For diagnostic purposes, the compounds according to the invention can, for
25 example, be radioactively labelled. Examples of radioactive labels are ³H, ¹⁴C, ²³¹I and ¹²⁵I. A preferred labelling method is the iodogen method (Fraker et al., 1978). In addition, the compounds according to the invention can be labelled by enzymes, fluorophores and chemophores. Examples of enzymes are alkaline phosphatase, β-galactosidase and glucose oxidase, an example of a fluorophore is fluorescein, an example of a chemophore is luminol, and automated detection systems, for
30 example for fluorescent colorations, are described, for example, in US 4,125,828 and US 4,207,554.

The present invention further relates to pharmaceutical compositions containing the compounds of the present invention and their use for the treatment and/or prophylaxis of diseases and disorders where the partial or total inactivation of adenosine A_{2A} and/or A_{2B} receptors could be beneficial.

5

The compounds of the present invention can be used for the preparation of pharmaceutical preparations, in particular by non-chemical methods. In this case, they are brought into a suitable dosage form together with at least one solid, liquid and/or semi-liquid excipient or adjuvant and optionally in combination with one or more further active compound(s).

10

The invention therefore furthermore relates to pharmaceutical preparations comprising at least one compound of the present invention and/or physiologically acceptable salts, derivatives, solvates and stereoisomers thereof, including mixtures thereof in all ratios. In particular, the invention also relates to pharmaceutical preparations which comprise further excipients and/or adjuvants, and also to pharmaceutical preparations which comprise at least one further medicament active compound.

15

20

In particular, the invention also relates to a process for the preparation of a pharmaceutical preparation, characterised in that a compound of the present invention and/or one of its physiologically acceptable salts, derivatives, solvates and stereoisomers, including mixtures thereof in all ratios, is brought into a suitable dosage form together with a solid, liquid or semi-liquid excipient or adjuvant and optionally with a further medicament active compound.

25

The pharmaceutical preparations according to the invention can be used as medicaments in human or veterinary medicine. The patient or host can belong to any mammal species, for example a primate species, particularly humans; rodents, including mice, rats and hamsters; rabbits; horses, cattle, dogs, cats, etc. Animal models are of interest for experimental investigations, where they provide a model for the treatment of a human disease.

30

Suitable carrier substances are organic or inorganic substances which are suitable for enteral (for example oral), parenteral or topical administration and do not react

with the novel compounds, for example water, vegetable oils (such as sunflower oil or cod-liver oil), benzyl alcohols, polyethylene glycols, gelatine, carbohydrates, such as lactose or starch, magnesium stearate, talc, lanolin or Vaseline. Owing to his expert knowledge, the person skilled in the art is familiar with which adjuvants are suitable for the desired medicament formulation. Besides solvents, for example water, physiological saline solution or alcohols, such as, for example, ethanol, propanol or glycerol, sugar solutions, such as glucose or mannitol solutions, or a mixture of the said solvents, gel formers, tablet assistants and other active-ingredient carriers, it is also possible to use, for example, lubricants, stabilisers and/or wetting agents, emulsifiers, salts for influencing the osmotic pressure, anti-oxidants, dispersants, antifoams, buffer substances, flavours and/or aromas or flavour correctants, preservatives, solubilisers or dyes. If desired, preparations or medicaments according to the invention may comprise one or more further active compounds, for example one or more vitamins.

If desired, preparations or medicaments according to the invention may comprise one or more further active compounds and/or one or more action enhancers (adjuvants).

The terms "pharmaceutical formulation" and "pharmaceutical preparation" are used as synonyms for the purposes of the present invention.

As used here, "pharmaceutically tolerated" relates to medicaments, precipitation reagents, excipients, adjuvants, stabilisers, solvents and other agents which facilitate the administration of the pharmaceutical preparations obtained therefrom to a mammal without undesired physiological side effects, such as, for example, nausea, dizziness, digestion problems or the like.

In pharmaceutical preparations for parenteral administration, there is a requirement for isotonicity, euhydration and tolerability and safety of the formulation (low toxicity), of the adjuvants employed and of the primary packaging. Surprisingly, the compounds according to the invention preferably have the advantage that direct use is possible and further purification steps for the removal of toxicologically unacceptable agents, such as, for example, high concentrations of organic solvents

or other toxicologically unacceptable adjuvants, are thus unnecessary before use of the compounds according to the invention in pharmaceutical formulations.

5 The invention particularly preferably also relates to pharmaceutical preparations comprising at least one compound according to the invention in precipitated non-crystalline, precipitated crystalline or in dissolved or suspended form, and optionally excipients and/or adjuvants and/or further pharmaceutical active compounds.

10 The compounds according to the invention preferably enable the preparation of highly concentrated formulations without unfavourable, undesired aggregation of the compounds according to the invention occurring. Thus, ready-to-use solutions having a high active-ingredient content can be prepared with the aid of compounds according to the invention with aqueous solvents or in aqueous media.

15 The compounds and/or physiologically acceptable salts and solvates thereof can also be lyophilised and the resultant lyophilisates used, for example, for the preparation of injection preparations.

20 Aqueous preparations can be prepared by dissolving or suspending compounds according to the invention in an aqueous solution and optionally adding adjuvants. To this end, defined volumes of stock solutions comprising the said further adjuvants in defined concentration are advantageously added to a solution or suspension having a defined concentration of compounds according to the invention, and the mixture is optionally diluted with water to the pre-calculated concentration. Alternatively, the adjuvants can be added in solid form. The amounts of stock solutions and/or water which are necessary in each case can subsequently
25 be added to the aqueous solution or suspension obtained. Compounds according to the invention can also advantageously be dissolved or suspended directly in a solution comprising all further adjuvants.

30 The solutions or suspensions comprising compounds according to the invention and having a pH of 4 to 10, preferably having a pH of 5 to 9, and an osmolality of 250 to 350 mOsmol/kg can advantageously be prepared. The pharmaceutical preparation can thus be administered directly substantially without pain intravenously, intra-arterially, intra-articularly, subcutaneously or percutaneously. In addition, the

preparation may also be added to infusion solutions, such as, for example, glucose solution, isotonic saline solution or Ringer's solution, which may also contain further active compounds, thus also enabling relatively large amounts of active compound to be administered.

5 Pharmaceutical preparations according to the invention may also comprise mixtures of a plurality of compounds according to the invention.

10 The preparations according to the invention are physiologically well tolerated, easy to prepare, can be dispensed precisely and are preferably stable with respect to assay, decomposition products and aggregates throughout storage and transport and during multiple freezing and thawing processes. They can preferably be stored in a stable manner over a period of at least three months to two years at refrigerator temperature (2-8°C) and at room temperature (23-27°C) and 60% relative atmospheric humidity (R.H.).

15 For example, the compounds according to the invention can be stored in a stable manner by drying and when necessary converted into a ready-to-use pharmaceutical preparation by dissolution or suspension. Possible drying methods are, for example, without being restricted to these examples, nitrogen-gas drying, vacuum-oven drying, lyophilisation, washing with organic solvents and subsequent
20 air drying, liquid-bed drying, fluidised-bed drying, spray drying, roller drying, layer drying, air drying at room temperature and further methods.

25 The term "effective amount" denotes the amount of a medicament or of a pharmaceutical active compound which causes in a tissue, system, animal or human a biological or medical response which is sought or desired, for example, by a researcher or physician.

30 In addition, the term "therapeutically effective amount" denotes an amount which, compared with a corresponding subject who has not received this amount, has the following consequence: improved treatment, healing, prevention or elimination of a disease, syndrome, disease state, complaint, disorder or prevention of side effects or also a reduction in the progress of a disease, complaint or disorder. The term

“therapeutically effective amount” also encompasses the amounts which are effective for increasing normal physiological function.

5 On use of preparations or medicaments according to the invention, the compounds according to the invention and/or physiologically acceptable salts and solvates thereof are generally used analogously to known, commercially available preparations or preparations, preferably in dosages of between 0.1 and 500 mg, in particular 5 and 300 mg, per use unit. The daily dose is preferably between 0.001 and 250 mg/kg, in particular 0.01 and 100 mg/kg, of body weight. The preparation can be administered one or more times per day, for example two, three or four
10 times per day. However, the individual dose for a patient depends on a large number of individual factors, such as, for example, on the efficacy of the particular compound used, on the age, body weight, general state of health, sex, nutrition, on the time and method of administration, on the excretion rate, on the combination with other medicaments and on the severity and duration of the particular disease.

15 A measure of the uptake of a medicament active compound in an organism is its bioavailability. If the medicament active compound is delivered to the organism intravenously in the form of an injection solution, its absolute bioavailability, i.e. the proportion of the pharmaceutical which reaches the systemic blood, i.e. the major circulation, in unchanged form, is 100%. In the case of oral administration of a
20 therapeutic active compound, the active compound is generally in the form of a solid in the formulation and must therefore first be dissolved in order that it is able to overcome the entry barriers, for example the gastrointestinal tract, the oral mucous membrane, nasal membranes or the skin, in particular the stratum corneum, or can be absorbed by the body. Data on the pharmacokinetics, i.e. on the bioavailability, can be obtained analogously to the method of J. Shaffer et al., J. Pharm. Sciences,
25 88 (1999), 313-318.

Furthermore, medicaments of this type can be prepared by means of one of the processes generally known in the pharmaceutical art.

30 Medicaments can be adapted for administration via any desired suitable route, for example by the oral (including buccal or sublingual), rectal, pulmonary, nasal, topical (including buccal, sublingual or transdermal), vaginal or parenteral (including

subcutaneous, intramuscular, intravenous, intradermal and in particular intra-articular) routes. Medicaments of this type can be prepared by means of all processes known in the pharmaceutical art by, for example, combining the active compound with the excipient(s) or adjuvant(s).

5

Parenteral administration is preferably suitable for administration of the medicaments according to the invention. In the case of parenteral administration, intra-articular administration is particularly preferred.

10

The invention thus preferably also relates to the use of a pharmaceutical preparation according to the invention for intra-articular administration in the treatment and/or prophylaxis of physiological and/or pathophysiological states selected from the group consisting of osteoarthritis, traumatic cartilage injuries, arthritis, pain, allodynia or hyperalgesia.

15

Intra-articular administration has the advantage that the compound according to the invention can be administered directly into the synovial fluid in the vicinity of the joint cartilage and is also able to diffuse from there into the cartilage tissue. Pharmaceutical preparations according to the invention can thus also be injected directly into the joint gap and thus develop their action directly at the site of action as intended.

20

The compounds according to the invention are also suitable for the preparation of medicaments to be administered parenterally having slow, sustained and/or controlled release of active compound. They are thus also suitable for the preparation of delayed-release formulations, which are advantageous for the patient since administration is only necessary at relatively large time intervals.

25

The medicaments adapted to parenteral administration include aqueous and non-aqueous sterile injection solutions comprising antioxidants, buffers, bacteriostatics and solutes, by means of which the formulation is rendered isotonic with the blood or synovial fluid of the recipient to be treated; as well as aqueous and non-aqueous sterile suspensions, which can comprise suspension media and thickeners. The

30

formulations can be delivered in single-dose or multi-dose containers, for example sealed ampoules and vials, and stored in the freeze-dried (lyophilised) state, so that only the addition of the sterile carrier liquid, for example water for injection purposes, immediately before use is necessary. Injection solutions and suspensions

prepared in accordance with the formulation can be prepared from sterile powders, granules and tablets.

5 The compounds according to the invention can also be administered in the form of liposome delivery systems, such as, for example, small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from various phospholipids, such as, for example, cholesterol, stearylamine or phosphatidylcholines.

10 The compounds according to the invention can also be coupled to soluble polymers as targeted medicament excipients. Such polymers can encompass polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamidophenol, polyhydroxyethylaspartamidophenol or polyethylene oxide polylysine, substituted by palmitoyl radicals. The compounds according to the invention can furthermore be coupled to a class of biodegradable polymers which are suitable for achieving slow
15 release of a medicament, for example polylactic acid, poly-epsilon-caprolactone, polyhydroxybutyric acid, polyorthoesters, polyacetals, polydihydroxypyrans, polycyanoacrylates, polylactic-co-glycolic acid, polymers, such as conjugates between dextran and methacrylates, polyphosphoesters, various polysaccharides and polyamines and poly-epsilon-caprolactone, albumin, chitosan, collagen or modified gelatine and crosslinked or amphipathic block copolymers of hydrogels.

20 Suitable for enteral administration (oral or rectal) are, in particular, tablets, dragees, capsules, syrups, juices, drops or suppositories, and suitable for topical use are ointments, creams, pastes, lotions, gels, sprays, foams, aerosols, solutions (for example solutions in alcohols, such as ethanol or isopropanol, acetonitrile, DMF,
25 dimethylacetamide, 1,2-propanediol or mixtures thereof with one another and/or with water) or powders. Also particularly suitable for topical uses are liposomal preparations.

30 In the case of formulation to give an ointment, the active compound can be employed either with a paraffinic or a water-miscible cream base. Alternatively, the active compound can be formulated to a cream with an oil-in-water cream base or a water-in-oil base.

Medicaments adapted to transdermal administration can be delivered as independent plasters for extended, close contact with the epidermis of the recipient. Thus, for example, the active compound can be supplied from the plaster by means of iontophoresis, as described in general terms in *Pharmaceutical Research*, 3 (6), 318 (1986).

It goes without saying that, besides the constituents particularly mentioned above, the medicaments according to the invention may also comprise other agents usual in the art with respect to the particular type of pharmaceutical formulation.

The invention also relates to a set (kit) consisting of separate packs of

- a) an effective amount of a compound of the present invention and/or physiologically acceptable salts, derivatives, solvates, prodrugs and stereoisomers thereof, including mixtures thereof in all ratios, and
- b) an effective amount of a further medicament active compound.

The set comprises suitable containers, such as boxes or cartons, individual bottles, bags or ampoules. The set may, for example, comprise separate ampoules each containing an effective amount of a compound of the present invention and/or pharmaceutically acceptable salts, derivatives, solvates, prodrugs and stereoisomers thereof, including mixtures thereof in all ratios, and an effective amount of a further medicament active compound in dissolved or lyophilised form.

Furthermore, the medicaments according to the invention can be used in order to provide additive or synergistic effects in certain known therapies and/or can be used in order to restore the efficacy of certain existing therapies.

Besides the compounds according to the invention, the pharmaceutical preparations according to the invention may also comprise further medicament active compounds, for example for use in the treatment of cancer, other anti-tumor medicaments. For the treatment of the other diseases mentioned, the pharmaceutical preparations according to the invention may also, besides the compounds according to the invention, comprise further medicament active compounds which are known to the person skilled in the art in the treatment thereof.

In one principal embodiment, methods are provided for enhancing an immune response in a host in need thereof. The immune response can be enhanced by reducing T cell tolerance, including by increasing IFN- γ release, by decreasing regulatory T cell production or activation, or by increasing antigen-specific memory T cell production in a host. In one embodiment, the method comprises
5 administering a compound of the present invention to a host in combination or alternation with an antibody. In particular subembodiments, the antibody is a therapeutic antibody. In one particular embodiment, a method of enhancing efficacy of passive antibody therapy is provided comprising administering a compound of the present invention in combination or alternation with one or more passive
10 antibodies. This method can enhance the efficacy of antibody therapy for treatment of abnormal cell proliferative disorders such as cancer, or can enhance the efficacy of therapy in the treatment or prevention of infectious diseases. The compound of the present invention can be administered in combination or alternation with antibodies such as rituximab, herceptin or erbitux, for example.

15 In another principal embodiment, a method of treating or preventing abnormal cell proliferation is provided comprising administering a compound of the present invention to a host in need thereof substantially in the absence of another anti-cancer agent.

20 In another principal embodiment, a method of treating or preventing abnormal cell proliferation in a host in need thereof is provided, comprising administering a first a compound of the present invention substantially in combination with a first anti-cancer agent to the host and subsequently administering a second A_{2A} and/or A_{2B} receptor antagonist. In one subembodiment, the second antagonist is administered
25 substantially in the absence of another anti-cancer agent. In another principal embodiment, a method of treating or preventing abnormal cell proliferation in a host in need thereof is provided, comprising administering a compound of the present invention substantially in combination with a first anti-cancer agent to the host and subsequently administering a second anti-cancer agent in the absence of the
30 antagonist.

Thus, the cancer treatment disclosed here can be carried out as therapy with a compound of the present invention or in combination with an operation, irradiation

or chemotherapy. Chemotherapy of this type can include the use of one or more active compounds of the following categories of antitumour active compounds:

- 5 (i) antiproliferative/antineoplastic/DNA-damaging active compounds and combinations thereof, as used in medical oncology, such as alkylating active compounds (for example cis-platin, carboplatin, cyclophosphamide, nitrogen mustard, melphalan, chlorambucil, busulphan and nitrosoureas); antimetabolites (for example antifolates such as fluoropyrimidines such as 5-fluorouracil and tegafur, raltitrexed, methotrexate, cytosine arabinoside, hydroxyurea and gemcitabine); antitumour antibiotics (for example anthracyclines, such as adriamycin, bleomycin, doxorubicin, daunomycin, epirubicin, idarubicin, mitomycin-C, dactinomycin and mithramycin);
- 10 antimitotic active compounds (for example vinca alkaloids, such as vincristine, vinblastine, vindesine and vinorelbine, and taxoids, such as taxol and taxotere); topoisomerase inhibitors (for example epipodophyllotoxins, such as etoposide and teniposide, amsacrine, topotecan, irinotecan and camptothecin) and cell-differentiating active compounds (for example all-trans-retinoic acid, 13-cis-retinoic acid and fenretinide);
- 15 (ii) cytostatic active compounds, such as anti-oestrogens (for example tamoxifen, toremifene, raloxifene, droloxifene and idoxifene), oestrogen receptor regulators (for example fulvestrant), anti-androgens (for example bicalutamide, flutamide, nilutamide and cyproterone acetate), LHRH antagonists or LHRH agonists (for example goserelin, leuprorelin and buserelin), progesterones (for example megestrol acetate), aromatase inhibitors (for example anastrozole, letrozole, vorazole and exemestane) and inhibitors of 5 α -reductase, such as finasteride;
- 20 (iii) active compounds which inhibit cancer invasion including for example metallo-proteinase inhibitors, like marimastat, and inhibitors of urokinase plasminogen activator receptor function;
- 25 (iv) inhibitors of growth factor function, for example growth factor antibodies, growth factor receptor antibodies, for example the anti-erbB2 antibody trastuzumab [HerceptinTM] and the anti-erbB1 antibody cetuximab [C225], farnesyl transferase inhibitors, tyrosine kinase inhibitors and serine/threonine kinase inhibitors, for example inhibitors of the epidermal growth factor family (for example EGFR family tyrosine kinase inhibitors, such as N-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-amine (gefitinib, AZD1839), N-(3-ethynylphenyl)-6,7-bis (2-methoxyethoxy)quinazolin-4-amine (erlotinib, OSI-774) and 6-acrylamido-N-(3-chloro-4-fluorophenyl)-7-(3-morpholinopropoxy)quinazolin-4-amine (CI 1033),
- 30

for example inhibitors of the platelet-derived growth factor family and, for example, inhibitors of the hepatocyte growth factor family;

- 5 (v) anti-angiogenic active compounds, such as bevacizumab, angiostatin, endostatin, linomide, batimastat, captopril, cartilage derived inhibitor, genistein, interleukin 12, lavendustin, medroxyprogesterone acetate, recombinant human platelet factor 4, tecogalan, thrombospondin, TNP-470, anti-VEGF monoclonal antibody, soluble VEGF-receptor chimaeric protein, anti-VEGF receptor antibodies, anti-PDGF receptors, inhibitors of integrins, tyrosine kinase inhibitors, serine/threonine kinase inhibitors, antisense oligonucleotides, antisense oligodeoxynucleotides, siRNAs, anti-VEGF aptamers, pigment epithelium derived factor and compounds which have been published in the international patent applications WO 97/22596, WO 97/30035, WO 97/32856 and WO 98/13354);
- 10 (vi) vessel-destroying agents, such as combretastatin A4 and compounds which have been published in the international patent applications WO 99/02166, WO 00/40529, WO 00/41669, WO 01/92224, WO 02/04434 and WO 02/08213;
- 15 (vii) antisense therapies, for example those directed to the targets mentioned above, such as ISIS 2503, an anti-Ras antisense;
- (viii) gene therapy approaches, including, for example, approaches for replacement of abnormal, modified genes, such as abnormal p53 or abnormal BRCA1 or BRCA2, GDEPT approaches (gene-directed enzyme pro-drug therapy), such as those which use cytosine deaminase, thymidine kinase or a bacterial nitroreductase enzyme, and approaches which increase the tolerance of a patient to chemotherapy or radiotherapy, such as multi-drug resistance therapy; and
- 20 (ix) immunotherapy approaches, including, for example, ex-vivo and in-vivo approaches for increasing the immunogenicity of tumour cells of a patient, such as transfection with cytokines, such as interleukin 2, interleukin 4 or granulocyte macrophage colony stimulating factor, approaches for decreasing T-cell anergy, approaches using transfected immune cells, such as cytokine-transfected dendritic cells, approaches for use of cytokine-transfected tumour cells and approaches for use of anti-idiotypic antibodies
- 25 (x) chemotherapeutic agents including for example abarelix, aldesleukin, alemtuzumab, alitretinoin, allopurinol, altretamine, amifostine, anastrozole, arsenic trioxide, asparaginase, BCG live, bevacizumab, bexarotene, bleomycin, bortezomib, busulfan, calusterone, camptothecin, capecitabine, carboplatin, carmustine, celecoxib, cetuximab, chlorambucil, cinacalcet, cisplatin, cladribine,
- 30

cyclophosphamide, cytarabine, dacarbazine, dactinomycin, darbepoetin alfa, daunorubicin, denileukin diftitox, dexrazoxane, docetaxel, doxorubicin, dromostanolone, epirubicin, epoetin alfa, estramustine, etoposide, exemestane, filgrastim, floxuridine, fludarabine, fluorouracil, fulvestrant and gemcitabine.

5

The medicaments from table 1 can preferably, but not exclusively, be combined with the compounds of the present invention.

	Table 1		
10	Alkylating active compounds	Cyclophosphamide Busulfan Ifosfamide Melphalan Hexamethylmelamine Thiotepa chloroambucil Dacarbazine Carmustine	Lomustine Procarbazine Altretamine Estramustine phosphate Mechloroethamine Streptozocin Temozolomide Semustine
15	Platinum active compounds	Cisplatin Oxaliplatin Spiroplatin Carboxyphthalatoplatinum Tetraplatin Ormiplatin Iproplatin	Carboplatin ZD-0473 (AnorMED) Lobaplatin (Aetema) Satraplatin (Johnson Matthey) BBR-3464 (Hoffmann-La Roche) SM-11355 (Sumitomo) AP-5280 (Access)
20	Antimetabolites	Azacytidine Gemcitabine Capecitabine 5-Fluorouracil Floxuridine 2-Chlorodesoxyadenosine 6-Mercaptopurine 6-Thioguanine Cytarabine 2-Fluorodesoxycytidine Methotrexate Idatrexate	Tomudex Trimetrexate Deoxycoformycin Fludarabine Pentostatin Raltitrexed Hydroxyurea Decitabine (SuperGen) Clofarabine (Bioenvision) Irofulven (MGI Pharma) DMDC (Hoffmann-La Roche) Ethinylcytidine (Taiho)
25	Topoisomerase inhibitors	Amsacrine Epirubicin Etoposide Teniposide or mitoxantrone Irinotecan (CPT-11) 7-ethyl-10-	Rubitecan (SuperGen) Exatecan mesylate (Daiichi) Quinamed (ChemGenex) Gimatecan (Sigma- Tau) Diflomotecan (Beaufour-Ipsen)
30			

5		hydroxycamptothecin Topotecan Dexrazoxanet (TopoTarget) Pixantrone (Novuspharma) Rebeccamycin analogue (Exelixis) BBR-3576 (Novuspharma)	TAS-103 (Taiho) Elsamitrucin (Spectrum) J-107088 (Merck & Co) BNP-1350 (BioNumerik) CKD-602 (Chong Kun Dang) KW-2170 (Kyowa Hakko)
10	Antitumour antibiotics	Dactinomycin (Actinomycin D) Doxorubicin (Adriamycin) Deoxyrubicin Valrubicin Daunorubicin (Daunomycin) Epirubicin Therarubicin Idarubicin Rubidazon Plicamycinp Porfiromycin Cyanomorpholinodoxorubicin Mitoxantron (Novantron)	Amonafide Azonafide Anthrapyrazole Oxantrazole Losoxantrone Bleomycin sulfate (Blenoxan) Bleomycinic acid Bleomycin A Bleomycin B Mitomycin C MEN-10755 (Menarini) GPX-100 (Gem Pharmaceuticals)
15	Antimitotic active compounds	Paclitaxel Docetaxel Colchicine Vinblastine Vincristine Vinoelbine Vindesine Dolastatin 10 (NCI) Rhizoxin (Fujisawa) Mivobulin (Warner-Lambert) Cemadotin (BASF) RPR 109881A (Aventis) TXD 258 (Aventis) Epothilone B (Novartis) T 900607 (Tularik) T 138067 (Tularik) Cryptophycin 52 (Eli Lilly) Vinflunine (Fabre) Auristatin PE (Teikoku Hormone) BMS 247550 (BMS) BMS 184476 (BMS) BMS 188797 (BMS) Taxoprexin (Protarga)	SB 408075 (GlaxoSmithKline) E7010 (Abbott) PG-TXL (Cell Therapeutics) IDN 5109 (Bayer) A 105972 (Abbott) A 204197 (Abbott) LU 223651 (BASF) D 24851 (ASTA Medica) ER-86526 (Eisai) Combretastatin A4 (BMS) Isohomohalichondrin-B (PharmaMar) ZD 6126 (AstraZeneca) PEG-Paclitaxel (Enzon) AZ10992 (Asahi) IDN-5109 (Indena) AVLB (Prescient NeuroPharma) Azaepothilon B (BMS) BNP- 7787 (BioNumerik) CA-4-prodrug (OXiGENE) Dolastatin-10 (NrH) CA-4 (OXiGENE)
20			
25			
30			
	Aromatase inhibitors	Aminoglutethimide Letrozole Anastrozole Formestan	Exemestan Atamestan (BioMedicines) YM-511 (Yamanouchi)

	Thymidylate Synthase inhibitors	Pemetrexed (Eli Lilly) ZD-9331 (BTG)	Nolatrexed (Eximias) CoFactor™ (BioKeys)
5	DNA antagonists	Trabectedin (PharmaMar) Glufosfamide (Baxter International) Albumin + 32P (isotope solutions) Thymectacin (NewBiotics) Edotreotid (Novartis)	Mafosfamide (Baxter International) Apaziquone (Spectrum Pharmaceuticals) O6-benzylguanine (Paligent)
10	Farnesyl transferase inhibitors	Arglabin (NuOncology Labs) Lonafarnib (Schering-Plough) BAY-43-9006 (Bayer)	Tipifarnib (Johnson & Johnson) Perillyl alcohol (DOR BioPharma)
	Pump inhibitors	CBT-1 (CBA Pharma) Tariquidar (Xenova) MS-209 (Schering AG)	Zosuquidar trihydrochloride (Eli Lilly) Biricodar dicitrate (Vertex)
15	Histone acetyl transferase inhibitors	Tacedinaline (Pfizer) SAHA (Aton Pharma) MS-275 (Schering AG)	Pivaloyloxymethyl butyrate (Titan) Depsipeptide (Fujisawa)
20	Metalloproteinase inhibitors Ribonucleoside reductase inhibitors	Neovastat (Aeterna Laboratories) Marimastat (British Biotech) Gallium maltolate (Titan) Triapin (Vion)	CMT -3 (CollaGenex) BMS-275291 (Celltech) Tezacitabine (Aventis) Didox (Molecules for Health)
	TNF-alpha agonists / antagonists	Virulizin (Lorus Therapeutics) CDC-394 (Celgene)	Revimid (Celgene)
25	Endothelin-A receptor antagonists	Atrasentan (Abbot) ZD-4054 (AstraZeneca)	YM-598 (Yamanouchi)
	Retinoic acid receptor agonists	Fenretinide (Johnson & Johnson) LGD-1550 (ligand)	Alitretinoin (Ligand)
30	Immunomodulators	Interferon Oncophage (Antigenics) GMK (Progenics) Adenocarcinoma vaccine (Biomira) CTP-37 (AVI BioPharma) JRX-2 (Immuno-Rx) PEP-005 (Peplin Biotech)	Dexosome therapy (Anosys) Pentrix (Australian Cancer Technology) JSF-154 (Tragen) Cancer vaccine (Intercell) Norelin (Biostar) BLP-25 (Biomira) MGV (Progenics)

	Synchrovax vaccines (CTL Immuno) Melanoma vaccines (CTL Immuno) p21-RAS vaccine (GemVax)	!3-Alethin (Dovetail) CLL-Thera (Vasogen)
5	Hormonal and antihormonal active compounds	Prednisone Methylprednisolone Prednisolone Aminoglutethimide Leuprolide Goserelin Leuporelin Bicalutamide Flutamide Octreotide Nilutamide Mitotan P-04 (Novogen) 2-Methoxyoestradiol (En_treMed) Arzoxifen (Eli Lilly)
10		
15	Photodynamic active compounds	Talaporfin (Light Sciences) Theralux (Theratechnologies) Motexafin-Gadolinium (Pharmacyclics) Pd bacteriopheophorbide (Yeda) Lutetium texaphyrin (Pharmacyclics) Hypericin
20	Tyrosine kinase inhibitors	Kahalide F (PharmaMar) CEP- 701 (Cephalon) CEP-751 (Cephalon) MLN518 (Millenium) PKC412 (Novartis) Phenoxodiol O Trastuzumab (Genentech) C225 (ImClone) rhu-Mab (Genentech) MDX-H210 (Medarex) 2C4 (Genentech) MDX-447 (Medarex) ABX-EGF (Abgenix) IMC-1C11 (ImClone)
25		
30	Various other active compounds	SR-27897 (CCK-A inhibitor, Sanofi-Synthelabo) Tocladesine (cyclic AMP agonist, Ribapharm) Alvocidib (CDK inhibitor, Aventis) CV-247 (COX-2 inhibitor, Ivy) BCX-1777 (PNP inhibitor, BioCryst) Ranpirnase (ribonuclease stimulant, Alfacell) Galarubicin (RNA synthesis inhibitor, Dong-A) Tirapazamine (reducing

	Medical)	agent, SRI International)
	P54 (COX-2 inhibitor,	N-Acetylcysteine
	Phytopharm)	(reducing agent,
	CapCell™ (CYP450	Zambon)
5	stimulant, Bavarian Nordic)	R-Flurbiprofen (NF-kappaB
	GCS-100 (gal3 antagonist,	inhibitor, Encore)
	GlycoGenesys)	3CPA (NF-kappaB inhibitor,
	G17DT immunogen (gastrin	Active Biotech)
	inhibitor, Aphton)	Seocalcitol (vitamin D
	Efaproxiral (oxygenator,	receptor agonist, Leo)
	Allos Therapeutics)	131-I-TM-601 (DNA
	PI-88 (heparanase inhibitor,	antagonist, TransMolecular)
	Progen)	Eflornithin (ODC inhibitor,
	Tesmilifen (histamine	ILEX Oncology)
10	antagonist, YM BioSciences)	Minodronic acid (osteoclast
	Histamine (histamine H2	inhibitor,
	receptor agonist, Maxim)	Yamanouchi)
	Tiazofurin (IMPDH inhibitor,	Indisulam (p53 stimulant,
	Ribapharm)	Eisai)
	Cilengitide (integrin antagonist,	Aplidin (PPT inhibitor,
	Merck KGaA)	PharmaMar)
	SR-31747 (IL-1 antagonist,	Rituximab (CD20 antibody,
15	Sanofi-Synthelabo)	Genentech)
	CCI-779 (mTOR kinase	Gemtuzumab (CD33
	inhibitor, Wyeth)	antibody, Wyeth Ayerst)
	Exisulind (PDE-V inhibitor,	PG2 (haematopoiesis
	Cell Pathways)	promoter, Pharmagenesis)
	CP-461 (PDE-V inhibitor, Cell	Immunol™ (triclosan
	Pathways)	mouthwash, Endo)
	AG-2037 (GART inhibitor,	Triacetyluridine (uridine
20	Pfizer)	prodrug, Wellstat)
	WX-UK1 (plasminogen	SN-4071 (sarcoma agent,
	activator inhibitor, Wilex)	Signature BioScience)
	PBI-1402 (PMN stimulant,	TransMID-107™
	ProMetic LifeSciences)	(immunotoxin, KS Biomedix)
	Bortezomib (proteasome	PCK-3145 (apoptosis pro-
	inhibitor, Millennium)	moter, Procyon)
	SRL-172 (T-cell stimulant,	Doranidazole (apoptosis pro-
	SR Pharma)	moter, Pola)
25	TLK-286 (glutathione-S	CHS-828 (cytotoxic agent,
	transferase inhibitor, Telik)	Leo)
	PT-100 (growth factor	trans-Retinoic acid (
	agonist, Point Therapeutics)	differentiator, NIH)
	Midostaurin (PKC inhibitor,	MX6 (apoptosis promoter,
	Novartis)	MAXIA)
	Bryostatin-1 (PKC stimulant,	Apomine (apoptosis
	GPC Biotech)	promoter, ILEX Oncology)
30	CDA-II (apoptosis promoter,	Urocidin (apoptosis promoter,
	Everlife)	Bioniche)
	SDX-101 (apoptosis promoter,	Ro-31-7453 (apoptosis pro-
	Salmedix)	moter, La Roche)
	Ceflatonin (apoptosis pro-	Brostallicin (apoptosis

	moter, ChemGenex)	promoter, Pharmacia)

Even without further embodiments, it is assumed that a person skilled in the art will be able to use the above description in the broadest scope. The preferred
 5 embodiments should therefore merely be regarded as descriptive disclosure which is absolutely not limiting in any way.

The following examples are thus intended to explain the invention without limiting it. Unless indicated otherwise, per cent data denote per cent by weight. All
 10 temperatures are indicated in degrees Celsius. "Conventional work-up": water is added if necessary, the pH is adjusted, if necessary, to values between 2 and 10, depending on the constitution of the end product, the mixture is extracted with ethyl acetate or dichloromethane, the phases are separated, the organic phase is dried over sodium sulfate, filtered and evaporated, and the product is purified by chromatography on silica gel and/or by crystallisation.

15 R_f values on silica gel; mass spectrometry: EI (electron impact ionisation): M⁺, FAB (fast atom bombardment): (M+H)⁺, THF (tetrahydrofuran), NMP (N-methylpyrrolidone), DMSO (dimethyl sulfoxide), EA (ethyl acetate), MeOH (methanol), TLC (thin-layer chromatography)

20

List of Abbreviations

	AUC	Area under the plasma drug concentration-time curve
	C _{max}	Maximum plasma concentration
	CL	Clearance
25	CV	Coefficient of variation
	CYP	Cytochrome P450
	DMSO	Dimethyl sulfoxide
	F	Bioavailability
	f _a	Fraction absorbed
	iv	Intravenous
	LC-MS/MS	Liquid chromatography tandem mass spectrometry
30	LLOQ	Lower limit of quantification
	NC	Not calculated
	ND	Not determined
	PEG	Polyethylene glycol

5	Pgp	Permeability glycoprotein
	PK	Pharmacokinetic(s)
	po	Per os (oral)
	$t_{1/2}$	Half-life
	t_{max}	Time at which maximum plasma concentration of drug is reached
	UPLC	Ultra performance liquid chromatography
	V_{ss}	Volume of distribution (at steady state)
	v/v	Volume to volume

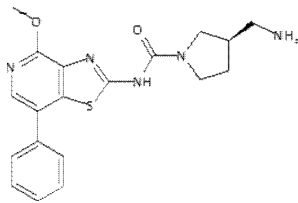
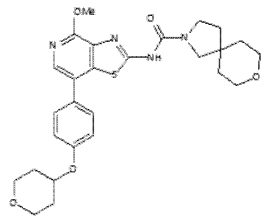
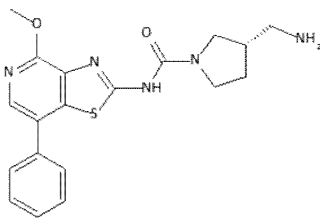
Example 1: Examples of compounds of the present invention

10

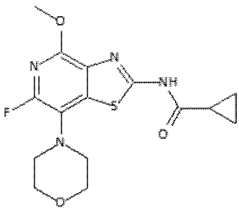
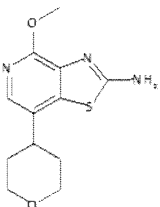
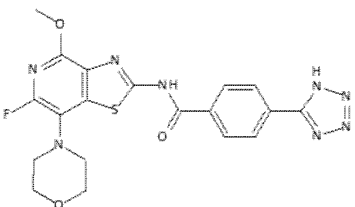
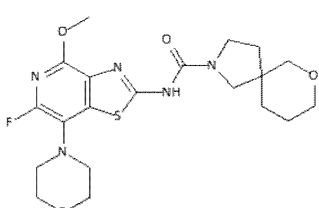
The invention especially relates to the compounds of table 2 and physiologically acceptable salts, derivatives, solvates, prodrugs and stereoisomers thereof, including mixtures thereof in all ratios.

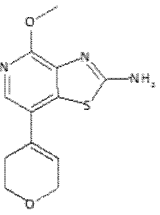
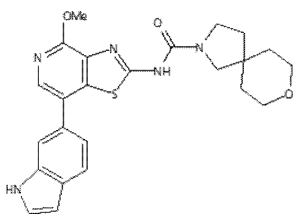
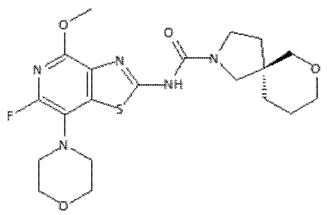
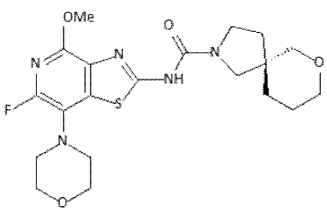
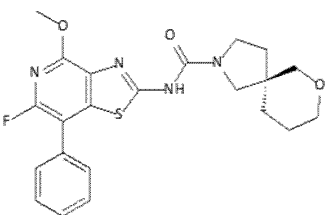
Table 2 – examples of compounds of the present invention

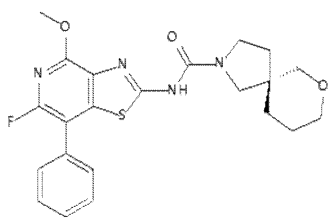
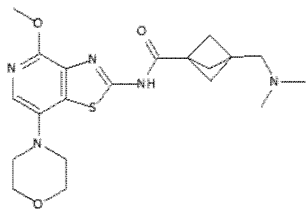
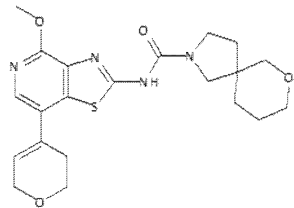
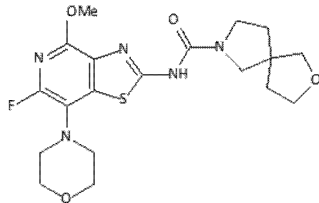
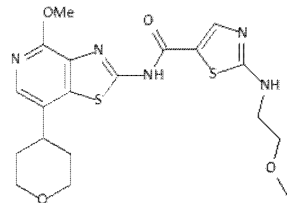
15

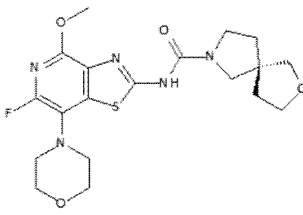
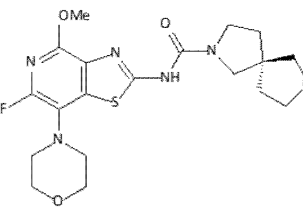
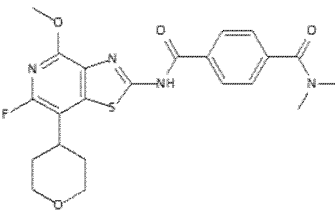
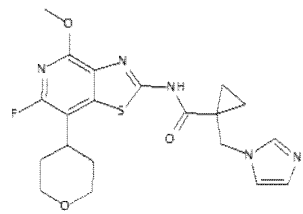
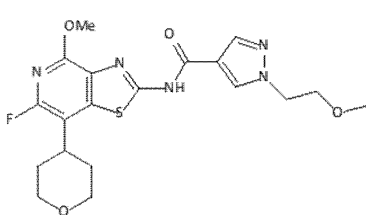
No.	Structure	IUPAC-Name	MW	[M+H] ⁺ 1
1		(R)-3-Aminomethyl-pyrrolidine-1-carboxylic acid (4-methoxy-7-phenyl-thiazolo[4,5-c]pyridin-2-yl)-amide	383,47	384
2		N-{4-methoxy-7-[4-(oxan-4-yloxy)phenyl]-[1,3]thiazolo[4,5-c]pyridin-2-yl}-8-oxa-2-azaspiro[4.5]decane-2-carboxamide	524,64	526
3		(S)-3-Aminomethyl-pyrrolidine-1-carboxylic acid (4-methoxy-7-phenyl-thiazolo[4,5-c]pyridin-2-yl)-amide	383,47	384

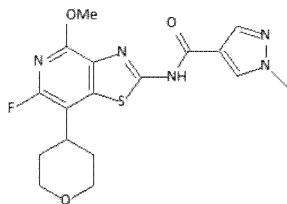
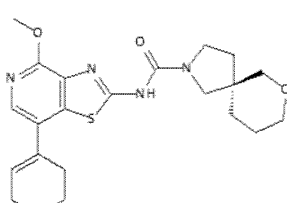
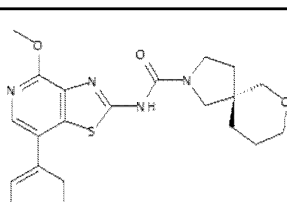
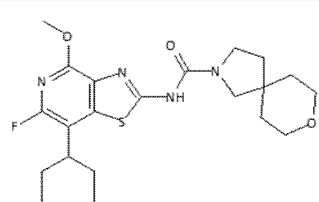
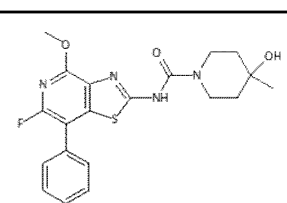
30

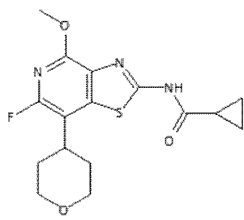
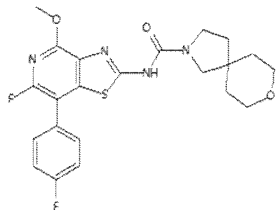
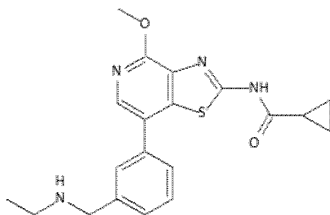
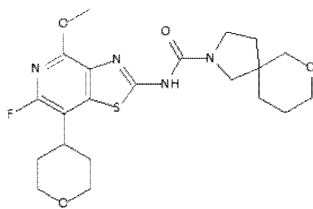
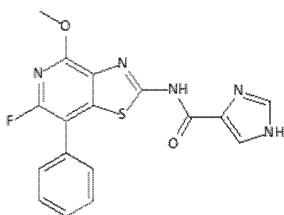
5			amide		
10	4		Cyclopropanecarboxylic acid (6-fluoro-4-methoxy-7-morpholin-4-yl-thiazolo[4,5-c]pyridin-2-yl)-amide	352,39	353
15	5		4-Methoxy-7-(tetrahydro-pyran-4-yl)-thiazolo[4,5-c]pyridin-2-ylamine	265,34	266
20	6		N-(6-Fluoro-4-methoxy-7-morpholin-4-yl-thiazolo[4,5-c]pyridin-2-yl)-4-(1H-tetrazol-5-yl)-benzamide	456,46	457
25	7		7-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid (6-fluoro-4-methoxy-7-morpholin-4-yl-thiazolo[4,5-c]pyridin-2-yl)-amide	451,52	453

5	8		7-(3,6-Dihydro-2H-pyran-4-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-ylamine	263,32	264
10	9		N-[7-(1H-indol-6-yl)-4-methoxy-[1,3]thiazolo[4,5-c]pyridin-2-yl]-8-oxa-2-azaspiro[4.5]decane-2-carboxamide	463,56	465
15	10		(R)-7-Oxa-2-azaspiro[4.5]decane-2-carboxylic acid (6-fluoro-4-methoxy-7-morpholin-4-yl-thiazolo[4,5-c]pyridin-2-yl)-amide	451,52	453
20	11		(5S)-N-[6-fluoro-4-methoxy-7-(morpholin-4-yl)-[1,3]thiazolo[4,5-c]pyridin-2-yl]-7-oxa-2-azaspiro[4.5]decane-2-carboxamide	451,52	453
25	12		(R)-7-Oxa-2-azaspiro[4.5]decane-2-carboxylic acid (6-fluoro-4-methoxy-7-phenyl-thiazolo[4,5-c]pyridin-2-yl)-amide	442,51	444
30					

5	13		(5S)-N-{6-fluoro-4-methoxy-7-phenyl-[1,3]thiazolo[4,5-c]pyridin-2-yl}-7-oxa-2-azaspiro[4.5]decane-2-carboxamide	442,51	444
10	14		3-Dimethylaminomethyl-bicyclo[1.1.1]pentane-1-carboxylic acid (4-methoxy-7-morpholin-4-yl-thiazolo[4,5-c]pyridin-2-yl)-amide	417,53	419
15	15		7-Oxa-2-azaspiro[4.5]decane-2-carboxylic acid [7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide	430,53	432
20	16		N-[6-fluoro-4-methoxy-7-(morpholin-4-yl)-[1,3]thiazolo[4,5-c]pyridin-2-yl]-2-oxa-7-azaspiro[4.4]nonane-7-carboxamide	437,49	438
25	17		N-[4-methoxy-7-(oxan-4-yl)-[1,3]thiazolo[4,5-c]pyridin-2-yl]-2-[(2-methoxyethyl)amino]-1,3-thiazole-5-carboxamide	449,55	451
30					

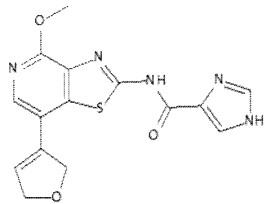
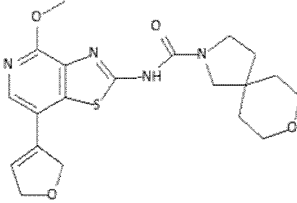
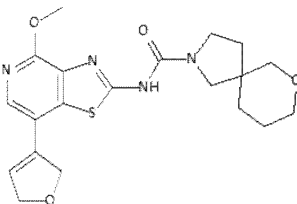
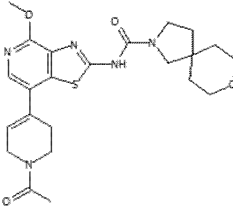
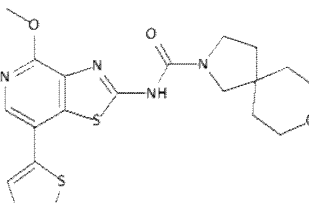
5	18		(R)-2-Oxa-7-aza-spiro[4.4]nonane-7-carboxylic acid (6-fluoro-4-methoxy-7-morpholin-4-yl-thiazolo[4,5-c]pyridin-2-yl)-amide	437,49	438
10	19		(5S)-N-[6-fluoro-4-methoxy-7-(morpholin-4-yl)-[1,3]thiazolo[4,5-c]pyridin-2-yl]-2-oxa-7-azaspiro[4.4]nonane-7-carboxamide	437,49	438
15	20		N-[6-Fluoro-4-methoxy-7-(tetrahydro-pyran-4-yl)-thiazolo[4,5-c]pyridin-2-yl]-N',N'-dimethyl-terephthalamide	458,51	460
20	21		1-Imidazol-1-ylmethyl-cyclopropanecarboxylic acid [6-fluoro-4-methoxy-7-(tetrahydro-pyran-4-yl)-thiazolo[4,5-c]pyridin-2-yl]-amide	431,49	432
25	22		N-[6-fluoro-4-methoxy-7-(oxan-4-yl)-[1,3]thiazolo[4,5-c]pyridin-2-yl]-1-(2-methoxyethyl)-1H-pyrazole-4-carboxamide	435,48	436
30					

5	23		N-[6-fluoro-4-methoxy-7-(oxan-4-yl)-[1,3]thiazolo[4,5-c]pyridin-2-yl]-1-methyl-1H-pyrazole-4-carboxamide	391,43	392
10	24		(R)-7-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide	430,53	432
15	25		(S)-7-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide	430,53	432
20	26		8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [6-fluoro-4-methoxy-7-(tetrahydro-pyran-4-yl)-thiazolo[4,5-c]pyridin-2-yl]-amide	450,53	452
25	27		4-Hydroxy-4-methyl-piperidine-1-carboxylic acid [6-fluoro-7-(4-fluoro-phenyl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide	434,47	435
30					

5	28		Cyclopropanecarboxylic acid [6-fluoro-4-methoxy-7-(tetrahydropyran-4-yl)-thiazolo[4,5-c]pyridin-2-yl]-amide	351,40	352
10	29		8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [6-fluoro-7-(4-fluoro-phenyl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide	460,50	462
15	30		Cyclopropanecarboxylic acid [7-(3-ethylaminomethyl-phenyl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide	382,49	383
20	31		7-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [6-fluoro-4-methoxy-7-(tetrahydro-pyran-4-yl)-thiazolo[4,5-c]pyridin-2-yl]-amide	450,53	452
25	32		1H-Imidazole-4-carboxylic acid (6-fluoro-4-methoxy-7-phenyl-thiazolo[4,5-c]pyridin-2-yl)-amide	369,38	370

5	33		N-[6-fluoro-4-methoxy-7-(oxan-4-yl)-[1,3]thiazolo[4,5-c]pyridin-2-yl]-2-oxa-7-azaspiro[4.4]nonane-7-carboxamide	436,51	438
10	34		(R)-7-Oxa-2-azaspiro[4.5]decane-2-carboxylic acid [6-fluoro-4-methoxy-7-(tetrahydro-pyran-4-yl)-thiazolo[4,5-c]pyridin-2-yl]-amide	450,53	452
15	35		(5S)-N-[6-fluoro-4-methoxy-7-(oxan-4-yl)-[1,3]thiazolo[4,5-c]pyridin-2-yl]-7-oxa-2-azaspiro[4.5]decane-2-carboxamide	450,53	452
20	36		1-Methyl-1H-pyrazole-4-carboxylic acid [4-methoxy-7-(2,2,2-trifluoro-ethoxy)-thiazolo[4,5-c]pyridin-2-yl]-amide	387,34	388
25	37		(R)-2-Oxa-7-azaspiro[4.4]nonane-7-carboxylic acid [6-fluoro-4-methoxy-7-(tetrahydro-pyran-4-yl)-thiazolo[4,5-c]pyridin-2-yl]-amide	436,51	438
30					

5	38		(5S)-N-[6-fluoro-4-methoxy-7-(oxan-4-yl)-[1,3]thiazolo[4,5-c]pyridin-2-yl]-2-oxa-7-azaspiro[4.4]nonane-7-carboxamide	436,51	438
10	39		8-Oxa-2-azaspiro[4.5]decane-2-carboxylic acid [7-(3-amino-phenyl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide	439,54	441
15	40		8-Oxa-2-azaspiro[4.5]decane-2-carboxylic acid [4-methoxy-7-(3-oxo-cyclopent-1-enyl)-thiazolo[4,5-c]pyridin-2-yl]-amide	428,51	430
20	41		Bicyclo[1.1.1]pentane-1,3-dicarboxylic acid [6-fluoro-4-methoxy-7-(tetrahydro-pyran-4-yl)-thiazolo[4,5-c]pyridin-2-yl]-amide (2-hydroxy-ethyl)-methyl-amide	478,54	480
25	42		N-[7-(2,5-dihydrofuran-3-yl)-4-methoxy-[1,3]thiazolo[4,5-c]pyridin-2-yl]cyclopropanecarboxamide	317,37	318
30					

5	43		N-[7-(2,5-dihydrofuran-3-yl)-4-methoxy-[1,3]thiazolo[4,5-c]pyridin-2-yl]-1H-imidazole-4-carboxamide	343,37	344
10	44		N-[7-(2,5-dihydrofuran-3-yl)-4-methoxy-[1,3]thiazolo[4,5-c]pyridin-2-yl]-8-oxa-2-azaspiro[4.5]decane-2-carboxamide	416,50	417
15	45		N-[7-(2,5-dihydrofuran-3-yl)-4-methoxy-[1,3]thiazolo[4,5-c]pyridin-2-yl]-7-oxa-2-azaspiro[4.5]decane-2-carboxamide	416,50	417
20	46		8-Oxa-2-azaspiro[4.5]decane-2-carboxylic acid [7-(1-acetyl-1,2,3,6-tetrahydropyridin-4-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide	471,58	473
25	47		8-Oxa-2-azaspiro[4.5]decane-2-carboxylic acid (4-methoxy-7-thiophen-2-yl-thiazolo[4,5-c]pyridin-2-yl)-amide	430,55	432
30					

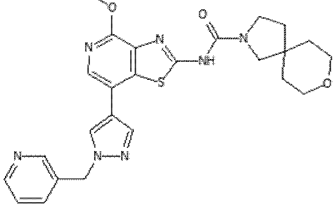
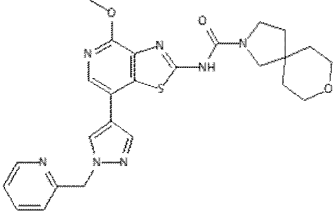
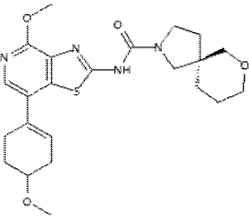
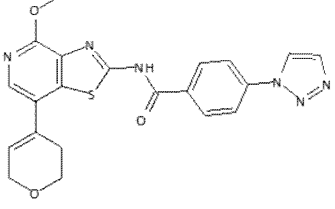
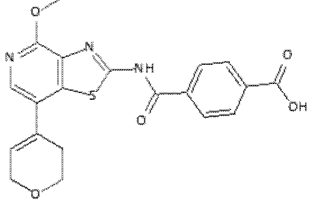
5	48		8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid (7-furan-2-yl-4-methoxy-thiazolo[4,5-c]pyridin-2-yl)-amide	414,48	415
10	49		8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [7-(3-ethylaminomethyl-phenyl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide	481,62	483
15	50		N-[6-Fluoro-4-methoxy-7-(tetrahydro-pyran-4-yl)-thiazolo[4,5-c]pyridin-2-yl]-N'-(2-hydroxy-ethyl)-N'-methyl-terephthalamide	488,54	490
20	51		8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid (4-methoxy-7-piperidin-1-yl-thiazolo[4,5-c]pyridin-2-yl)-amide	431,56	433
25	52		8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid (7-furan-3-yl-4-methoxy-thiazolo[4,5-c]pyridin-2-yl)-amide	414,48	415
30					

5	53		8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [4-methoxy-7-(4-methyl-piperazin-1-yl)-thiazolo[4,5-c]pyridin-2-yl]-amide	446,57	448
10	54		8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [4-methoxy-7-(3-methoxy-phenyl)-thiazolo[4,5-c]pyridin-2-yl]-amide	454,55	456
15	55		N-{[6-cyano-4-methoxy-1,3]thiazolo[4,5-c]pyridin-2-yl}-1-(2-methoxyethyl)-1H-pyrazole-4-carboxamide	358,38	359
20	56		8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [4-methoxy-7-(6-methyl-pyridazin-3-yl)-thiazolo[4,5-c]pyridin-2-yl]-amide	440,53	442
25	57		8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid (7-azetidin-1-yl-4-methoxy-thiazolo[4,5-c]pyridin-2-yl)-amide	403,50	405

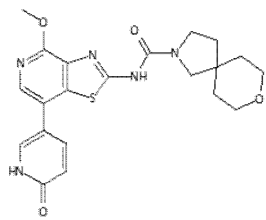
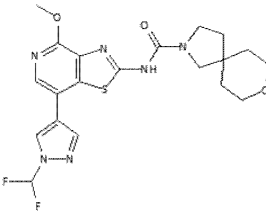
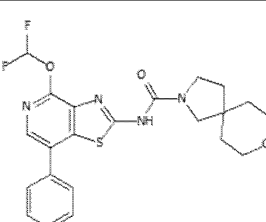
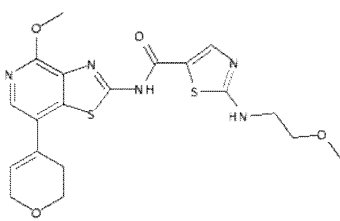
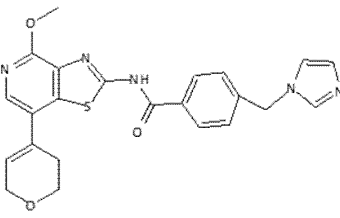
5	58		8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [7-(3-hydroxy-azetidin-1-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide	419,50	421
10	59		8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid (7-cyclohex-1-enyl-4-methoxy-thiazolo[4,5-c]pyridin-2-yl)-amide	428,55	430
15	60		1H-Imidazole-4-carboxylic acid (4-methoxy-7-phenyl-thiazolo[4,5-c]pyridin-2-yl)-amide	351,39	352
20	61		N4-[7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-[1,3]thiazolo[4,5-c]pyridin-2-yl]-N1,N1-dimethylbenzene-1,4-dicarboxamide	438,51	440
25	62		8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid (7-cyclohexyl-4-methoxy-thiazolo[4,5-c]pyridin-2-yl)-amide	430,57	432
30					

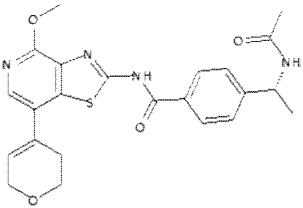
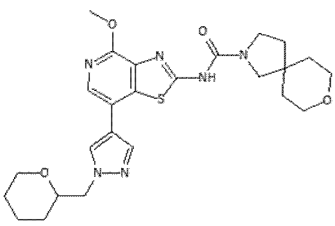
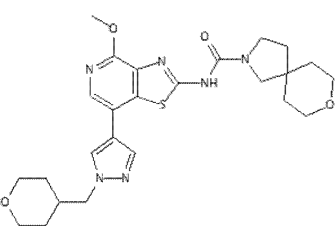
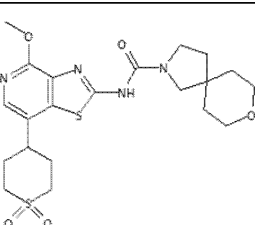
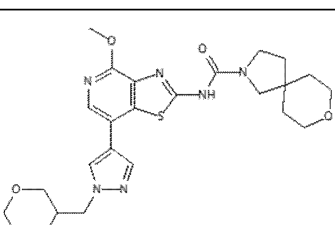
5	63		8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [7-(4,4-difluorocyclohex-1-enyl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide	464,53	466
10	64		8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [7-(3,6-dihydro-2H-thiopyran-4-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide	446,59	448
15	65		1H-Imidazole-4-carboxylic acid [7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide	357,39	358
20	66		N-[4-methoxy-7-(4-methoxycyclohex-1-en-1-yl)-[1,3]thiazolo[4,5-c]pyridin-2-yl]-8-oxa-2-azaspiro[4.5]decane-2-carboxamide	458,58	460
25	67		8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [4-methoxy-7-(2-methyl-thiazol-4-yl)-thiazolo[4,5-c]pyridin-2-yl]-amide	445,57	447

30

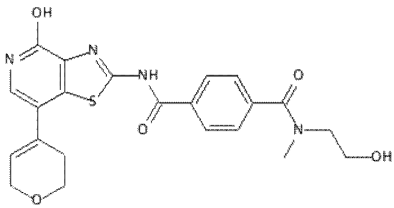
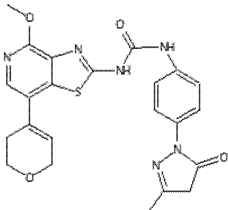
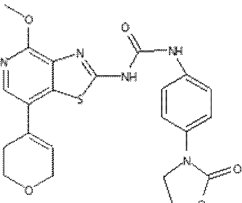
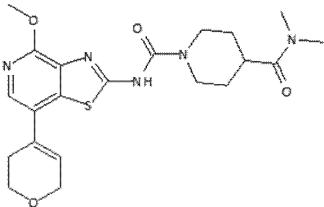
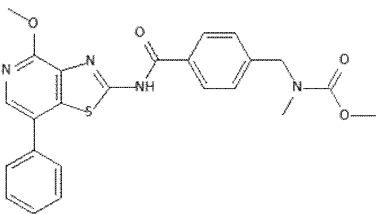
5	68		8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [4-methoxy-7-(1-pyridin-3-ylmethyl-1H-pyrazol-4-yl)-thiazolo[4,5-c]pyridin-2-yl]-amide	505,60	507
10	69		8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [4-methoxy-7-(1-pyridin-2-ylmethyl-1H-pyrazol-4-yl)-thiazolo[4,5-c]pyridin-2-yl]-amide	505,60	507
15	70		(5R)-N-[4-methoxy-7-(4-methoxycyclohex-1-en-1-yl)-[1,3]thiazolo[4,5-c]pyridin-2-yl]-7-oxa-2-azaspiro[4.5]decane-2-carboxamide	458,58	460
20	71		N-[7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-[1,3]thiazolo[4,5-c]pyridin-2-yl]-4-(1H-1,2,3-triazol-1-yl)benzamide	434,48	435
25	72		4-[[7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-[1,3]thiazolo[4,5-c]pyridin-2-yl]carbamoyl]benzoic acid	411,44	412
30					

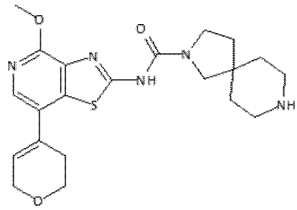
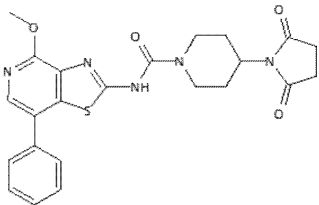
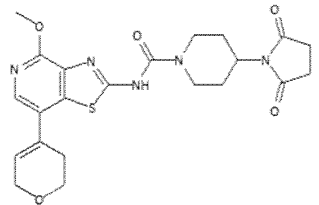
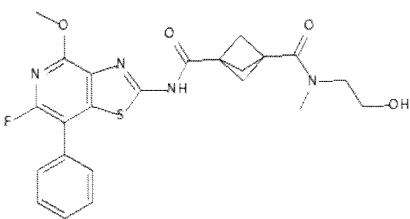
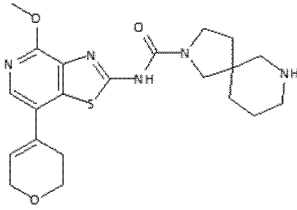
5	73		8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid (7-[1,4]dioxan-2-yl-4-methoxy-thiazolo[4,5-c]pyridin-2-yl)-amide	434,51	436
10	74		8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid {7-[1-(2,2-difluoroethyl)-1H-pyrazol-4-yl]-4-methoxy-thiazolo[4,5-c]pyridin-2-yl}-amide	478,52	480
15	75		8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [4-methoxy-7-(1-pyridin-4-ylmethyl-1H-pyrazol-4-yl)-thiazolo[4,5-c]pyridin-2-yl]-amide	505,60	507
20	76		8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [7-(1-benzyl-1H-pyrazol-4-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide	504,61	506
25	77		(5S)-N-[4-methoxy-7-(4-methoxycyclohex-1-en-1-yl)-[1,3]thiazolo[4,5-c]pyridin-2-yl]-7-oxa-2-azaspiro[4.5]decane-2-carboxamide	458,58	460
30					

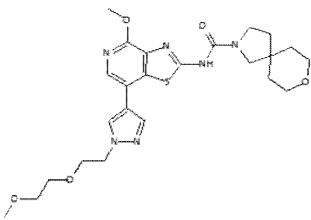
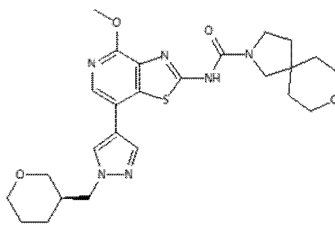
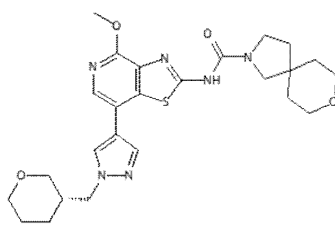
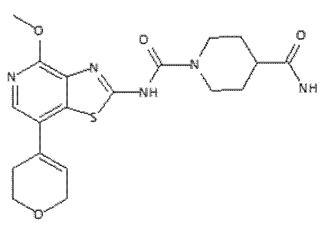
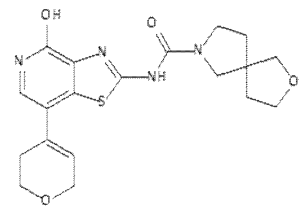
5	78		8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [4-methoxy-7-(6-oxo-1,6-dihydropyridin-3-yl)-thiazolo[4,5-c]pyridin-2-yl]-amide	441,51	443
10	79		8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [7-(1-difluoromethyl-1H-pyrazol-4-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide	464,49	465
15	80		8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid (4-difluoromethoxy-7-phenyl-thiazolo[4,5-c]pyridin-2-yl)-amide	460,50	462
20	81		N-[7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-[1,3]thiazolo[4,5-c]pyridin-2-yl]-2-[(2-methoxyethyl)amino]-1,3-thiazole-5-carboxamide	447,54	449
25	82		N-[7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-[1,3]thiazolo[4,5-c]pyridin-2-yl]-4-[(1H-imidazol-1-yl)methyl]benzamide	447,52	449
30					

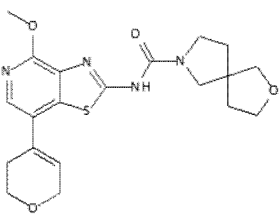
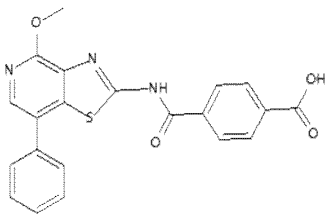
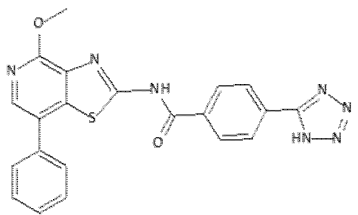
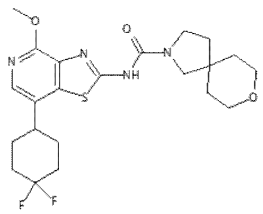
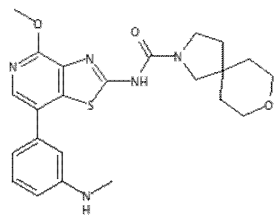
5	83		N-[7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-[1,3]thiazolo[4,5-c]pyridin-2-yl]-4-[(1R)-1-acetamidoethyl]benzamide	452,53	454
10	84		8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid {4-methoxy-7-[1-(tetrahydro-pyran-2-ylmethyl)-1H-pyrazol-4-yl]-thiazolo[4,5-c]pyridin-2-yl}-amide	512,63	514
15	85		8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid {4-methoxy-7-[1-(tetrahydro-pyran-4-ylmethyl)-1H-pyrazol-4-yl]-thiazolo[4,5-c]pyridin-2-yl}-amide	512,63	514
20	86		8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [7-(1,1-dioxo-hexahydro-1H-thiopyran-4-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide	480,61	482
25	87		8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid {4-methoxy-7-[1-(tetrahydro-pyran-3-ylmethyl)-1H-pyrazol-4-yl]-thiazolo[4,5-c]pyridin-2-yl}-amide	512,63	514
30					

5	88		N-[7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-[1,3]thiazolo[4,5-c]pyridin-2-yl]-4-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)piperidine-1-carboxamide	469,52	471
10	89		3-[7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-[1,3]thiazolo[4,5-c]pyridin-2-yl]-1-[4-(2-oxopyrrolidin-1-yl)phenyl]urea	465,53	467
15	90		N-[4-({[7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-[1,3]thiazolo[4,5-c]pyridin-2-yl]carbamoyl}amino)phenyl]-2-(dimethylamino)acetamide	482,56	484
20	91		N-[7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-[1,3]thiazolo[4,5-c]pyridin-2-yl]-4-(2,4-dioxo-1,3-thiazolidin-3-yl)piperidine-1-carboxamide	489,57	491
25	92		N-[4-({[7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-[1,3]thiazolo[4,5-c]pyridin-2-yl]carbamoyl}amino)-2-methylphenyl]acetamide	453,52	455
30					

5	93		N4-[7-(3,6-dihydro-2H-pyran-4-yl)-4-hydroxy-[1,3]thiazolo[4,5-c]pyridin-2-yl]-N1-(2-hydroxyethyl)-N1-methylbenzene-1,4-dicarboxamide	454,50	456
10	94		3-[7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-[1,3]thiazolo[4,5-c]pyridin-2-yl]-1-[4-(3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-1-yl)phenyl]urea	478,53	480
15	95		3-[7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-[1,3]thiazolo[4,5-c]pyridin-2-yl]-1-[4-(2-oxo-1,3-oxazolidin-3-yl)phenyl]urea	467,50	469
20	96		N1-[7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-[1,3]thiazolo[4,5-c]pyridin-2-yl]-N4,N4-dimethylpiperidine-1,4-dicarboxamide	445,54	447
25	97		[4-(4-Methoxy-7-phenyl-thiazolo[4,5-c]pyridin-2-ylcarbamoyl)-benzyl]-methyl-carbamic acid methyl ester	462,53	464
30					

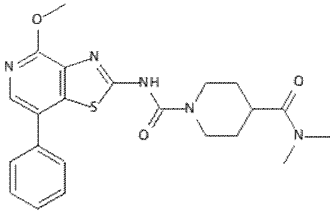
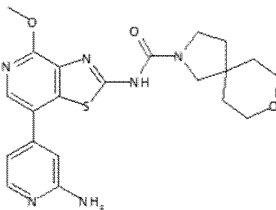
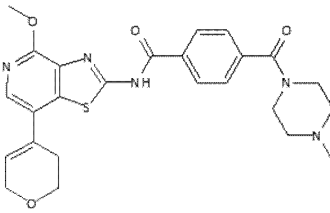
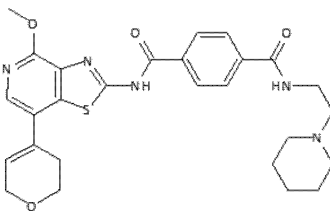
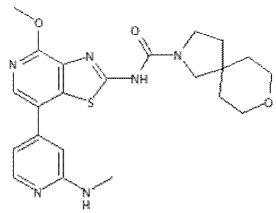
5	98		2,8-Diaza-spiro[4.5]decane-2-carboxylic acid [7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide	429,54	431
10	99		4-(2,5-Dioxo-pyrrolidin-1-yl)-piperidine-1-carboxylic acid (4-methoxy-7-phenyl-thiazolo[4,5-c]pyridin-2-yl)-amide	465,53	467
15	100		4-(2,5-Dioxo-pyrrolidin-1-yl)-piperidine-1-carboxylic acid [7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide	471,54	473
20	101		Bicyclo[1.1.1]pentane-1,3-dicarboxylic acid (6-fluoro-4-methoxy-7-phenyl-thiazolo[4,5-c]pyridin-2-yl)-amide (2-hydroxy-ethyl)-methyl-amide	470,52	472
25					
30	102		2,7-Diaza-spiro[4.5]decane-2-carboxylic acid [7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide	429,54	431

5	103		8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid (4-methoxy-7-{1-[2-(2-methoxyethoxy)-ethyl]-1H-pyrazol-4-yl}-thiazolo[4,5-c]pyridin-2-yl)-amide	516,62	518
10	104		8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid (4-methoxy-7-{1-[(R)-1-(tetrahydropyran-3-yl)methyl]-1H-pyrazol-4-yl}-thiazolo[4,5-c]pyridin-2-yl)-amide	512,63	514
15	105		8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid (4-methoxy-7-{1-[(S)-1-(tetrahydropyran-3-yl)methyl]-1H-pyrazol-4-yl}-thiazolo[4,5-c]pyridin-2-yl)-amide	512,63	514
20	106		N1-[7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-[1,3]thiazolo[4,5-c]pyridin-2-yl]piperidine-1,4-dicarboxamide	417,49	418
25	107		N-[7-(3,6-dihydro-2H-pyran-4-yl)-4-hydroxy-[1,3]thiazolo[4,5-c]pyridin-2-yl]-2-oxa-7-azaspiro[4.4]nonane-7-carboxamide	402,47	403
30					

5	108		N-[7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-[1,3]thiazolo[4,5-c]pyridin-2-yl]-2-oxa-7-azaspiro[4.4]nonane-7-carboxamide	416,50	417
10	109		4-({4-methoxy-7-phenyl-[1,3]thiazolo[4,5-c]pyridin-2-yl}carbamoyl)benzoic acid	405,43	406
15	110		N-{4-methoxy-7-phenyl-[1,3]thiazolo[4,5-c]pyridin-2-yl}-4-(1H-1,2,3,4-tetrazol-5-yl)benzamide	429,46	430
20	111		8-Oxa-2-azaspiro[4.5]decane-2-carboxylic acid [7-(4,4-difluorocyclohexyl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide	466,55	468
25	112		8-Oxa-2-azaspiro[4.5]decane-2-carboxylic acid [4-methoxy-7-(3-methylamino-phenyl)-thiazolo[4,5-c]pyridin-2-yl]-amide	453,56	455
30					

5	113		8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [4-methoxy-7-(5-methyl-thiophen-2-yl)-thiazolo[4,5-c]pyridin-2-yl]-amide	444,58	446
10	114		8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [4-methoxy-7-(5-methyl-furan-2-yl)-thiazolo[4,5-c]pyridin-2-yl]-amide	428,51	430
15	115		4-[(4-methoxy-7-{1-[(pyridin-3-yl)methyl]-1H-pyrazol-4-yl}-[1,3]thiazolo[4,5-c]pyridin-2-yl)carbamoyl]benzoic acid	486,51	488
20	116		N-[7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-[1,3]thiazolo[4,5-c]pyridin-2-yl]-1H-pyrazole-4-carboxamide	357,39	358
25	117		N-{4-methoxy-7-phenyl-[1,3]thiazolo[4,5-c]pyridin-2-yl}-1H-pyrazole-4-carboxamide	351,39	352

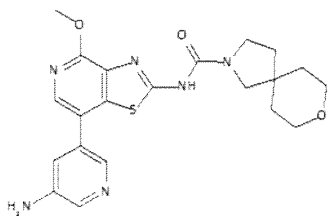
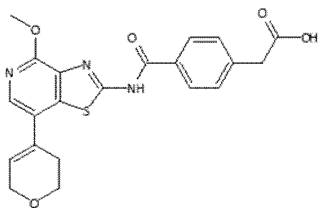
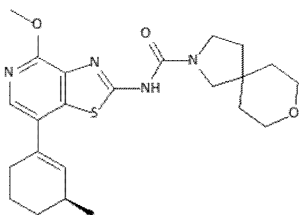
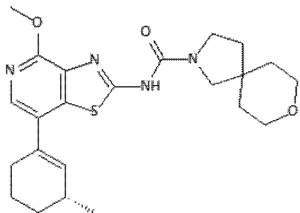
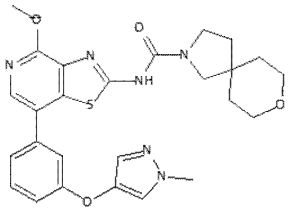
5	118		8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid (4-methoxy-7-{1-[(S)-1-(tetrahydropyran-2-yl)methyl]-1H-pyrazol-4-yl}-thiazolo[4,5-c]pyridin-2-yl)-amide	512,63	514
10	119		8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid (4-methoxy-7-{1-[(R)-1-(tetrahydropyran-2-yl)methyl]-1H-pyrazol-4-yl}-thiazolo[4,5-c]pyridin-2-yl)-amide	512,63	514
15	120		8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [7-(3-methanesulfonylamino-phenyl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide	517,63	519
20	121		(R)-2,7-Diaza-spiro[4.5]decane-2-carboxylic acid [7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide	429,54	431
25	122		(S)-2,7-Diaza-spiro[4.5]decane-2-carboxylic acid [7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide	429,54	431
30					

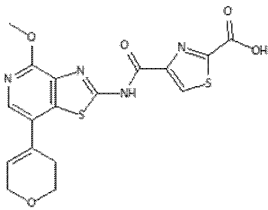
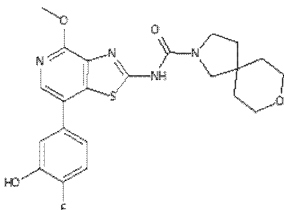
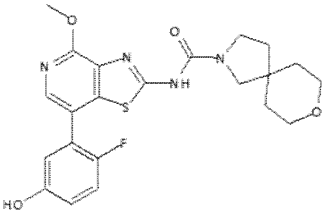
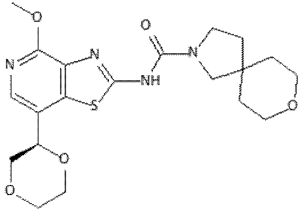
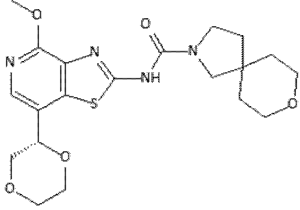
5	123		Piperidine-1,4-dicarboxylic acid 4-dimethylamide 1-[(4-methoxy-7-phenyl-thiazolo[4,5-c]pyridin-2-yl)-amide]	439,54	441
10	124		8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [7-(2-amino-pyridin-4-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide	440,53	442
15	125		N-[7-(3,6-Dihydro-2H-pyran-4-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-4-(4-methyl-piperazine-1-carbonyl)-benzamide	493,59	495
20	126		N-[7-(3,6-Dihydro-2H-pyran-4-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-N'-(2-piperidin-1-yl-ethyl)-terephthalamide	521,64	523
25	127		8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [4-methoxy-7-(2-methylamino-pyridin-4-yl)-thiazolo[4,5-c]pyridin-2-yl]-amide	454,55	456
30					

5	128		8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [4-methoxy-7-(5-methyl-cyclohex-1-enyl)-thiazolo[4,5-c]pyridin-2-yl]-amide	442,58	444
10	129		N-[7-(3,6-Dihydro-2H-pyran-4-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-4-(4-hydroxy-4-methyl-piperidine-1-carbonyl)-benzamide	508,60	510
15	130		8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [7-(3-fluoro-5-methanesulfonyl-aminophenyl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide	535,62	537
20	131		4-(2,5-Dioxo-imidazolidin-1-yl)-piperidine-1-carboxylic acid [7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide	472,52	474
25					
30	132		8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [4-methoxy-7-(3-methyl-3,6-dihydro-2H-pyran-4-yl)-thiazolo[4,5-c]pyridin-2-yl]-amide	444,55	446

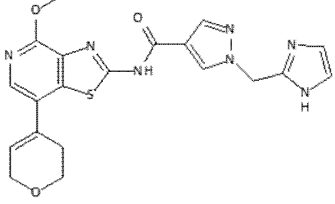
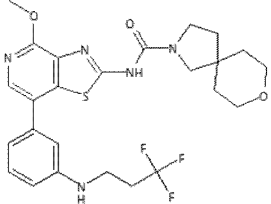
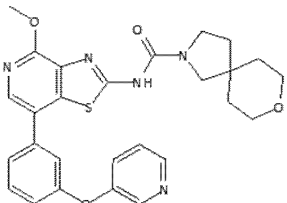
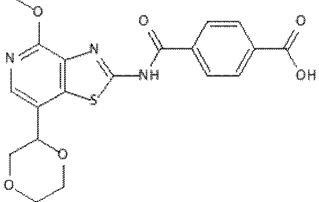
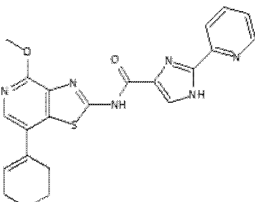
5	133		499,56	501
10	134		461,58	463
15	135		407,45	408
20	136		429,50	430
25	137		466,52	468
30				

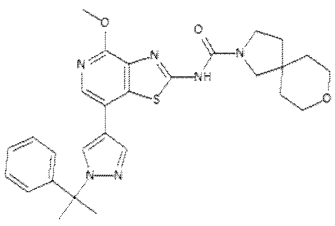
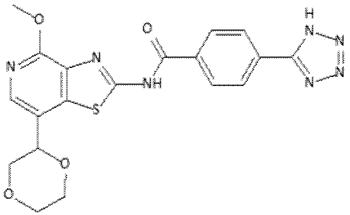
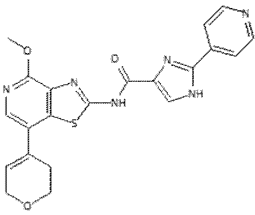
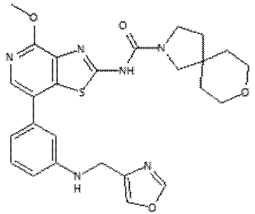
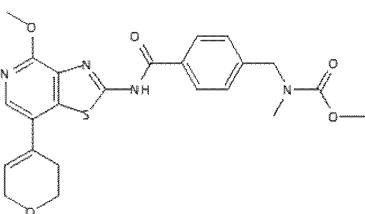
5	138		8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [7-(5-amino-2-fluoro-pyridin-3-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide	458,52	460
10	139		N-(2-Azetidin-1-yl-ethyl)-N'-[7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-terephthalamide	493,59	495
15	140		2-Pyridin-3-yl-1H-imidazole-4-carboxylic acid [7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide	434,48	435
20	141		N-{4-methoxy-7-[3-(trifluoromethyl)phenyl]-[1,3]thiazolo[4,5-c]pyridin-2-yl}-8-oxa-2-azaspiro[4.5]decane-2-carboxamide	492,52	494
25	142		8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [7-(5-amino-6-fluoro-pyridin-3-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide	458,52	460
30					

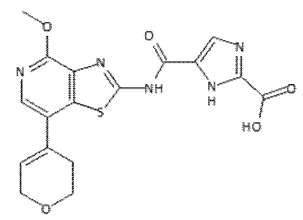
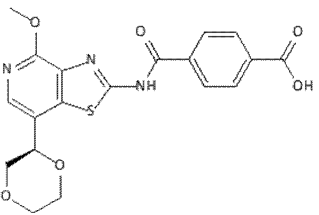
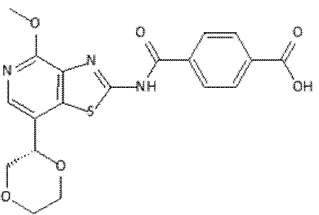
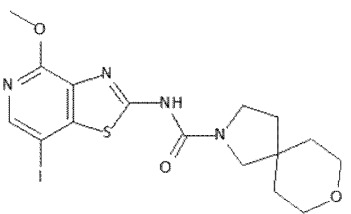
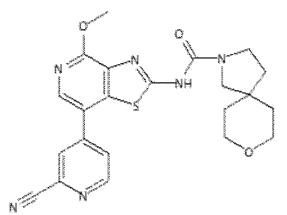
5	143		8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [7-(5-amino-pyridin-3-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide	440,53	442
10	144		{4-[7-(3,6-Dihydro-2H-pyran-4-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-ylcarbamoyl]-phenyl}-acetic acid	425,46	426
15	145		8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [4-methoxy-7-((S)-3-methyl-cyclohex-1-enyl)-thiazolo[4,5-c]pyridin-2-yl]-amide	442,58	444
20	146		8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [4-methoxy-7-((R)-3-methyl-cyclohex-1-enyl)-thiazolo[4,5-c]pyridin-2-yl]-amide	442,58	444
25	147		8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid {4-methoxy-7-[3-(1-methyl-1H-pyrazol-4-yloxy)-phenyl]-thiazolo[4,5-c]pyridin-2-yl}-amide	520,61	522
30					

5	148		4-[7-(3,6-Dihydro-2H-pyran-4-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-ylcarbamoyl]-thiazole-2-carboxylic acid	418,45	419
10	149		8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [7-(4-fluoro-3-hydroxy-phenyl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide	458,51	460
15	150		8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [7-(2-fluoro-5-hydroxy-phenyl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide	458,51	460
20	151		8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid ((R)-7-[1,4]dioxan-2-yl-4-methoxy-thiazolo[4,5-c]pyridin-2-yl)-amide	434,51	436
25	152		8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid ((S)-7-[1,4]dioxan-2-yl-4-methoxy-thiazolo[4,5-c]pyridin-2-yl)-amide	434,51	436
30					

5	153		440,52	442
10	154		432,48	433
15	155		469,57	471
20	156		433,49	434
25	157		434,48	435
30				

5	158		1-(1H-imidazol-2-ylmethyl)-1H-pyrazole-4-carboxylic acid [7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide	437,48	438
10	159		8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid {4-methoxy-7-[3-(3,3,3-trifluoropropylamino)-phenyl]-thiazolo[4,5-c]pyridin-2-yl}-amide	535,59	537
15	160		8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid {4-methoxy-7-[3-(pyridin-3-yloxy)-phenyl]-thiazolo[4,5-c]pyridin-2-yl}-amide	517,61	519
20	161		N-(7-[1,4]dioxan-2-yl-4-methoxy-thiazolo[4,5-c]pyridin-2-yl)-terephthalamic acid	415,42	416
25	162		2-Pyridin-2-yl-1H-imidazole-4-carboxylic acid [7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide	434,48	435
30					

5	163		8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid {4-methoxy-7-[1-(1-methyl-1-phenyl-ethyl)-1H-pyrazol-4-yl]-thiazolo[4,5-c]pyridin-2-yl}-amide	532,67	534
10	164		N-(7-[1,4]Dioxan-2-yl-4-methoxy-thiazolo[4,5-c]pyridin-2-yl)-4-(1H-tetrazol-5-yl)-benzamide	439,45	440
15	165		2-Pyridin-4-yl-1H-imidazole-4-carboxylic acid [7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide	434,48	435
20	166		8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid (4-methoxy-7-{3-[(oxazol-4-ylmethyl)-amino]-phenyl}-thiazolo[4,5-c]pyridin-2-yl)-amide	520,61	522
25	167		{4-[7-(3,6-Dihydro-2H-pyran-4-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-ylcarbamoyl]-benzyl}-methyl-carbamic acid methyl ester	468,53	470
30					

5	168		5-[7-(3,6-Dihydro-2H-pyran-4-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-ylcarbamoyl]-1H-imidazole-2-carboxylic acid	401,40	402
10	169		N-((R)-7-[1,4]Dioxan-2-yl-4-methoxy-thiazolo[4,5-c]pyridin-2-yl)-terephthalamic acid	415,42	416
15	170		N-((S)-7-[1,4]Dioxan-2-yl-4-methoxy-thiazolo[4,5-c]pyridin-2-yl)-terephthalamic acid	415,42	416
20	171		8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid (7-iodo-4-methoxy-thiazolo[4,5-c]pyridin-2-yl)-amide	474,32	475
25	172		8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [7-(2-cyano-pyridin-4-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide	450,52	452
30					

5	173		(5R)-N-[7-(3,6-dihydro-2H-pyran-4-yl)-4-(2H3)methoxy-[1,3]thiazolo[4,5-c]pyridin-2-yl]-7-oxa-2-azaspiro[4.5]decane-2-carboxamide	433,54	435
10	174		(5S)-N-[7-(3,6-dihydro-2H-pyran-4-yl)-4-(2H3)methoxy-[1,3]thiazolo[4,5-c]pyridin-2-yl]-7-oxa-2-azaspiro[4.5]decane-2-carboxamide	433,54	435

Table 3 – NMR profiles of the compounds of the present invention

The Nos. recited herein corresponds to the numbering of the compounds disclosed in table 2.

20	No.	NMR
	1	¹ H NMR (400 MHz, DMSO, ppm) :7.97 (s, 1H), 7.70-7.66 (m, 2H), 7.58-7.51 (m, 2H), 7.47-7.41 (m, 1H), 4.02 (s, 3H), 3.55 (s, 3H), 3.31(s,2H), 2.60 (d, J = 6.9 Hz, 1H), 2.22 (s, 1H), 1.96 (s, 1H), 1.64 (s, H).
25	2	¹ H NMR (400 MHz, DMSO-d ₆)11.34 (s,1H), 7.97 (s,1H), 7.68-7.54 (m,2H), 7.25-7.08 (m, 2H), 4.65 (dq, J=8.3, 4.2,3.8 Hz,1H), 4.02 (s,3H), 3.87 (dt, J=11.5, 4.4 Hz, 2H), 3.81-3.39 (m,10H), 2.08 -1.72 (m, 4H), 1.62 (dtd, J =13.1, 9.1,4.1 Hz, 2H), 1.49 (d, J = 5.7 Hz, 4H).
	3	¹ H NMR (400 MHz, DMSO, ppm) :7.97 (s, 1H), 7.70-7.66 (m, 2H), 7.58-7.51 (m, 2H), 7.47-7.41 (m, 1H), 4.02 (s, 3H), 3.55 (s, 3H), 3.31(s,2H), 2.60 (d, J = 6.9 Hz, 1H), 2.22 (s, 1H), 1.96 (s, 1H), 1.64 (s, H).
30	4	(400MHz,DMSO,ppm):12.89(s,1H),3.96(s,3H),3.73-3.70(m,4H),3.06-3.05(m,4H),1.98-1.92(m,1H),1.01-0.99(m,4H).
	5	¹ H NMR(400MHz,DMSO,ppm):7.64(s,3H),4.02-3.92(m,2H),3.89(s,3H),3.46(m,2H),2.77(m,1H), 1.87-1.69(m,4H).

5	6	(400MHz,DMSO,ppm):13.26(s,1H),8.27(d,J=8.4,2H),8.19(d,J=8.4,2H),3.99(s,3H),3.78-3.75(m,4H),3.11-3.10(m,4H).
	7	(400MHz,DMSO,ppm):11.30(s,1H),3.93(s,3H),3.73-3.71(m,4H),3.61-3.23(m,8H),3.16-3.14(m,4H),1.82-1.53(m,6H).
	8	(400MHz,DMSO,ppm):7.78(s,1H),7.67-7.63(m,2H),6.11(s,1H),4.25-4.24(m,2H),3.92-3.82(m,5H),3.32-3.30(m,2H).
10	9	¹ H NMR (400 MHz, DMSO,ppm) : 11.32 (d, J = 10.5 Hz, 2H), 8.04 (s, 1H), 7.70-7.68 (d, J = 8.1 Hz, 2H), 7.45-7.43 (t, J = 2.7 Hz, 1H), 7.32-7.30 (dd, J = 8.1, 1.7 Hz, 1H), 6.51 (t, J = 2.5 Hz, 1H), 4.04 (s, 3H), 3.71-3.39 (m, 7H), 3.31 (s, 1H), 1.82 (m, 2H), 1.50 (t, J = 5.4 Hz, 4H).
	10	(400MHz,DMSO,ppm):11.30(s,1H),3.93(s,3H),3.73-3.71(m,4H),3.61-3.46(m,6H),3.41-3.38(m,1H), 3.32-3.29(m,1H),3.20-3.17(m,4H),1.84-1.49(m,6H).
	11	(400MHz,DMSO,ppm):11.30(s,1H),3.93(s,3H),3.73-3.71(m,4H),3.61-3.46(m,6H),3.41-3.38(m,1H), 3.32-3.29(m,1H),3.18-3.17(m,4H),1.81-1.48(m,6H).
15	13	¹ H NMR (400 MHz, DMSO-d ₆ ,ppm) : 11.37 (s, 1H), 7.61-7.58 (m, 2H), 7.56 - 7.52 (m, 2H), 7.50 - 7.44 (m, 1H), 4.02 (s, 3H), 3.67 - 3.36 (m, 6H), 3.32 - 3.26 (m, 2H), 1.88 - 1.46 (m, 6H).
	14	¹ H NMR (400 MHz, CD ₃ OD-d ₄):7.63 (s, 1H), 4.07 (s, 3H), 3.89 (d, J = 4.8 Hz, 4H), 3.18 ? 3.14 (m, 4H), 2.54 (s, 2H), 2.32 (s, 6H), 2.20 (s, 6H).
20	15	¹ H NMR (300MHz,DMSO,ppm):11.37(s,1H),7.95(s,1H),6.25(s,1H),4.30-4.29(m,2H),3.99(s,3H),3.89(t,J=5.4Hz,2H),3.61-3.29(m,8H),2.55-2.51(m,2H),1.82-1.54(m,6H).
	16	¹ H NMR (400MHz,DMSO,ppm):11.32(s,1H),3.93(s,3H),3.80-3.72(m,6H),3.58-3.29(m,6H),3.06-3.05(m,4H), 1.92-1.84(m,4H).
25	17	(400MHz,DMSO,ppm):12.97(s,1H),8.69(s,1H),8.31(s,1H),7.88(s,1H),4.02-4.00(m,5H),3.55-3.32(m,6H),3.29(s,3H),3.01-2.99(m,1H),1.93-1.79(m,4H).
	18	¹ H NMR (400MHz,DMSO,ppm):11.33(s,1H),3.94(s,3H),3.80-3.72(m,6H),3.58-3.30(m,6H),3.06-3.05(m,4H), 1.91-1.82(m,4H).
30	19	¹ H NMR (400MHz,DMSO,ppm):11.33(s,1H),3.94(s,3H),3.82-3.71(m,6H),3.61-3.30(m,6H),3.06-3.05(m,4H), 1.91-1.82(m,4H).
	20	¹ H NMR (400 MHz, DMSO, ppm) : 13.32 (s, 1H), 8.20 ? 8.18 (d, J = 8.0 Hz, 2H), 7.59 ? 7.57 (d, J = 7.9 Hz, 2H), 4.02 - 3.99 (m, 5H), 3.54 ? 3.52 (t, J = 11.6 Hz, 2H), 3.21 ? 3.15 (m, 1H), 3.01 (s, 3H), 2.91(s,

		3H), 2.12 ? 2.04 (m, 2H), 1.70 ? 1.67 (m, 2H).
5	21	1H NMR (400 MHz, DMSO-d ₆ , ppm) : 12.41 (s, 1H) 7.69 (s, 1H), 7.21 (s, 1H), 6.86 (s, 1H), 4.37 (s, 2H), 4.01 - 3.98 (m, 5H), 3.48 (t, J = 11.6 Hz, 2H), 3.20 - 3.12 (m, 1H) , 2.02 (d, J = 11.4 Hz, 2H), 1.64 (d, J = 13.1 Hz, 2H), 1.47 (s, 2H), 1.22 (s, 2H).
	22	1H NMR (400 MHz, DMSO-d ₆) 12.90 (s, 1H), 8.54 (s, 1H), 8.23 (s, 1H), 4.35 (t, J = 5.2 Hz, 2H), 3.98 (s, 5H), 3.71 (t, J = 5.1 Hz, 2H), 3.50 (t, J = 11.6 Hz, 2H), 3.25 (d, J = 0.9 Hz, 3H), 3.20-3.08 (m, 1H), 2.05 (d, J = 13.5 Hz, 2H), 1.68 (d, J = 12.8 Hz, 2H).
10	23	1H NMR (400 MHz, DMSO, ppm) : 12.90 (s, 1H), 8.50 (s, 1H), 8.20 (s, 1H), 4.01 - 3.98 (m, 5H), 3.92 (s, 3H), 3.53 - 3.48 (m, 2H), 3.20 - 3.13 (m, 1H), 2.10 - 2.01 (m, 2H), 1.68 - 1.65 (d, J = 12.7 Hz, 2H).
	24	1H NMR (400MHz, DMSO, ppm): 11.35 (s,1H), 7.94 (s,1H), 6.24 (s,1H), 4.29-4.28 (m,2H), 3.99 (s,3H), 3.88-3.85 (m, 2H), 3.49-3.29 (m,8H), 2.55-2.50 (m,2H), 1.83-1.53 (m,6H).
15	25	1H NMR (400MHz, DMSO-d ₆ , ppm): 11.35 (s,1H), 7.94 (s,1H), 6.24 (s,1H), 4.29-4.28 (m,2H), 3.99 (s,3H), 3.88-3.85 (m, 2H), 3.61-3.29 (m,8H), 2.55-2.50 (m,2H), 1.83-1.53 (m,6H).
	26	1H NMR (400MHz,DMSO-d ₆ ,ppm):11.31(s,1H),3.99-3.94(m,5H),3.61-3.45(m,10H),3.12(t,J=12.4Hz,1H),2.03(q,J=12.5Hz,2H),1.82(s,2H),1.65-1.62(m,2H),1.50(s,4H).
20	27	(400MHz,DMSO-d ₆ ,ppm):11.52(s,1H),7.67-7.64(m,2H),7.41-7.36(m,2H),4.40(s,1H),4.02(s,3H),3.83-3.80(m,2H),3.28-3.25(m,2H),1.46-1.41(m,4H),1.13(s,3H).
	28	1H NMR (400 MHz, DMSO-d ₆)12.93 (s, 1H), 4.08-3.91 (m, 5H), 3.47 (t, J=11.6 Hz, 2H), 3.19-3.06 (m, 1H), 2.13-1.89 (m, 3H), 1.64 (d, J=13.0 Hz, 2H), 1.09-0.88 (m, 4H)
25	29	1H NMR (400MHz,DMSO-d ₆ ,ppm):11.37(s,1H),7.67-7.64(m,2H),7.41-7.37(m,2H),4.02(s,3H),3.61-3.32(m,8H),1.86-1.71(m,2H),1.49(s,4H).
	30	1H NMR (300 MHz, DMSO-d ₆ , ppm) 8.02 (s, 1H), 7.60 (s, 1H), 7.52 - 7.33 (m, 3H), 4.02 (s, 3H), 3.74 (s, 2H), 2.57 - 2.50 (m, 2H), 1.92 (d, J = 4.7 Hz, 1H), 1.06 - 0.96 (m, 3H), 0.96 - 0.86 (m, 4H).
30	31	1H NMR (400 MHz, DMSO-d ₆)11.34 (s, 1H), 4.05 ? 3.89 (m, 5H), 3.70 ? 3.36 (m, 8H), 3.29 (s, 2H), 3.12 (t, J = 12.3 Hz, 1H), 2.11 ? 1.95 (m, 1H), 1.60 (m, J = 35.5, 12.5 Hz, 6H).
	32	1H NMR (400 MHz, DMSO-d ₆ , ppm) : 12.81 (s, 1H) 8.11 (s, 1H), 7.89 (s, 1H), 7.64 (d, J = 7.6 Hz, 2H), 7.57 (t, J = 7.5 Hz, 2H), 7.49 (t, J = 7.4 Hz, 1H), 4.05 (s, 3H).

5	33	1H NMR (400MHz,DMSO-d6,ppm):11.37(s,1H),3.99-3.94(m,5H),3.80-3.76(m,2H),3.58-3.48(m,8H),3.20-3.12(m,1H),2.05-2.04(m,2H),2.02-1.85(m,4H),1.70-1.60(m,2H).
	34	1H NMR (400 MHz, DMSO-d6) 11.34 (s, 1H), 3.94 (s, 5H), 3.69-3.36 (m, 8H), 3.30-3.25 (m, 1H), 3.12 (s, 2H), 2.06 -1.93 (m, 2H), 1.74-1.39 (m, 8H).
	35	1H NMR (400 MHz, DMSO-d6)11.34 (s, 1H), 3.94 (s, 5H), 3.69-3.36 (m, 8H), 3.30-3.25 (m, 1H), 3.12 (s, 2H), 2.06-1.93 (m, 2H), 1.74-1.39 (m, 8H).
10	36	1H NMR (300 MHz, DMSO-d6): 8.85 (s, 1H), 8.24 (s, 1H), 7.75 (d, J = 9.8 Hz, 1H), 6.89 (s, 1H), 4.70 (d, J = 8.9 Hz, 2H), 3.87 (s, 3H), 3.72 (s, 3H).
	37	HNMR (400MHz,DMSO-d6,ppm):11.37(s,1H),3.99-3.94(m,5H),3.80-3.76(m,2H),3.58-3.48(m,8H),3.16-3.10(m,1H),2.04-1.84(m,6H),1.70-1.60(m,2H).
15	38	HNMR (400MHz,DMSO-d6,ppm):11.37(s,1H),3.99-3.94(m,5H),3.80-3.76(m,2H),3.58-3.48(m,8H),3.16-3.10(m,1H),2.08-1.85(m,6H),1.70-1.60(m,2H).
	39	1H NMR (400 MHz, DMSO-d6, ppm) : 11.31 (s, 1H), 7.93 (s, 1H), 7.16 (t, J = 7.8 Hz, 1H), 6.84 (t, J = 2.0 Hz, 1H), 6.78 - 6.73 (m, 1H), 6.66 - 6.59 (m, 1H), 5.30 (s, 2H), 4.02 (s, 3H), 3.69 - 3.44 (m, 4H), 1.81 (s, 2H), 1.50 (t, J = 5.4 Hz, 4H).
20	40	1H NMR (400 MHz, DMSO-d6, ppm) : 11.48 (s, 1H), 8.38 (d, J = 4.5 Hz, 1H), 6.50 (s, 1H), 4.06 (d, J = 1.1 Hz, 3H), 3.69 - 3.43 (m, 8H), 3.31 (s, 2H), 3.20 (s, 2H), 1.83 (s, 2H), 1.50 (t, J = 5.4 Hz, 4H).
	41	1H NMR (400MHz, DMSO-d6, ppm): 12.81 (s, 1H), 4.84-4.66 (m, 1H), 4.00-3.96 (m, 5H), 3.53-3.46 (m, 5H), 3.31-3.30 (m, 1H), 3.18-3.09 (m, 2H), 2.82 (s, 2H), 2.50-2.40 (m, 6H), 2.07-1.94 (m, 2H), 1.65 (d, J = 12.8 Hz, 2H).
25	42	1H NMR (500 MHz, DMSO-d6) d 13.02 (s, 1H), 7.87 (s, 1H), 6.38 – 6.36 (m, 1H), 5.06 – 5.02 (m, 2H), 4.82 – 4.79 (m, 2H), 4.03 (s, 3H), 2.03 – 1.95 (m, 1H), 1.03 – 0.93 (m, 4H).
	43	1H NMR (500 MHz, DMSO-d6) d 12.89 – 12.74 (m, 1H), 11.94 – 11.87 (m, 1H), 8.49 – 8.46 (m, 1H), 8.31 – 8.29 (m, 1H), 7.92 (s, 1H), 6.46 – 6.43 (m, 1H), 5.09 – 5.05 (m, 2H), 4.86 – 4.82 (m, 2H), 4.05 (s, 3H).
30	44	1H NMR (500 MHz, DMSO-d6) d 11.43 – 11.34 (m, 1H), 7.81 (s, 1H), 6.37 – 6.35 (m, 1H), 5.06 – 5.02 (m, 2H), 4.83 – 4.79 (m, 2H), 4.01 (s, 3H), 3.68 – 3.27 (m, 8H), 1.92 – 1.73 (m, 2H), 1.54 – 1.48 (m, 4H).

5	45	1H NMR (400 MHz, DMSO-d6) d 11.45 – 11.36 (m, 1H), 7.81 (s, 1H), 6.38 – 6.35 (m, 1H), 5.06 – 5.02 (m, 2H), 4.83 – 4.79 (m, 2H), 4.01 (s, 3H), 3.68 – 3.44 (m, 4H), 3.44 – 3.38 (m, 1H), 3.34 – 3.29 (m, 1H), 3.29 – 3.11 (m, 2H), 1.91 – 1.47 (m, 6H).
	46	1H NMR (400 MHz, DMSO-d6, ppm) : 11.32 (s, 1H), 7.91 (d, J = 5.6 Hz, 1H), 6.17 (s, 1H), 4.18 (d, J = 24.9 Hz, 2H), 3.99 (s, 3H), 3.77 - 3.39 (m, 10H), 2.64 - 2.53 (m, 2H), 2.07 (d, J = 13.3 Hz, 3H), 1.81 (s, 2H), 1.50 (t, J = 5.4 Hz, 4H).
	47	1H NMR (400MHz, DMSO-d6, ppm): 11.42 (s, 1H), 8.21 (s, 1H), 7.69 (d, J = 4.0 Hz, 1H), 7.53 (d, J = 2.8 Hz, 1H), 7.25 (dd, J = 5.2, 3.6 Hz, 1H), 4.03 (s, 3H), 3.62-3.29 (m, 8H), 1.83 (s, 2H), 1.51 (s, 4H).
10	48	1H NMR (400MHz, DMSO-d6, ppm): 11.38 (s, 1H), 8.36 (s, 1H), 7.90 (d, J = 1.2 Hz, 1H), 6.96 (d, J = 3.2 Hz, 1H), 6.71 (dd, J = 3.2, 2.0 Hz, 1H), 4.03 (s, 3H), 3.62-3.29 (m, 8H), 1.86-1.82 (m, 2H), 1.51 (s, 4H).
15	49	1H NMR (400 MHz, DMSO-d6, ppm) : 7.99 (s, 1H), 7.63 (d, J = 1.8 Hz, 1H), 7.56 - 7.43 (m, 2H), 7.40 (dt, J = 7.6, 1.5 Hz, 1H), 4.03 (s, 3H), 3.80 (s, 2H), 3.71 - 3.45 (m, 8H), 2.58 (q, J = 7.1 Hz, 2H), 1.80 (s, 2H), 1.49 (t, J = 5.4 Hz, 4H), 1.05 (t, J = 7.1 Hz, 3H).
	50	1H NMR (400 MHz, DMSO-d6) 13.31 (s, 1H), 8.18 (t, J = 8.8 Hz, 2H), 7.57 (d, J=7.6 Hz, 2H), 4.83 (s, 1H), 4.00 (s, 5H), 3.64 (d, J=5.9 Hz, 1H), 3.52 (t, J=11.6 Hz, 4H), 3.30-3.12 (m, 2H), 2.97 (d, J=27.7 Hz, 3H), 2.08 (q, J=12.2 Hz, 2H), 1.69 (d, J=12.8 Hz, 2H).
	51	1H NMR (400 MHz, DMSO-d6, ppm) : 11.27 (s, 1H), 7.53 (s, 1H), 3.93 (s, 3H), 3.74 - 3.39 (m, 8H), 3.03 (t, J = 5.3 Hz, 4H), 1.82 (s, 2H), 1.69 (t, J = 5.5 Hz, 4H), 1.61 - 1.45 (m, 6H).
20	52	1H NMR (400MHz, DMSO-d6, ppm): 11.38 (s, 1H), 8.16 (s, 1H), 8.10 (s, 1H), 7.87 (s, 1H), 7.03 (s, 1H), 4.01 (s, 3H), 3.62-3.29 (m, 8H), 1.83 (s, 2H), 1.51 (s, 4H)
25	53	1H NMR (400 MHz, CDOH-d4, ppm) : 7.58-7.56 (m, 1H), 4.06 (s, 3H), 3.82 - 3.58 (m, 6H), 3.47 (s, 2H), 3.20 (s, 4H), 2.69 (s, 4H), 2.40 (s, 3H), 1.96 (s, 2H), 1.65 (t, J = 5.4 Hz, 4H).
	54	1H NMR (300 MHz, DMSO-d6): 11.38 (s, 1H), 8.06 (s, 1H), 7.47-7.45 (m, 1H), 7.22-7.21 (m, 2H), 7.04 (dd, J = 8.3, 2.6 Hz, 1H), 4.04 (s, 3H), 3.84 (s, 3H), 3.58-3.33 (m, 8H), 1.82 (s, 2H), 1.51 (s, 4H).
	55	1H NMR (400 MHz, DMSO-d6, ppm) : 8.50 (s, 1H), 8.31 (d, J = 6.4 Hz, 1H), 8.18 (s, 1H), 4.33 (t, J = 5.2 Hz, 2H), 4.03 (d, J = 3.0 Hz, 3H), 3.71 (t, J = 5.1 Hz, 2H), 3.25 (s, 3H).
30	56	1H NMR (400 MHz, DMSO-d6, ppm) : 11.19 (s, 1H), 8.76 (s, 1H), 8.45 (d, J = 9.0 Hz, 1H), 7.72 (d, J = 8.9 Hz, 1H), 4.08 (s, 3H), 3.74 - 3.39 (m, 8H), 2.69 (s, 3H), 1.83 (s, 2H), 1.53 (t, J = 5.5 Hz, 4H).

5	57	1H NMR (400 MHz, DMSO-d6, ppm) : 11.25 (s, 1H), 7.06 (s, 1H), 3.99 - 3.81 (m, 7H), 3.70 - 3.42 (m, 8H), 2.35 - 2.26 (m, 2H), 1.80 (s, 2H), 1.49 (t, J = 5.4 Hz, 4H).
	58	1H NMR (400 MHz, DMSO-d6, ppm) : 11.28 (s, 1H), 7.09 (s, 1H), 5.69 (d, J = 6.6 Hz, 1H), 4.57 (q, J = 6.1 Hz, 1H), 4.19 - 4.12 (m, 2H), 3.89 (s, 3H), 3.69 - 3.45 (m, 10H), 1.82 (s, 2H), 1.49 (t, J = 5.4 Hz, 4H).
	59	1H NMR (400 MHz, DMSO-d6, ppm) : 11.28 (s, 1H), 7.86 (s, 1H), 6.15 (s, 1H), 3.97 (s, 3H), 3.67 - 3.43 (m, 8H), 2.46 - 2.40 (m, 2H), 2.26 - 2.20 (m, 2H), 1.88 - 1.71 (m, 4H), 1.69 - 1.62 (m, 2H), 1.49 (t, J = 5.4 Hz, 4H).
10	60	1H NMR (400 MHz, DMSO-d6, ppm) : 12.83 (s, 1H), 8.12 (d, J = 17.3 Hz, 2H), 7.91 (s, 1H), 7.72 (d, J = 7.6 Hz, 2H), 7.58 (t, J = 7.6 Hz, 2H), 7.48 (t, J = 7.5 Hz, 1H), 4.07 (s, 3H).
15	61	1H NMR (700 MHz, DMSO-d6) delta 13.36 - 13.29 (m, 1H), 8.21 - 8.18 (m, 2H), 8.05 (s, 1H), 7.60 - 7.57 (m, 2H), 6.33 - 6.31 (m, 1H), 4.32 (q, J = 2.8 Hz, 2H), 4.04 (s, 3H), 3.89 (t, J = 5.4 Hz, 2H), 3.03 - 2.88 (m, 6H), 2.61 - 2.57 (m, 2H).
	62	1H NMR (400 MHz, DMSO-d6, ppm) : 11.28 (s, 1H), 7.75 (s, 1H), 3.94 (s, 3H), 3.62 (s, 2H), 3.56-3.42 (m, 5H), 2.69 - 2.60 (m, 1H), 1.94 - 1.70 (m, 7H), 1.68 - 1.34 (m, 8H), 1.32-1.20 (m, 1H).
	63	HNMR (400 MHz, DMSO, ppm): 11.34 (s, 1H), 7.92 (s, 1H), 6.03 (s, 1H), 3.99 (s, 3H), 3.62-3.33 (m, 8H), 2.85-2.67 (m, 4H), 2.28-2.18(m, 2H), 1.81-1.77 (m, 2H), 1.60-1.40 (m, 4H) .
20	64	1H NMR (400 MHz, DMSO-d6, ppm) : 11.31 (s, 1H), 7.86 (d, J = 1.5 Hz, 1H), 6.28 (s, 1H), 3.98 (s, 3H), 3.73 - 3.40 (m, 8H), 3.35 (d, J = 3.3 Hz, 2H), 2.88 (t, J = 5.7 Hz, 2H), 2.68 (s, 2H), 1.83 (s, 2H), 1.50 (t, J = 5.4 Hz, 4H).
25	65	1H NMR (400 MHz, DMSO-d6, ppm): 13.19-13.10 (m, 1H), 12.27-12.18 (m, 1H), 8.15 (s, 1H), 8.01 (s, 1H), 7.90 (s, 1H), 6.29(s, 1H), 4.32-4.32 (m, 2H), 4.02 (s, 3H), 3.90-3.87 (m, 2H), 2.58-2.57 (m, 2H).
	67	1H NMR (400 MHz, DMSO-d6, ppm) : 11.20 (s, 1H), 8.51 (s, 1H), 8.04 (d, J = 1.3 Hz, 1H), 4.03 (s, 3H), 3.69 - 3.43 (m, 8H), 2.78 (s, 3H), 1.82 (s, 2H), 1.51 (t, J = 5.4 Hz, 4H).
	68	1H NMR (400 MHz, DMSO-d6, ppm) : 11.38 (s, 1H), 8.58 (d, J = 2.3 Hz, 1H), 8.52 (dd, J = 4.8, 1.6 Hz, 1H), 8.38 (s, 1H), 8.15 (s, 1H), 7.98 (s, 1H), 7.72 (dt, J = 7.9, 2.0 Hz, 1H), 7.40 (dd, J = 7.9, 4.8 Hz, 1H), 5.50 (s, 2H), 3.99 (s, 3H), 3.69 - 3.42 (m, 8H), 1.81 (d, J = 26.9 Hz, 2H), 1.50 (t, J = 5.2 Hz, 4H).
30	69	1H NMR (400 MHz, DMSO-d6)11.32 (s, 1H), 8.55 (dt, J = 5.0, 1.4 Hz, 1H), 8.36 (s, 1H), 8.18 (s, 1H), 7.99 (d, J = 0.8 Hz, 1H), 7.80 (td, J =

		7.7, 1.8 Hz, 1H), 7.36 ? 7.30 (m, 1H), 7.13 (d, J = 7.9 Hz, 1H), 5.55 (s, 2H), 4.00 (s, 3H), 3.76 ? 3.38 (m, 8H), 1.84 (s, 2H), 1.50 (s, 4H).
5	70	¹ H NMR (400 MHz, DMSO-d ₆) delta 11.30 - 11.24 (m, 1H), 7.87 (s, 1H), 6.06 - 6.02 (m, 1H), 3.98 (s, 3H), 3.66 - 3.43 (m, 5H), 3.43 - 3.12 (m, 4H), 3.31 (s, 3H), 2.62 - 1.47 (m, 12H).
	71	¹ H NMR (400 MHz, DMSO-d ₆) delta 13.56 - 13.16 (m, 1H), 9.00 (d, J = 1.2 Hz, 1H), 8.40 - 8.36 (m, 2H), 8.19 - 8.14 (m, 2H), 8.06 (s, 1H), 8.05 (d, J = 1.2 Hz, 1H), 6.34 - 6.31 (m, 1H), 4.35 - 4.31 (m, 2H), 4.05 (s, 3H), 3.90 (t, J = 5.4 Hz, 2H), 2.63 - 2.57 (m, 2H).
10	73	¹ H NMR (400 MHz, DMSO-d ₆ , ppm): 11.25 (s, 1H), 7.84 (s, 1H), 4.82-4.79 (m, 1H), 3.96-3.92 (m, 4H), 3.84-3.78 (m, 3H), 3.66-3.49 (m, 10H), 1.83-1.70 (m, 2H), 1.51-1.48 (m, 4H).
	74	¹ H NMR (400 MHz, DMSO-d ₆ , ppm) : 11.39 (s, 1H), 8.26 (s, 1H), 8.17 (s, 1H), 8.04 (d, J = 0.8 Hz, 1H), 6.43 (tt, J = 54.9, 3.8 Hz, 1H), 4.75 (td, J = 15.1, 3.8 Hz, 2H), 4.01 (s, 3H), 3.71 - 3.40 (m, 8H), 1.84 (s, 2H), 1.51 (t, J = 5.4 Hz, 4H).
15	75	¹ H NMR (400 MHz, DMSO-d ₆ , ppm) : 11.38 (s, 1H), 8.56 - 8.53 (m, 2H), 8.38 (d, J = 0.9 Hz, 1H), 8.18 (s, 1H), 8.03 (d, J = 0.9 Hz, 1H), 7.21 - 7.17 (m, 2H), 5.53 (s, 2H), 4.00 (s, 3H), 3.70 - 3.42 (m, 8H), 1.83 (s, 2H), 1.50 (t, J = 5.2 Hz, 4H).
	76	¹ H NMR (400 MHz, DMSO-d ₆ , ppm) : 11.37 (s, 1H), 8.32 (s, 1H), 8.15 (s, 1H), 7.96 (s, 1H), 7.41 - 7.23 (m, 5H), 5.45 (s, 2H), 3.99 (s, 3H), 3.68 - 3.42 (m, 8H), 1.81 (d, J = 25.8 Hz, 2H), 1.50 (t, J = 5.2 Hz, 4H).
20	77	¹ H NMR (400 MHz, DMSO-d ₆) delta 11.30 - 11.24 (m, 1H), 7.86 (s, 1H), 6.06 - 6.02 (m, 1H), 3.98 (s, 3H), 3.67 - 3.43 (m, 5H), 3.43 - 3.11 (m, 4H), 3.31 (s, 3H), 2.62 - 1.46 (m, 12H).
	78	¹ H NMR (300 MHz, DMSO-d ₆ , ppm): 11.95 (s, 1H), 11.41 (s, 1H), 7.95 (s, 1H), 7.80-7.69 (m, 2H), 6.53 (d, J = 9.6 Hz, 1H), 4.01 (s, 3H), 3.62-3.49 (m, 8H), 1.95-1.70 (m, 2H), 1.65-1.40(m, 4H).
25	79	¹ H NMR (400 MHz, DMSO, ppm): 11.45(s, 1H), 8.67(s, 1H), 8.32-8.24(m, 1H), 8.09-7.75 (m, 2H), 4.02(s, 3H), 3.63-3.30(m, 8H), 1.86-1.79(m, 2H), 1.51(s, 4H)
	80	¹ H NMR (400 MHz, DMSO-d ₆) 11.57 (s, 1H), 8.08 (d, J = 8.6 Hz, 1H), 7.89 (s, 1H), 7.72 (d, J = 7.9 Hz, 2H), 7.54 (dt, J = 32.6, 7.5 Hz, 3H), 3.52 (s, 7H), 3.30 (s, 1H), 1.81 (d, J = 38.2 Hz, 2H), 1.50 (s, 4H).
30	82	¹ H NMR (400 MHz, DMSO-d ₆) d 14.88 – 14.65 (m, 1H), 13.30 (s, 1H), 9.39 – 9.36 (m, 1H), 8.22 – 8.18 (m, 2H), 8.06 (s, 1H), 7.87 – 7.85 (m, 1H), 7.76 – 7.74 (m, 1H), 7.61 – 7.58 (m, 2H), 6.33 – 6.30 (m, 1H), 5.60 – 5.56 (m, 2H), 4.32 (q, J = 2.7 Hz, 2H), 4.04 (s, 3H), 3.89 (t, J = 5.4 Hz, 2H), 2.62 – 2.56 (m, 2H).

5	83	1H NMR (400 MHz, DMSO-d6) delta 13.19 (s, 1H), 8.41 (d, J = 7.8 Hz, 1H), 8.14 - 8.08 (m, 2H), 8.05 (s, 1H), 7.51 - 7.46 (m, 2H), 6.34 - 6.31 (m, 1H), 4.96 (quint, J = 7.2 Hz, 1H), 4.32 (q, J = 2.7 Hz, 2H), 4.04 (s, 3H), 3.89 (t, J = 5.4 Hz, 2H), 2.62 - 2.56 (m, 2H), 1.86 (s, 3H), 1.36 (d, J = 7.0 Hz, 3H).
	84	1H NMR (400MHz,DMSO,ppm):8.15-8.12(m,3H),7.91(s,1H),4.21-4.19(m,2H),3.99(s,3H),3.52-3.51(m,9H),3.33(m,2H),2.50-2.49(m,3H),1.50-1.46(m,9H).
10	85	1H NMR (400MHz,DMSO,ppm):11.38(s,1H),8.17-8.14(m,2H),7.92(s,1H),4.12-3.99(m,2H),3.85-3.82(m,3H),3.62(s,2H),3.52-3.49(m,8H),3.30-3.20(m,2H),2.13-2.08(m,1H),1.86(s,2H),1.80-1.79(m,4H),1.51-1.42(m,2H),1.29(s,2H).
	87	1H NMR (400MHz,DMSO,ppm): 11.41(s, 1H), 8.17 - 8.15 (m, 2H), 7.92 (s, 1H), 4.12 (s, 2H),3.99(s, 3H), 3.75-3.18(m, 12H), 2.15(s, 1H), 1.95-1.28 (m, 10H).
15	88	1H NMR (500 MHz, DMSO-d6) delta 12.02 - 11.09 (m, 1H), 7.94 (s, 1H), 6.97 (s, 2H), 6.26 - 6.24 (m, 1H), 4.36 - 4.30 (m, 2H), 4.29 (q, J = 2.8 Hz, 2H), 4.15 - 4.07 (m, 1H), 4.00 (s, 3H), 3.87 (t, J = 5.4 Hz, 2H), 2.99 - 2.91 (m, 2H), 2.58 - 2.54 (m, 2H), 2.10 - 2.00 (m, 2H), 1.71 - 1.65 (m, 2H).
	89	1H NMR (400 MHz, DMSO-d6) delta 11.57 - 10.66 (m, 1H), 9.51 (s, 1H), 7.96 (s, 1H), 7.65 - 7.60 (m, 2H), 7.52 - 7.47 (m, 2H), 6.27 - 6.25 (m, 1H), 4.30 (q, J = 2.7 Hz, 2H), 4.01 (s, 3H), 3.88 (t, J = 5.4 Hz, 2H), 3.82 (t, J = 7.0 Hz, 2H), 2.59 - 2.53 (m, 2H), 2.50 - 2.45 (m, 2H), 2.10 - 2.02 (m, 2H).
20	90	1H NMR (400 MHz, DMSO-d6) delta 10.74 - 10.71 (m, 1H), 10.06 - 10.02 (m, 1H), 9.99 - 9.89 (m, 1H), 7.96 (s, 1H), 7.60 - 7.56 (m, 2H), 7.52 - 7.47 (m, 2H), 6.27 - 6.24 (m, 1H), 4.30 (q, J = 2.8 Hz, 2H), 4.15 - 4.11 (m, 2H), 4.01 (s, 3H), 3.88 (t, J = 5.4 Hz, 2H), 2.91 - 2.86 (m, 6H), 2.59 - 2.53 (m, 2H).
	91	1H NMR (400 MHz, DMSO-d6) delta 11.76 - 11.45 (m, 1H), 7.98 - 7.92 (m, 1H), 6.29 - 6.14 (m, 1H), 4.38 - 4.23 (m, 5H), 4.17 - 4.12 (m, 2H), 4.02 - 3.96 (m, 3H), 3.91 - 3.83 (m, 2H), 3.01 - 2.88 (m, 2H), 2.59 - 2.52 (m, 2H), 2.24 - 2.09 (m, 2H), 1.71 - 1.59 (m, 2H).
25	92	1H NMR (400 MHz, DMSO-d6) d 11.48 – 10.98 (m, 1H), 9.54 (s, 1H), 9.26 (s, 1H), 7.97 (s, 1H), 7.38 (d, J = 2.4 Hz, 1H), 7.31 (d, J = 8.6 Hz, 1H), 7.26 (dd, J = 8.6, 2.5 Hz, 1H), 6.29 – 6.25 (m, 1H), 4.32 – 4.29 (m, 2H), 4.01 (s, 3H), 3.88 (t, J = 5.4 Hz, 2H), 2.60 – 2.54 (m, 2H), 2.19 (s, 3H), 2.04 (s, 3H).
	94	1H NMR (500 MHz, DMSO-d6) d 11.95 – 11.08 (m, 1H), 10.05 (s, 1H), 7.97 (s, 1H), 7.66 – 7.59 (m, 4H), 6.28 – 6.26 (m, 1H), 5.56 – 5.55 (m, 1H), 4.31 (q, J = 2.8 Hz, 2H), 4.02 (s, 3H), 3.88 (t, J = 5.4

		Hz, 2H), 2.59 – 2.54 (m, 2H), 2.20 (s, 3H).
5	95	¹ H NMR (400 MHz, DMSO-d ₆) δ 11.35 – 11.02 (m, 1H), 9.51 (s, 1H), 7.97 (s, 1H), 7.57 – 7.50 (m, 4H), 6.29 – 6.25 (m, 1H), 4.47 – 4.40 (m, 2H), 4.32 – 4.29 (m, 2H), 4.09 – 4.03 (m, 2H), 4.01 (s, 3H), 3.90 – 3.85 (m, 2H), 2.60 – 2.54 (m, 2H).
	96	¹ H NMR (400 MHz, DMSO-d ₆) δ 11.79 – 11.47 (m, 1H), 7.95 (s, 1H), 6.27 – 6.23 (m, 1H), 4.31 – 4.28 (m, 2H), 4.26 – 4.23 (m, 2H), 4.00 (s, 3H), 3.87 (t, J = 5.4 Hz, 2H), 3.04 (s, 3H), 3.02 – 2.86 (m, 3H), 2.81 (s, 3H), 2.58 – 2.52 (m, 2H), 1.72 – 1.62 (m, 2H), 1.52 – 1.39 (m, 2H).
10	97	¹ H NMR (400 MHz, DMSO-d ₆) δ 13.25 (s, 1H), 8.14 (d, J = 8.8 Hz, 3H), 7.73 (d, J = 7.4 Hz, 2H), 7.58 (t, J = 7.5 Hz, 2H), 7.48 (t, J = 7.4 Hz, 1H), 7.39 (s, 2H), 4.52 (s, 2H), 4.08 (d, J = 1.1 Hz, 3H), 3.64 (d, J = 9.6 Hz, 3H), 2.85 (s, 3H).
	98	¹ H NMR (400 MHz, Methanol-d ₄ , ppm): 7.86 (s, 1H), 6.26 (s, 1H), 4.37-4.35 (m, 2H), 4.09 (s, 3H), 4.01-3.96 (m, 2H), 3.62 (s, 2H), 3.49-3.44(m, 2H), 2.99-2.86(m, 4H), 2.63-2.61 (m, 2H), 2.00-1.92 (m, 2H), 1.70-1.65 (m, 4H).
15	99	¹ H NMR (400MHz,DMSO,ppm):11.68(s, 1H), 8.04(s, 1H), 7.71-7.69(m, 2H), 7.57-7.54(m, 2H), 7.47-7.46(m, 1H), 4.33-4.30(m, 2H), 4.04-4.01(m, 4H), 2.99-2.98(m, 2H),2.58-2.49(m, 4H), 2.16-2.14(m, 2H), 1.58-1.56(m, 2H).
	100	¹ H NMR (400MHz,DMSO,ppm):11.62(s, 1H), 7.93(s, 1H), 6.25(s, 1H), 4.29-4.28(m, 5H), 3.98(s, 3H), 3.88-3.85(m, 2H), 2.92(s, 2H), 2.58-2.49(m, 6H), 2.16-2.14(m, 2H), 1.58-1.55(m, 2H).
20	101	¹ H NMR (400MHz,DMSO,ppm):7.62-7.60(m,2H),7.57-7.56(m,2H),7.54-7.48(m,1H),4.04-3.44(m,4H),3.33-3.30(m,4H),3.08(s,1H),2.81(s,2H),2.51-2.37(m,6H),1.23(s,1H).
	102	¹ H NMR (400 MHz, Methanol-d ₄ , ppm): 7.88 (s, 1H), 6.25 (s, 1H), 4.37-4.36 (m, 2H), 4.09 (s, 3H), 3.99-3.96 (m, 2H), 3.62-3.60 (m, 2H), 3.53-3.50(m, 1H), 3.37-3.34(m, 1H), 2.92-2.76(m, 4H), 2.63-2.61 (m, 2H), 1.98-1.91 (m, 2H), 1.71-1.69 (m, 4H).
25	103	¹ H NMR (400 MHz, DMSO-d ₆ , ppm): 11.37 (s, 1H), 8.17-8.13 (m, 2H), 7.92 (s, 1H), 4.37-4.35 (m, 2H), 4.00 (s, 3H), 3.83-3.80 (m, 2H), 3.62-3.50 (m, 9H), 3.44-3.42 (m, 3H),3.21 (s, 3H), 1.90-1.70 (m, 2H), 1.51-1.48 (m, 4H).
	104	¹ H NMR (400 MHz, Methanol-d ₄ , ppm): 8.08 (s, 2H), 7.93 (s, 1H), 4.18-4.16 (m, 2H), 4.12 (s, 3H), 3.83-3.75 (m, 4H), 3.72-3.62 (m, 4H), 3.53-3.47 (m, 3H), 3.32-3.29 (m, 1H), 2.26-2.24 (m, 1H), 1.97-1.80 (m, 2H), 1.73-1.71 (m, 1H), 1.67-1.64 (m, 1H), 1.63-1.60 (m, 5H), 1.40-1.36 (m, 1H).
30	105	¹ H NMR (400 MHz, Methanol-d ₄ , ppm): 8.09 (s, 2H), 7.93 (s, 1H),

		4.19-4.16 (m, 2H), 4.12 (s, 3H), 3.84-3.75 (m, 4H), 3.72-3.62 (m, 4H), 3.53-3.48 (m, 3H), 3.32-3.29 (m, 1H), 2.26-2.24 (m, 1H), 1.97-1.80 (m, 2H), 1.74-1.71 (m, 1H), 1.67-1.64 (m, 1H), 1.62-1.60 (m, 5H), 1.40-1.36 (m, 1H).
5	106	¹ H NMR (700 MHz, DMSO-d ₆) δ 11.55 – 11.50 (m, 1H), 7.94 (s, 1H), 7.30 – 7.27 (m, 1H), 6.82 – 6.79 (m, 1H), 6.26 – 6.24 (m, 1H), 4.29 (q, J = 2.7 Hz, 2H), 4.22 – 4.17 (m, 2H), 3.99 (s, 3H), 3.87 (t, J = 5.5 Hz, 2H), 2.95 – 2.88 (m, 2H), 2.57 – 2.54 (m, 2H), 2.37 – 2.32 (m, 1H), 1.76 – 1.72 (m, 2H), 1.50 – 1.43 (m, 2H).
10	107	¹ H NMR (400 MHz, DMSO-d ₆) δ 11.37 – 11.30 (m, 1H), 7.94 (s, 1H), 6.25 – 6.23 (m, 1H), 4.29 (q, J = 2.7 Hz, 2H), 3.99 (s, 3H), 3.87 (t, J = 5.4 Hz, 2H), 3.81 – 3.76 (m, 2H), 3.59 – 3.52 (m, 4H), 3.47 – 3.38 (m, 2H), 2.58 – 2.53 (m, 2H), 1.97 – 1.88 (m, 2H), 1.91 – 1.82 (m, 2H).
	108	¹ H NMR (400 MHz, DMSO-d ₆) δ 11.37 – 11.30 (m, 1H), 7.94 (s, 1H), 6.25 – 6.23 (m, 1H), 4.29 (q, J = 2.7 Hz, 2H), 3.99 (s, 3H), 3.87 (t, J = 5.4 Hz, 2H), 3.81 – 3.76 (m, 2H), 3.59 – 3.52 (m, 4H), 3.47 – 3.38 (m, 2H), 2.58 – 2.53 (m, 2H), 1.97 – 1.88 (m, 2H), 1.91 – 1.82 (m, 2H).
15	109	¹ H NMR (400 MHz, DMSO-d ₆) δ 13.46 – 13.40 (m, 1H), 13.40 – 13.23 (m, 1H), 8.26 – 8.21 (m, 2H), 8.15 (s, 1H), 8.11 – 8.07 (m, 2H), 7.76 – 7.72 (m, 2H), 7.62 – 7.56 (m, 2H), 7.52 – 7.46 (m, 1H), 4.09 (s, 3H).
	110	¹ H NMR (500 MHz, DMSO-d ₆) δ 13.46 – 13.31 (m, 1H), 8.37 – 8.33 (m, 1H), 8.24 – 8.18 (m, 2H), 8.16 – 8.14 (m, 1H), 7.76 – 7.73 (m, 2H), 7.63 – 7.56 (m, 3H), 7.52 – 7.47 (m, 1H), 4.12 – 4.08 (m, 3H).
20	112	¹ H NMR (400 MHz, DMSO-d ₆) δ 11.32 (s, 1H), 7.98 (s, 1H), 7.23 (t, J = 7.8 Hz, 1H), 6.92 ? 6.73 (m, 2H), 6.60 (d, J = 8.9 Hz, 1H), 5.90 (d, J = 5.2 Hz, 1H), 4.02 (s, 3H), 3.71 ? 3.38 (m, 7H), 3.32 (s, 1H), 2.72 (d, J = 5.0 Hz, 3H), 1.83 (s, 2H), 1.50 (s, 4H)
	113	¹ H NMR (400 MHz, DMSO-d ₆) δ 11.41 (s, 1H), 8.13 (s, 1H), 7.30 (d, J = 3.6 Hz, 1H), 6.92 (d, J = 3.5 Hz, 1H), 4.01 (s, 3H), 3.57 (d, J = 47.7 Hz, 7H), 2.52 (s, 3H), 1.84 (s, 2H), 1.51 (s, 4H).
25	115	¹ H NMR (500 MHz, DMSO-d ₆) δ 13.52 – 13.20 (m, 2H), 8.61 – 8.60 (m, 1H), 8.53 (dd, J = 4.8, 1.7 Hz, 1H), 8.47 – 8.45 (m, 1H), 8.27 – 8.24 (m, 3H), 8.11 – 8.08 (m, 2H), 8.03 (d, J = 0.8 Hz, 1H), 7.74 (dt, J = 7.9, 2.0 Hz, 1H), 7.43 – 7.39 (m, 1H), 5.53 (s, 2H), 4.05 (s, 3H).
30	116	¹ H NMR (400 MHz, DMSO-d ₆) δ 13.97 – 12.99 (m, 1H), 12.85 (s, 1H), 8.57 – 8.27 (m, 2H), 8.01 (s, 1H), 6.31 – 6.27 (m, 1H), 4.31 (q, J = 2.8 Hz, 2H), 4.06 – 4.01 (m, 3H), 3.89 (t, J = 5.4 Hz, 2H), 2.61 – 2.55 (m, 2H).
	117	¹ H NMR (500 MHz, DMSO-d ₆) δ 13.50 - 13.46 (m, 1H), 12.89 - 12.87 (m, 1H), 8.61 - 8.58 (m, 1H), 8.25 - 8.21 (m, 1H), 8.11 (s, 1H), 7.74 - 7.71 (m, 2H), 7.60 - 7.56 (m, 2H), 7.50 - 7.46 (m, 1H), 4.08 (s,

		3H).
5	118	¹ H NMR (400MHz,DMSO,ppm):11.96(s,1H),8.14-8.11(m,2H),7.91(s,1H),4.21-4.00(m,2H),3.87-3.85(m,3H),3.73-3.67(m,1H),3.62(s,3H),3.52-3.50(m,4H),3.34-3.31(m,3H),1.80(S,3H),1.78(S,1H),1.60-1.50(m,7H),1.46-1.42(m,1H)
	119	¹ H NMR (400MHz,DMSO,ppm):11.96(s,1H),8.14-8.11(m,2H),7.91(s,1H),4.21-4.00(m,2H),3.87-3.85(m,3H),3.73-3.67(m,1H),3.62(s,3H),3.52-3.50(m,4H),3.34-3.31(m,3H),1.80(S,3H),1.78(S,1H),1.60-1.50(m,7H),1.46-1.42(m,1H)
10	120	¹ H NMR (400 MHz, DMSO-d ₆ , ppm): 11.37 (s, 1H), 10.01 (s, 1H), 8.01 (s, 1H), 7.53-7.49 (m, 2H), 7.41-7.39 (m, 1H), 7.29-7.27 (m, 1H), 4.04 (s, 3H), 3.62-3.45 (m, 8H), 3.08 (s, 3H), 1.90-1.70 (m, 2H), 1.51-1.48 (m, 4H).
	121	¹ H NMR (400 MHz, Methanol-d ₄ , ppm): 7.88 (s, 1H), 6.26 (s, 1H), 4.37-4.36 (m, 2H), 4.09 (s, 3H), 3.98-3.96 (m, 2H), 3.62-3.60 (m, 2H), 3.52-3.50(m, 1H), 3.36-3.33(m, 1H), 2.89-2.72(m, 4H), 2.63-2.61 (m, 2H), 1.98-1.91 (m, 2H), 1.71-1.69 (m, 4H).
15	122	¹ H NMR (400 MHz, Methanol-d ₄ , ppm): 7.88 (s, 1H), 6.26 (s, 1H), 4.37-4.36 (m, 2H), 4.09 (s, 3H), 3.98-3.96 (m, 2H), 3.62-3.60 (m, 2H), 3.52-3.50(m, 1H), 3.36-3.33(m, 1H), 2.89-2.72(m, 4H), 2.63-2.61 (m, 2H), 1.98-1.91 (m, 2H), 1.71-1.61 (m, 4H).
	123	¹ H NMR (400 MHz, DMSO-d ₆ , ppm): 11.57(s, 1H), 8.03 (s, 1H), 7.70-7.68 (m, 2H), 7.57-7.53 (m, 2H), 7.47-7.44 (m, 1H), 4.23-4.20 (m, 2H), 4.04 (s, 3H), 3.04 (s, 3H), 2.99-2.88 (m, 3H), 2.81 (s, 3H), 1.68-1.66 (m, 2H), 1.50-1.46 (m, 2H).
20	124	¹ H NMR (400MHz,DMSO,ppm):11.398(s,1H),8.05-8.02(m,2H),6.78-6.73(m,2H),6.19(s,2H),4.03-3.97(m,3H),3.53-3.31(m,8H),1.50-1.49(m,6H).
	126	¹ H NMR (400MHz,DMSO,ppm):8.66 (s, 1H), 8.24-8.22 (d, J = 8.5 Hz, 2H), 8.04 ? 7.98 (m, 3H), 6.33 ? 6.32 (m, 1H), 4.33-4.32 (m, J = 2.8 Hz, 2H), 4.04-3.90 (m, 3H), 3.89 (t, J = 5.4 Hz, 2H), 3.46-3.31(d, J = 6.5 Hz, 2H), 2.67-2.50 (m, J = 1.8 Hz, 8H), 2.33-1.42(d, J = 5.7 Hz, 7H)
25	127	¹ H NMR (400 MHz, DMSO, ppm): 11.395 (s, 1H), 8.11-8.07 (m, 2H), 6.78-6.70(m, 3H), 4.03 (s, 3H), 3.62-3.31 (m, 8H), 2.50-2.49 (m, 3H), 1.81-1.79(m, 2H), 1.50 (s, 4H).
	129	¹ H NMR (400MHz,DMSO,ppm):13.31(s,1H), 8.21-8.19(m,2H), 8.05(s,1H), 7.57-7.55(m,2H), 6.32(s,1H), 4.44(s,1H), 4.34-4.32(m,2H), 4.04(s,5H), 3.91-3.88(m,2H), 3.31(s,2H), 2.60-2.59(m,2H), 1.60-1.58(m,4H), 1.162(s,3H).
	130	¹ H NMR (400MHz, DMSO, ppm): 11.40 (s, 1H), 11.32 (s, 1H), 8.05

5		(s, 1H), 7.34 (s, 1H), 7.23-7.21 (m, 1H), 7.09-7.06 (m, 1H), 4.04 (s, 3H), 3.53-3.31 (m, 8H), 3.14 (s, 3H), 1.86-1.81 (m, 2H), 1.60-1.50 (m, 4H).
	131	(400MHz,DMSO,ppm):11.6(s,1H), 8.03(s,1H), 7.95(s,1H), 6.25(s,1H), 4.33-4.29(m,4H), 4.05-4.00(m,4H), 3.88-3.85(m,4H), 2.96-2.90(m,2H), 2.55(s,2H), 2.18-2.14(m,2H), 1.64-1.61(m,2H).
	132	¹ H NMR (400 MHz, DMSO-d ₆ , ppm): 7.92 (s, 2H), 6.14 (s, 1H), 4.27-4.25 (m, 2H), 4.01 (s, 3H), 3.95-3.94 (m, 3H), 3.87-3.84 (m, 2H), 3.63-3.50 (m, 6H), 3.45-3.40 (m, 2H), 3.28-3.27 (m, 1H), 1.87-1.75 (m, 2H), 1.60-1.44 (m, 4H).
10	133	(400MHz,DMSO,ppm):11.292(s,1H), 7.62(s,1H), 3.94(s,3H), 3.65-3.31(m,10H), 2.84-2.75(m,3H), 2.03-1.99(m,1H), 1.90-1.69(m,4H), 1.51-1.47(m,5H).
	134	(400MHz,DMSO,ppm):11.27(s,1H), 7.56(s,1H), 3.93(s,3H), 3.62-3.53(m,2H), 3.52-3.39(m,8H), 3.38-3.31(m,3H), 3.24-3.21(m,1H), 2.74-2.68(m,2H), 2.09-1.99(m,1H), 1.98-1.78(m,3H), 1.77-1.45(m,5H), 1.41-1.1.25(m,1H).
15	135	(400 MHz, DMSO-d ₆)9.59 (d, J = 6.9 Hz, 1H), 8.79 (s, 1H), 7.98 (s, 1H), 7.81 (d, J = 9.0 Hz, 1H), 7.58 (d, J = 14.9, 7.2 Hz, 1H), 7.23 (t, J = 6.9 Hz, 1H), 6.31 (s, 1H), 4.33 (q, J = 2.8 Hz, 2H), 4.02 (s, 3H), 3.94 ? 3.84 (m, 2H), 2.58 (s, 2H).
	136	(400MHz , DMSO , ppm) : 11.44-11.39 ,(m , 1H) , 8.28-8.19 (m , 2H) , 6.30 (s , 1H) , 4.54 (s, 2H) , 4.03 (s , 3H) , 3.62-3.32 (m , 8H) , 1.89-1.76 (m , 2H) , 1.50-0.86 (m , 4H).
20	137	(400MHz,DMSO,ppm):11.64(s,1H), 8.03(s,2H), 7.71-7.69(m,2H), 7.57-7.54(m,2H), 7.47-7.44(m,1H), 4.34-4.30(m,2H), 4.04(s,4H), 3.85(s,2H), 2.95-2.89(m,2H), 2.30-2.13(m,2H), 1.63-1.61(m,2H).
	138	¹ H NMR (400 MHz, DMSO-d ₆) 11.39 (s, 1H), 7.95 (d, J = 1.5 Hz, 1H), 7.56 (t, J = 2.5 Hz, 1H), 7.28 (m, J = 8.6, 2.9 Hz, 1H), 5.46 (s, 2H), 4.04 (s, 3H), 3.80 ? 3.39 (m, 8H), 1.86 (d, J = 38.0 Hz, 2H), 1.50 (s, 4H).
25	139	(400MHz,DMSO,ppm):8.57(m,1H)?8.23-8.21(m,2H)?7.96-7.94(m,3H)?6.32(s,1H)?4.33(s,2H)?4.02-3.88(m,5H)?3.31-3.23(m,6H)?2.67-2.51(m,4H)?2.03-2.01(m,2H).
	140	¹ H NMR (400MHz , DMSO , ppm) : 9.21-9.206 ,(m , 1H), 8.61-8.43 (m , 1H) , 8.09-7.95 (m , 1H) , 7 .61-7.58 (m, 1H) , 6.32 (s , 1H) , 4.89-4.83 (m , 1H) , 4.13-3.40 (m , 1H) , 3.62-3.21 (m , 2H) , 3.15-3.00 (m , 5H) , 2.87-2.65 (m , 2H)
30	141	(400MHz , DMSO , ppm) : 11.408 ,(s , 1H) , 8.11-8.00 (m , 1H) , 7.99 (s , 2H) , 7 .82-7.78 (m, 2H) , 4.05 (s , 3H) , 3.62-3.31 (m , 7H) , 1.85-1.83 (m , 2H) , 1.51-1.23 (m , 4H).

5	142	(400MHz , DMSO , ppm) : 11.39(s , 1H) , 7.98 (s , 1H) , 7.57-7.56 (m , 1H) , 7.43-7.40 (s, 1H) , 5.73(s , 2H) , 4.03 (s , 3H) , 3.61-3.31 (m , 8H) , 2.07-1.77 (m , 2H) , 1.50 (s , 4H) .
	143	(400MHz,DMSO,ppm):11.38(s,1H), 8.00-7.99(m,3H), 7.19-7.17(m,1H), 5.58(s,2H), 4.03(s,3H), 3.61-3.31(m,8H), 1.99-1.78(m,2H), 1.50(s,4H).
	144	(400MHz , DMSO , ppm) : 8.10-8.08 ,(m , 2H) , 7.96 (s , 1H) , 7.41-7.39 (m , 2H) , 6.31 (s , 1H) , 4.33 -4.31(m , 2H) , 4.04-4.01 (m , 3H) , 3.90-3.87 (m , 2H) , 3.64-3.31 (m , 2H) , 2.54-2.32 (m , 2H) .
10	145	1H NMR (400 MHz, DMSO-d6, ppm): 11.26 (s, 1H), 7.86 (s, 1H), 6.00 (s, 1H), 3.97 (s, 3H), 3.65-3.62 (m, 2H), 3.52-3.31 (m, 6H), 2.40-2.33 (m, 3H), 1.90-1.76 (m, 4H), 1.71-1.70 (m, 1H), 1.66-1.50 (m, 4H), 1.30-1.20 (m, 1H), 1.10-1.02 (m, 3H).
	146	1H NMR (400 MHz, DMSO-d6, ppm): 11.26 (s, 1H), 7.85 (s, 1H), 6.00 (s, 1H), 3.97 (s, 3H), 3.65-3.62 (m, 2H), 3.52-3.31 (m, 6H), 2.40-2.33 (m, 3H), 1.87-1.82 (m, 4H), 1.68-1.64 (m, 1H), 1.51-1.48 (m, 4H), 1.30-1.20 (m, 1H), 1.10-1.02 (m, 3H).
15	147	(400MHz,DMSO,ppm):11.37(s,1H), 8.02(s,1H), 7.80(s,1H), 7.54-7.29(m,4H), 7.06-7.04(m,1H), 4.03(s,3H), 3.83(s,3H), 3.62-3.49(m,8H), 1.83-1.81(m,2H), 1.50(s,4H).
	148	1H NMR (400 MHz, DMSO-d6) ? 12.66 (s, 1H), 8.78 (s, 1H), 8.05 (s, 1H), 7.63-6.98(m, 1H), 6.31 (s, 1H), 4.32 (s, 2H), 4.03 (s, 3H), 3.89 (s, 2H), 2.59 (s, 2H).
20	149	(400MHz,DMSO,ppm):11.34-11.33(m,1H), 10.19(s,1H), 7.95(s,1H), 7.32-7.24(m,2H), 7.09-7.05(m,1H), 4.02(s,3H), 3.62-3.31(m,8H), 1.81(s,2H), 1.50(s,4H).
	150	(400MHz,DMSO,ppm):11.36(s,1H), 9.67(s,1H), 7.93(s,1H), 7.21-7.17(m,1H), 6.94-6.91(m,1H), 6.87-6.84(m,1H), 4.04(s,3H), 3.61-3.49(m,8H), 1.84-1.80(m,2H),1.50(s,4H).
25	151	1H NMR (400 MHz, DMSO-d6, ppm): 11.25 (s, 1H), 7.84 (s, 1H), 4.82-4.79 (m, 1H), 3.96-3.92 (m, 4H), 3.84-3.78 (m, 3H), 3.66-3.49 (m, 10H), 1.83-1.70 (m, 2H), 1.51-1.48 (m, 4H).
	152	1H NMR (400 MHz, DMSO-d6, ppm): 11.25 (s, 1H), 7.84 (s, 1H), 4.82-4.79 (m, 1H), 3.96-3.92 (m, 4H), 3.84-3.78 (m, 3H), 3.66-3.49 (m, 10H), 1.83-1.70 (m, 2H), 1.51-1.48 (m, 4H).
30	153	(400MHz , DMSO , ppm) : 11.310(s , 1H) , 9.70 (s , 1H) , 7.98 (s , 1H) , 7.34-7.31 (m , 1H) , 7.09-7.06 (m , 2H) , 6.85-6.82 (m , 1H) , 4.03 (s , 3H) , 3.65-3.23 (m , 8H) , 1.82 (s , 2H) , 1.51-1.49 (s , 4H).
	154	1H NMR (300 MHz, DMSO-d6) ? 8.28 (s, 1H), 7.87 (s, 1H), 7.05 (s, 2H), 6.28 (s, 1H), 4.30 (d, J = 2.8 Hz, 2H), 3.98 (s, 3H), 3.87 (t, J =

		5.4 Hz, 2H), 2.70 (s, 2H), 2.56 (s, 2H).
5	155	¹ H NMR (400MHz, DMSO-d ₆ , ppm): 11.06 (s, 1H), 8.63-8.62(m, 2H), 7.29 (s, 1H), 6.91 (s, 1H), 4.05 (s, 3H), 3.63-3.29 (m, 8H), 2.86-2.85 (m, 3H), 2.49-2.47 (m, 2H), 1.82-1.74 (m, 2H), 1.51-1.44 (m, 4H).
	156	¹ H NMR (300 MHz, DMSO-d ₆) ? 9.24 (s, 1H), 8.46 (s, 1H), 8.00 (s, 1H), 7.91 ? 7.81 (m, 2H), 7.56 (dd, J = 8.6, 7.2 Hz, 2H), 7.45 ? 7.35 (m, 1H), 6.32 ? 6.24 (m, 1H), 4.30 (q, J = 2.8 Hz, 2H), 4.02 (s, 3H), 3.87 (t, J = 5.4 Hz, 2H), 2.62 ? 2.52 (m, 2H).
	157	¹ H NMR (300 MHz, DMSO-d ₆) ? 13.12 (s, 1H), 9.46 (s, 1H), 8.72 (d, J = 5.2 Hz, 2H), 8.58 (s, 1H), 8.13 ? 7.79 (m, 3H), 6.27 (s, 1H), 4.30 (s, 2H), 4.15 ? 3.72 (m, 5H), 2.56 (s, 2H).
10	158	¹ H NMR (300 MHz, DMSO-d ₆) ? 12.92 (s, 1H), 12.21 (s, 1H), 8.55 (s, 1H), 8.20 (s, 1H), 7.99 (s, 1H), 7.12 (s, 1H), 6.89 (s, 1H), 6.33 ? 6.19 (m, 1H), 5.40 (s, 2H), 4.30 (q, J = 2.8 Hz, 2H), 4.01 (s, 3H), 3.87 (t, J = 5.4 Hz, 2H), 2.56 (s, 2H).
15	159	(400MHz, DMSO, ppm) : 11.310(s, 1H), 7.986(s, 1H), 7.27-7.24 (m, 1H), 6.85-6.83 (m, 2H), 6.67-6.65(m, 1H), 6.03-6.00 (m, 1H), 4.023 (s, 3H), 3.61 (s, 2H), 3.53-3.50 (m, 5H), 3.40-3.31 (m, 3H), 2.63-2.52 (m, 2H), 2.50-1.82 (m, 6H) .
	160	(400MHz,DMSO,ppm):11.37(s,1H),8.48-8.47(m,1H),8.41-8.40(m,1H),8.04(s,1H),7.60-7.58(m,2H),7.57-7.49(m,2H),7.38-7.37(m,1H),7.11-7.09(m,1H),4.03(s,3H),3.63-3.62(m,2H),3.52-3.49(m,6H),1.82-1.80(s,2H),1.50(s,4H).
20	161	¹ H NMR (400 MHz, DMSO-d ₆) 8.22 (d, J = 8.2 Hz, 2H), 8.06 (d, J = 8.4 Hz, 2H), 7.93 (s, 1H), 4.88 (d, J = 10.1, 2.9 Hz, 1H), 4.01 (s, 4H), 3.94 ? 3.77 (m, 3H), 3.75 ? 3.48 (m, 2H).
	162	(400MHz, DMSO, ppm) : 13.6-13.5(m, 1H), 12.46-12.43(m, 1H), 8.67-8.66 (m, 1H), 8.25-8.23 (m, 2H), 8.17-7.96(m, 2H), 7.48-7.45 (m, 1H), 6.31 (s, 1H), 4.33-4.32 (m, 2H), 4.03 (s, 3H), 3.91-3.88 (m, 2H), 2.67-2.50 (m, 2H) .
25	163	(400MHz,DMSO,ppm):11.37(s,1H),8.31(s,1H),8.17(s,1H),7.95(s,1H),7.33-7.24(m,3H),7.06-7.04(m,2H),4.00(s,3H),3.62-3.32(m,8H),2.12-1.99(s,6H),1.99-1.75(s,2H),1.65-1.35(s,4H),1.35-1.10(s,3H),0.99-0.75(s,1H).
30	164	¹ H NMR (400 MHz, DMSO-d ₆) 13.27 (s, 1H), 8.32 (d, J = 8.4 Hz, 2H), 8.20 (d, J = 8.3 Hz, 2H), 7.97 (d, J = 0.7 Hz, 1H), 7.08 (s, 1H), 4.90 (dd, J = 9.9, 3.0 Hz, 1H), 4.03 (s, 4H), 3.94 ? 3.79 (m, 3H), 3.68 (td, J = 11.6, 2.7 Hz, 1H), 3.59 (dd, J = 11.6, 10.2 Hz, 1H).
	165	(400MHz, DMSO, ppm) : 8.80-8.02(m, 2H), 7.58(m, 1H), 6.30 (s, 3H), 4.68 (s, 1H), 4.33-4.28(m, 2H), 4.10-3.48 (m, 3H), 3.30-3.12 (m, 2H), 2.89-2.42 (m, 2H) .

5	166	(400MHz, DMSO, ppm) : 11.29(s, 1H), 8.32(s, 1H), 8.01-7.94 (m, 2H), 7.24-7.20 (m, 1H), 6.91-6.83(m, 2H), 6.69 (s, 1H), 6.29-6.26 (m, 1H), 4.22-4.21 (m, 2H), 4.02 (s, 3H), 3.62-3.30 (m, 8H), 1.81-1.78 (m, 2H), 1.81-1.50 (m, 4H).
	167	¹ H NMR (400 MHz, DMSO-d ₆) : 8.15 (d, J = 8.2 Hz, 2H), 8.04 (s, 1H), 7.42 (s, 2H), 6.32 (s, 1H), 4.52 (s, 2H), 4.32 (q, J = 2.8 Hz, 2H), 4.04 (s, 3H), 3.89 (t, J = 5.4 Hz, 2H), 3.65 (s, 3H), 2.85 (s, 3H), 2.59 (s, 2H).
	168	(400MHz, DMSO, ppm): 8.01(s, 1H), 7.94(s, 1H), 6.29(s, 1H), 4.32(s, 2H), 4.02(s, 3H), 3.90(m, 2H), 2.65-2.54(m, 2H).
10	169	¹ H NMR (400 MHz, DMSO-d ₆) : 8.22 (d, J = 8.2 Hz, 2H), 8.06 (d, J = 8.4 Hz, 2H), 7.93 (s, 1H), 4.88 (d, J = 10.1, 2.9 Hz, 1H), 4.01 (s, 4H), 3.94 ? 3.77 (m, 3H), 3.75 ? 3.48 (m, 2H).
	170	¹ H NMR (400 MHz, DMSO-d ₆) : 8.22 (d, J = 8.2 Hz, 2H), 8.06 (d, J = 8.4 Hz, 2H), 7.93 (s, 1H), 4.88 (d, J = 10.1, 2.9 Hz, 1H), 4.01 (s, 4H), 3.94 ? 3.77 (m, 3H), 3.75 ? 3.48 (m, 2H).
15	171	¹ H NMR (400MHz, DMSO-d ₆ , ppm): 11.44 (s, 1H), 8.09 (s, 1H), 3.97 (s, 3H), 3.62-3.29 (m, 8H), 1.83-1.80 (m, 2H), 1.60-1.50 (m, 6H).
	172	(400MHz, DMSO, ppm): 11.49(s, 1H), 8.89(m, 1H), 8.39(s, 1H), 8.29(s, 1H), 8.06(m, 1H), 7.80-7.22(m, 3H), 4.07-4.04(m, 3H), 3.62-3.32(m, 8H), 1.98-1.83(s, 2H), 1.61-1.45(m, 4H), 1.28-1.15(m, 1H).
20	173	¹ H NMR (400 MHz, DMSO-d ₆) : 11.32 (s, 1H), 7.93 (s, 1H), 6.23 (tt, J = 2.9, 1.4 Hz, 1H), 4.29 (q, J = 2.8 Hz, 2H), 3.86 (t, J = 5.4 Hz, 2H), 3.73 ? 3.35 (m, 6H), 3.32 (s, 1H), 3.19 (s, 1H), 2.55 (dh, J = 6.0, 3.4, 2.7 Hz, 2H), 1.82 (s, 1H), 1.72 ? 1.45 (m, 5H)
	174	¹ H NMR (400 MHz, DMSO-d ₆) : 11.32 (s, 1H), 7.93 (s, 1H), 6.23 (tt, J = 2.9, 1.4 Hz, 1H), 4.29 (q, J = 2.8 Hz, 2H), 3.86 (t, J = 5.4 Hz, 2H), 3.73 ? 3.35 (m, 6H), 3.32 (s, 1H), 3.19 (s, 1H), 2.55 (dh, J = 6.0, 3.4, 2.7 Hz, 2H), 1.82 (s, 1H), 1.72 ? 1.45 (m, 5H).
25		

Example 2: Preparation of the compounds of the present invention and analytical methods

All solvents used were commercially available and used without further purification. Reactions were typically run using anhydrous solvents under an inert atmosphere

of nitrogen. Flash column chromatography was generally carried out using Silica gel 60 (0.035-0.070 mm particle size).

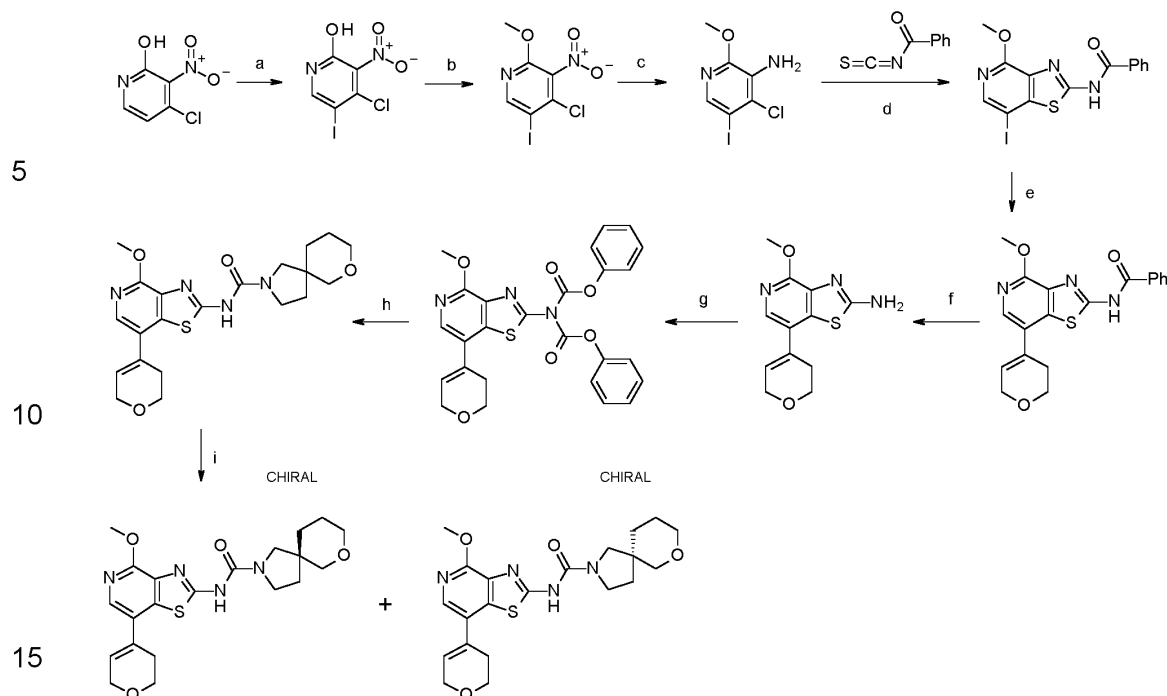
5 All NMR experiments were recorded either on Bruker Mercury Plus 400 NMR Spectrometer equipped with a Bruker 400 BBFO probe at 400 MHz for proton NMR or on Bruker Mercury Plus 300 NMR Spectrometer equipped with a Bruker 300 BBFO probe at 300 MHz for proton NMR. All deuterated solvents contained typically 0.03% to 0.05% v/v tetramethylsilane, which was used as the reference signal (set at $\delta = 0.00$ for both ^1H and ^{13}C).

10 LC-MS analyses were performed on a SHIMADZU LC-MS machine consisting of an UFLC 20-AD system and LCMS 2020 MS detector. The column used was a Shim-pack XR-ODS, 2.2 μm , 3.0 x 50 mm. A linear gradient was applied, starting at 95 % A (A: 0.05% TFA in water) and ending at 100% B (B: 0.05% TFA in acetonitrile) over 2.2 min with a total run time of 3.6 min. The column temperature was at 40°C
15 with the flow rate at 1.0 mL/min. The Diode Array detector was scanned from 200-400 nm. The mass spectrometer was equipped with an electro spray ion source (ES) operated in a positive or negative mode. The mass spectrometer was scanned between m/z 90-900 with a scan time of 0.6 s. If not otherwise stated.

- 20 1. (5R)-N-[7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-7-oxa-2-azaspiro[4.5]decane-2-carboxamide 24
and (5S)-N-[7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-7-oxa-2-azaspiro[4.5]decane-2-carboxamide 25

25

30



a. 4-chloro-5-iodo-3-nitropyridin-2-ol

Into a 250-mL round-bottom flask was placed 4-chloro-3-nitropyridin-2-ol (10.0 g, 54.4 mmol, 95%), N-iodo-succinimide (NIS, 14.2 g, 59.9 mmol, 95%) in acetonitrile (115 mL). The solution was stirred for 1 h overnight at 80°C in an oil bath. The mixture was concentrated and the precipitate formed collected by filtration. The residue was washed with twice with petrol ether (500 mL) dried under vacuum at 60°C overnight. This resulted in 4-chloro-5-iodo-3-nitropyridin-2-ol (16.5 g, 97.9%, 97% purity) as a yellow solid. MS: $m/z = 300.9$ $[M+H]^+$.

b. 4-chloro-5-iodo-2-methoxy-3-nitropyridine

Into a 500-mL round-bottom flask was placed 4-chloro-5-iodo-3-nitropyridin-2-ol (16.5 g, 53.3 mmol, 97%), Ag_2CO_3 (15.5 g, 53.3 mmol, 95%) in toluene (310 mL). To this suspension CH_3I (15.9 g, 107 mmol, 95%) was added at 50°C and the mixture was stirred at 80°C for 4 h. The precipitate was collected by filtration and discarded. The filtrate was evaporated to dryness under vacuum and the residue purified by silica gel chromatography with ethyl acetate/petroleum ether (15:85).

This resulted in 4-chloro-5-iodo-2-methoxy-3-nitropyridine (9.90 g, 52.6%, 89% purity) as a light yellow solid. MS: m/z = 315.5 $[M+H]^+$.

c. 4-chloro-5-iodo-2-methoxypyridin-3-amine

5 Into a 250-mL 3-necked round-bottom flask was placed 4-chloro-5-iodo-2-methoxy-3-nitropyridine (9.90 g, 28.0 mmol, 89%), iron (16.5 g, 281 mmol, 95%) and NH_4Cl (9.40 g, 174 mmol, 99%) in ethanol (152 mL) and water (30 mL). The mixture was stirred for 2 h at 80°C in an oil bath. The reaction mixture was filtered over Celite, washed with ethanol and the mother liquor was concentrated to dryness. The residue was stirred for 30 min. with 100 mL water at 60°C and dried in vacuo. This resulted
10 in 4-chloro-5-iodo-2-methoxypyridin-3-amine (7.20 g, 75%, 83% purity) as an off-white solid. It was used without further purification in the next step. MS: m/z = 285.9 $[M+H]^+$.

d. N-[7-iodo-4-methoxy-[1,3]thiazolo[4,5-c]pyridin-2-yl]benzamide

15 Into a 500-mL round-bottom flask was placed 4-chloro-5-iodo-2-methoxypyridin-3-amine (7.20 g, 21.0 mmol, 83%) in acetone (150 mL) and benzoyl isothiocyanate (5.21 g, 31.5 mmol, 99%) was added dropwise at room temperature. The solution was stirred for 1 h at 50 °C in an oil bath. The solids were collected by filtration, washed with acetone and dried in vacuo to give N-[7-iodo-4-methoxy-
20 [1,3]thiazolo[4,5-c]pyridin-2-yl]benzamide (8.73 g, 91%, 90% purity) as a white solid. MS: m/z = 412.2 $[M+H]^+$.

e. N-[7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-[1,3]thiazolo[4,5-c]pyridin-2-yl]benzamide

To a solution of N-[7-iodo-4-methoxy-[1,3]thiazolo[4,5-c]pyridin-2-yl]benzamide
25 (6.00 g, 13.1 mmol, 90%) and 2-(3,6-dihydro-2H-pyran-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (6.13 g, 27.7 mmol, 95%) in dioxane (200 mL) and water (40.00 mL) were added NaOH (2.90 g, 68.9 mmol, 95%) and $Pd(dppf)Cl_2^*$ dichloromethane (1.20 g, 1.40 mmol, 95%). After stirring for 1 h at 100°C under a nitrogen atmosphere, the mixture was concentrated to dryness under vacuo. The residue was purified by silica gel chromatography with ethyl acetate/hexane (95:5).
30 This resulted in 3.32 g (62%, 90% purity) of N-[7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-[1,3]thiazolo[4,5-c]pyridin-2-yl]benzamide as colorless solid. MS: m/z = 368.1 $[M+H]^+$.

f. 7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-[1,3]thiazolo[4,5-c]pyridin-2-amine

To a stirred mixture of N-[7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-[1,3]thiazolo[4,5-c]pyridin-2-yl]benzamide (3.27 g, 8.00 mmol, 90%) in water/methanol (1:1, 300 mL) was added NaOH (3.36 g, 80.0 mmol, 95%) at room temperature under nitrogen atmosphere. The mixture was stirred for overnight at 90°C under nitrogen atmosphere and evaporated to dryness. The residue was taken up in water and extracted 3 times with dichloromethane (100 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and evaporated to dryness. The residue was purified by silica gel column chromatography, eluted with petrol ether/ethyl acetate (1:1) to afford 7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-[1,3]thiazolo[4,5-c]pyridin-2-amine (1.50 g, 68%, 96% purity) as a light brownish solid. MS: *m/z* = 264.1 [M+H]⁺.

g. phenyl N-[7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-[1,3]thiazolo[4,5c]pyridin-2-yl]-N-(phenoxycarbonyl)carbamate

To a stirred solution of 7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-[1,3]thiazolo[4,5-c]pyridin-2-amine (600 mg, 2.19 mmol, 96%) and phenyl chloroformate (1.81 g, 11.0 mmol, 95%) in THF (50 mL) was added K₂CO₃ (1.59 g, 11.0 mmol, 95%) and pyridine (913 mg, 11.0 mmol, 95%) at room temperature under nitrogen atmosphere. The mixture was stirred for 6 h at 50° and then after re-cooling to room temperature quenched by the addition of water (300 mL). The mixture was extracted 3 times with dichloromethane (200 mL), the combined organic layers were washed once with brine (200 mL), dried over anhydrous Na₂SO₄, filtered, and evaporated to dryness under reduced pressure. This resulted in phenyl N-[7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-[1,3]thiazolo[4,5-c]pyridin-2-yl]-N-(phenoxycarbonyl)carbamate (1.00 g, 69%, 76% purity) as a light yellow solid. The crude product was used in the next step directly without further purification. MS: *m/z* = 504.1 [M+H]⁺.

h. N-[7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-[1,3]thiazolo[4,5-c]pyridin-2-yl]-7-oxa-2-azaspiro[4.5]decane-2-carboxamide

To a mixture of phenyl N-[7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-[1,3]thiazolo[4,5-c]pyridin-2-yl]-N-(phenoxycarbonyl)carbamate (1.00 g, 1.52 mmol,

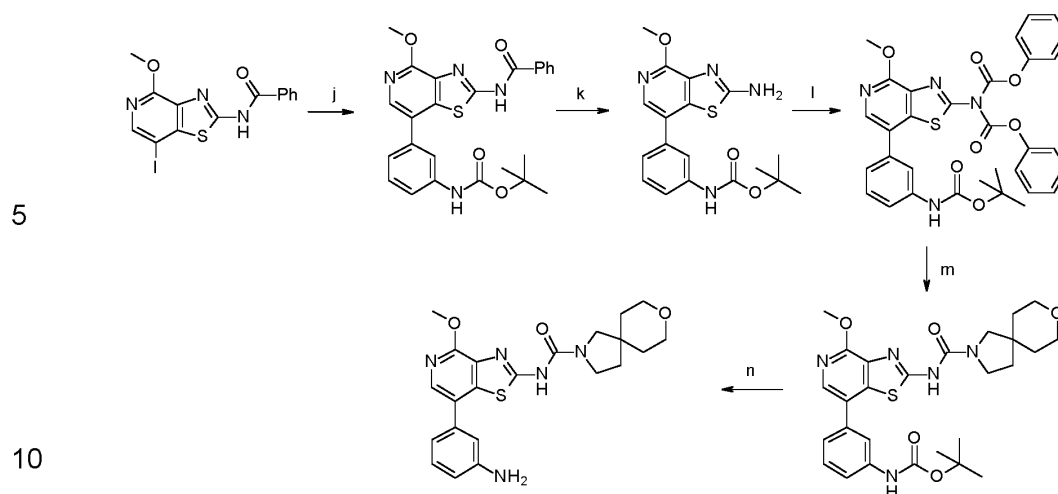
76.) and bis(7-oxa-2-azaspiro[4.5]decane), oxalic acid (1.19 g, 3.03 mmol, 95%) in THF (50 mL) was added diisopropylethyl amine (1.24 g, 9.09 mmol, 95%) at room temperature under nitrogen atmosphere. The mixture was stirred for 1 h at 60°. After re-cooling to room temperature, the mixture was extracted twice with dichloromethane (100 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and evaporated to dryness. The residue was purified by silica gel column chromatography, eluted with petrol ether/ethyl acetate (1:1) to afford N-[7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-[1,3]thiazolo[4,5-c]pyridin-2-yl]-7-oxa-2-azaspiro[4.5]decane-2-carboxamide (600 mg, 92%) as a white solid. HPLC: 99.9 % purity, RT = 1.17 min. MS: m/z = 431.1 [M+H]⁺. ¹H NMR (300 MHz, DMSO-d₆) δ 11.37 (s, 1H), 7.95 (s, 1H), 6.25 (s, 1H), 4.30-4.29 (m, 2H), 3.99 (s, 3H), 3.89 (t, J=5.4Hz, 2H), 3.61-3.29 (m, 8H), 2.55-2.51 (m, 2H), 1.82-1.54 (m, 6H).

i. **(5R)-N-[7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-7-oxa-2-azaspiro[4.5]decane-2-carboxamide 24**
and (5S)-N-[7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-7-oxa-2-azaspiro[4.5]decane-2-carboxamide 25

N-[7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-[1,3]thiazolo[4,5-c]pyridin-2-yl]-7-oxa-2-azaspiro[4.5]decane-2-carboxamide (450 mg, 1.044 mmol, 1 equiv, 99.9%) was purified by chiral-preparative HPLC (Preparative HPLC-032, column: ChiralPak IA, 2*25cm, 5 μm; mobile phase, dichloromethane:ethanol (20:80); detector, UV). This resulted in (5R)-N-[7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-[1,3]thiazolo[4,5-c]pyridin-2-yl]-7-oxa-2-azaspiro[4.5]decane-2-carboxamide (178 mg, 39%) as a white solid. HPLC: 99.7 % purity, RT (chiral) = 3.86 min, 100% ee. MS: m/z = 431.2 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 11.36 (s, 1H), 7.94 (s, 1H), 6.24 (s, 1H), 4.29-4.27 (m, 2H), 3.97 (s, 3H), 3.88 (t, J=5.2 Hz, 2H), 3.51-3.19 (m, 8H), 2.55-2.50 (m, 2H), 1.83-1.53 (m, 6H) and (5S)-N-[7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-[1,3]thiazolo[4,5-c]pyridin-2-yl]-7-oxa-2-azaspiro[4.5]decane-2-carboxamide (171 mg, 38%) as a white solid. HPLC: 99.8 % purity, RT (chiral) = 5.23 min, 99.9% ee. MS: m/z = 431.2 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 11.35 (s, 1H), 7.94 (s, 1H), 6.24 (s, 1H), 4.29-4.28 (m, 2H), 3.99 (s, 3H), 3.88-3.85 (m, 2H), 3.61-3.29 (m, 8H), 2.55-2.50 (m, 2H), 1.83-1.53 (m, 6H).

2. **N-[7-(3-aminophenyl)-4-methoxy-[1,3]thiazolo[4,5-c]pyridin-2-yl]-8-oxa-2-azaspiro[4.5]decane-2-carboxamide 39**

119



j. N-[3-(2-benzamido-4-methoxy-1,3-benzothiazol-7-yl)phenyl]carbamate

To a solution of N-(7-iodo-4-methoxy-1,3-benzothiazol-2-yl)benzamide (400 mg, 0.878 mmol, 90%) and (3-[[[(tert-butoxy)carbonyl]amino]phenyl]boronic acid (328 mg, 1.32 mmol, 95%) in 1,4-dioxane and water were added NaOH (369 mg, 8.78 mmol, 95%) and Pd(dppf)Cl₂* dichloromethane (113 mg, 0.132 mmol, 95%) under inert atmosphere of nitrogen. After stirring for overnight at 100°C under a nitrogen atmosphere, the mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with petrol ether/ethyl acetate (0-100%, 40min) to afford tert-butyl N-[3-(2-benzamido-4-methoxy-1,3-benzothiazol-7-yl)phenyl]carbamate (390 mg, 86%, 92% purity) as a yellow solid. MS: m/z = 477.0 [M+H]⁺.

k. tert-butyl N-[3-(2-amino-4-methoxy-thiazolo[4,5-c]pyridin-7-yl)phenyl]carbamate

To a stirred solution of tert-butyl N-[3-(2-benzamido-4-methoxy-[1,3]thiazolo[4,5-c]pyridin-7-yl)phenyl]carbamate (390 mg, 0.753 mmol, 92%) in MeOH was added NaOH (318 mg, 7.55 mmol, 95%) dissolved in water (10 mL) dropwise at room temperature. The mixture was stirred at 90°C overnight, was concentrated under vacuum and the aqueous layer extracted 3 time with dichloromethane (30mL). The combined organic layers were dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure to dryness to yield in tert-butyl N-[3-(2-amino-4-methoxy-thiazolo[4,5-c]pyridin-7-yl)phenyl]carbamate (220 mg, 54%,

69% purity) as a yellow solid. The crude product was used in the next step directly without further purification. MS: $m/z = 372.9$ $[M+H]^+$.

l. Phenyl N-[7-(3-[[tert-butoxy)carbonyl]amino]phenyl)-4-methoxy-[1,3]thiazolo[4,5-c]pyridin-2-yl]-N-(phenoxycarbonyl)carbamate

To a stirred mixture of tert-butyl N-(3-[2-amino-4-methoxy-[1,3]thiazolo[4,5-c]pyridin-7-yl]phenyl)carbamate (220 mg, 0.405 mmol, 69%) and K_2CO_3 (294 mg, 2.02 mmol, 95%) in THF (15 mL) were added phenyl carbonochloridate (333 mg, 2.02 mmol, 95%) and pyridine (168 mg, 2.02 mmol, 95%) dropwise at room temperature under nitrogen atmosphere. The mixture was stirred additional 4h at 50°. The reaction mixture was concentrated under vacuum, diluted with water (30mL) and extracted 3 times with dichloromethane (30 mL). The combined organic layers were dried over anhydrous Na_2SO_4 . After filtration, the filtrate was concentrated under reduced pressure to yield in phenyl N-[7-(3-[[tert-butoxy)carbonyl]amino]phenyl)-4-methoxy-[1,3]thiazolo[4,5-c]pyridin-2-yl]-N-(phenoxycarbonyl)carbamate (350 mg, 74%, 52% purity) as a yellow solid. The crude product was used in the next step directly without further purification. MS: $m/z = 613.3$ $[M+H]^+$.

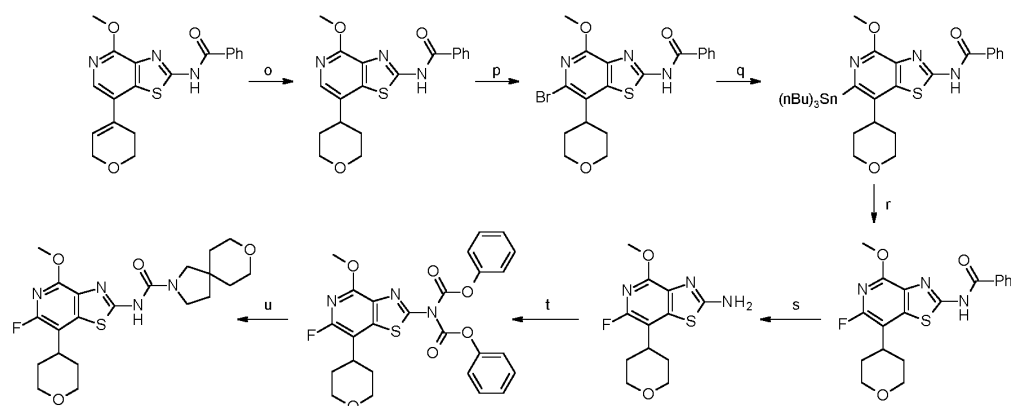
m. N-[4-methoxy-7-(1-methyl-1H-pyrazol-4-yl)-[1,3]thiazolo[4,5-c]pyridin-2-yl]-4-(methoxymethyl)benzamide, 14

To a stirred mixture of phenyl N-[7-(3-[[tert-butoxy)carbonyl]amino]phenyl)-4-methoxy-[1,3]thiazolo[4,5-c]pyridin-2-yl]-N-(phenoxycarbonyl)carbamate (350 mg, 0.297 mmol, 52%) and 8-oxa-2-azaspiro[4.5]decane hydrochloride (111 mg, 0.594 mmol, 95%) in THF was added diisopropylethylamine (242 mg, 1.78 mmol, 95%) dropwise at room temperature under nitrogen atmosphere. The mixture was stirred overnight at 60° and then concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with petrol ether/ethyl acetate (1:1) to afford tert-butyl N-[3-[4-methoxy-2-([8-oxa-2-azaspiro[4.5]decane-2-carbonyl]amino)-[1,3]thiazolo[4,5-c]pyridin-7-yl]phenyl]carbamate (176 mg, 89%, 81% purity) as a yellow solid. MS: $m/z = 540.3$ $[M+H]^+$.

n. N-[7-(3-aminophenyl)-4-methoxy-[1,3]thiazolo[4,5-c]pyridin-2-yl]-8-oxa-2-azaspiro[4.5]decane-2-carboxamide 39

To a stirred mixture of tert-butyl N-[3-[4-methoxy-2-([8-oxa-2-azaspiro[4.5]decane-2-carbonyl)amino]-1,3]thiazolo[4,5-c]pyridin-7-yl]phenyl]carbamate (176 mg, 0.264 mmol, 81%) in MeOH was added 4 N HCl solution in 1,4-dioxane (2.00 mL, 8.00 mmol, 95%) dropwise at 0°C. The mixture was stirred additional 2h at room temperature, concentrated to dryness and purified by preparative HPLC (2#SHIMADZU (HPLC-01), column: XBridge Prep OBD C18 Column, 30x150mm 5 μ m; mobile phase: water/ACN (30% Phase B up to 60% in 8 min); detector, 254 UV) to yield in N-[7-(3-aminophenyl)-4-methoxy-1,3]thiazolo[4,5-c]pyridin-2-yl]-8-oxa-2-azaspiro[4.5]decane-2-carboxamide (60.0 mg, 80%, 99% purity) as white solid. HPLC: 99.0 % purity, RT = 3.19 min. MS: m/z = 440.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆, ppm) : 11.31 (s, 1H), 7.93 (s, 1H), 7.16 (t, J = 7.8 Hz, 1H), 6.84 (t, J = 2.0 Hz, 1H), 6.78 - 6.73 (m, 1H), 6.66 - 6.59 (m, 1H), 5.30 (s, 2H), 4.02 (s, 3H), 3.69 - 3.44 (m, 4H), 1.81 (s, 2H), 1.50 (t, J = 5.4 Hz, 4H).

3. N-(6-fluoro-4-methoxy-7-tetrahydropyran-4-yl-thiazolo[4,5-c]pyridin-2-yl)-8-oxa-2-azaspiro[4.5]decane-2-carboxamide



o. N-[4-methoxy-7-(oxan-4-yl)-1,3]thiazolo[4,5-c]pyridin-2-yl]benzamide

To a solution of N-[7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-1,3]thiazolo[4,5-c]pyridin-2-yl]benzamide (4.10 g, 9.90 mmol, 89%) in 100 mL MeOH was added Pd/C (10%, 19.6g) under nitrogen atmosphere in a 500 mL round-bottom flask. The mixture was stirred at 50°C for 3 days under hydrogen atmosphere, filtered through a Celite pad and concentrated under reduced pressure to dryness. The residue was purified by silica gel column chromatography, eluted with petrol ether/ethyl acetate

(1:1) to afford N-[4-methoxy-7-(oxan-4-yl)-[1,3]thiazolo[4,5-c]pyridin-2-yl]benzamide (2.60 g, 54%, 76% purity) as a yellow solid. MS: $m/z = 370.1$ $[M+H]^+$.

p. N-[6-bromo-4-methoxy-7-(oxan-4-yl)-[1,3]thiazolo[4,5-c]pyridin-2-yl]benzamide

5

Into a 50-mL round-bottom flask, was placed N-[4-methoxy-7-(oxan-4-yl)-[1,3]thiazolo[4,5-c]pyridin-2-yl]benzamide (2.60 g, 5.34 mmol, 76%), N-bromosuccinimide (1.20 g, 6.40 mmol, 95%) in DMF (30 mL). The resulting solution was stirred 18 h at room temperature. The reaction was then stopped by the addition of water and concentrated to dryness. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (0-50%) to obtain N-[6-bromo-4-methoxy-7-(oxan-4-yl)-[1,3]thiazolo[4,5-c]pyridin-2-yl]benzamide (2.50 g, 92%, 88 purity) as a yellow solid. MS: $m/z = 449.1$ $[M+H]^+$.

10

q. N-[4-methoxy-7-(oxan-4-yl)-6-(trimethylstannyl)-[1,3]thiazolo[4,5-c]pyridin-2-yl]benzamide

15

Into a 50-mL pressure tank reactor purged and maintained with an inert atmosphere of nitrogen was placed N-[6-bromo-4-methoxy-7-(oxan-4-yl)-[1,3]thiazolo[4,5-c]pyridin-2-yl]benzamide (2.50 g, 4.92 mmol, 88%), $Pd(PPh_3)_4$ (1.44 g, 1.18 mmol, 95%) and hexamethyldistannane (1.70 g, 4.92 mmol, 95%) in dioxane (35 mL). The resulting mixture was stirred for 1 h at 110°C. The reaction was then stopped by the addition of water and concentrated to dryness. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (0-50%). This resulted in 2.30 g (70%, 79% purity) of N-[4-methoxy-7-(oxan-4-yl)-6-(trimethylstannyl)-[1,3]thiazolo[4,5-c]pyridin-2-yl]benzamide as a white solid. MS: $m/z = 449.1$ $[M+H]^+$.

20

r. N-[6-fluoro-4-methoxy-7-(oxan-4-yl)-[1,3]thiazolo[4,5-c]pyridin-2-yl]benzamide

25

Into a 100-mL round-bottom flask was placed N-[4-methoxy-7-(oxan-4-yl)-6-(trimethylstannyl)-[1,3]thiazolo[4,5-c]pyridin-2-yl]benzamide (2.30 g, 3.43 mmol, 79%), Selectfluor® (2.56 g, 6.85 mmol, 95%) in acetonitrile (50 mL). The resulting solution was stirred for 18 h at room temperature. The reaction was then stopped by the addition of water and concentrated to dryness. The residue was applied onto a silica gel column with ethyl acetate/hexane (0-50%). This resulted in 1.50 g (91%,

30

81% purity) of N-[6-fluoro-4-methoxy-7-(oxan-4-yl)-[1,3]thiazolo[4,5-c]pyridin-2-yl]benzamide as a white solid. MS: m/z = 388.1 $[M+H]^+$.

s. 6-fluoro-4-methoxy-7-(oxan-4-yl)-[1,3]thiazolo[4,5-c]pyridin-2-amine

5 Into a 20-mL sealed tube purged and maintained with an inert atmosphere of nitrogen, was placed N-[6-fluoro-4-methoxy-7-(oxan-4-yl)-[1,3]thiazolo[4,5-c]pyridin-2-yl]benzamide (1.50 g, 3.12 mmol, 81%) in MeOH (20 mL). NaOH (1.27 g, 31.2 mmol, 98%) dissolved in water (20 mL) was added at rt and the resulting solution was stirred for 16 h at 100°C. The resulting mixture was concentrated and the aqueous solution extracted 3 times with 100 mL of dichloromethane. After filtration
10 the filtrate was evaporated to dryness and used without further purification to result in 6-fluoro-4-methoxy-7-(oxan-4-yl)-[1,3]thiazolo[4,5-c]pyridin-2-amine (320 mg, 32%, 89% purity) as an off-white solid. MS: m/z = 284.1 $[M+H]^+$.

t. Phenyl N-[6-fluoro-4-methoxy-7-(oxan-4-yl)-[1,3]thiazolo[4,5-c]pyridin-2-yl]-N-(phenoxycarbonyl)carbamate

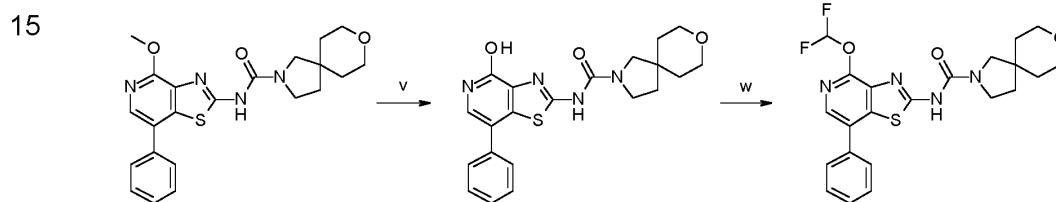
15 To a mixture of 6-fluoro-4-methoxy-7-(oxan-4-yl)-[1,3]thiazolo[4,5-c]pyridin-2-amine (25 mg, 0.078 mmol, 89%) and K_2CO_3 (56.9 mg, 0.391 mmol, 95%) in THF (3.00 mL) was added phenyl chloroformate (64.5 mg, 0.391 mmol, 95%) and pyridine (32.6 mg, 0.391 mmol, 95%) dropwise at room temperature. The resulting mixture was stirred for 6 h at 50°C under nitrogen atmosphere. The reaction was stopped
20 by the addition of water (10 mL) and the resulting mixture was extracted twice with dichloromethane (10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4 , filtered and evaporated to dryness under reduced pressure to obtain N-[6-fluoro-4-methoxy-7-(oxan-4-yl)-[1,3]thiazolo[4,5-c]pyridin-2-yl]-N-(phenoxycarbonyl)carbamate (60.0 mg, 73%, 50% purity). The
25 crude product was used in the next step directly without further purification. MS: m/z = 524.1 $[M+H]^+$.

u. N-[6-fluoro-4-methoxy-7-(oxan-4-yl)-[1,3]thiazolo[4,5-c]pyridin-2-yl]-8-oxa-2-azaspiro[4.5]decane-2-carboxamide

30 To a mixture of phenyl N-[6-fluoro-4-methoxy-7-(oxan-4-yl)-[1,3]thiazolo[4,5-c]pyridin-2-yl]-N-(phenoxycarbonyl)carbamate (50 mg, 0.047 mmol, 50%) and 8-oxa-2-azaspiro[4.5]decane hydrochloride (26.5 mg, 0.142 mmol, 95%) in THF (3.00 mL) was added diisopropylethylamine (38.6 mg, 0.284 mmol, 95%) at room

temperature. The resulting mixture was stirred for 16 h at 60°C under nitrogen atmosphere. The mixture was diluted with water (10 mL) and extracted 3 times with dichloromethane (10 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and evaporated to dryness under reduced pressure. The crude product was purified by preparative HPLC (2#SHIMADZU (HPLC-01): column: XBridge Prep OBD C18 30x150 mm, 5 µm; mobile phase: water/acetonitrile, detector: UV). This resulted in N-[6-fluoro-4-methoxy-7-(oxan-4-yl)-[1,3]thiazolo[4,5-c]pyridin-2-yl]-8-oxa-2-azaspiro[4.5]decane-2-carboxamide (12.4 mg, 57%) as a light yellow solid. HPLC: 97.9% purity, RT = 5.93 min. MS: m/z = 451.2 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆, ppm): 11.31 (s, 1H), 3.99-3.94 (m, 5H), 3.61-3.45 (m, 10H), 3.12 (t, J=12.4 Hz, 1H), 2.03 (q, J=12.5 Hz, 2H), 1.82 (s, 2H), 1.65-1.62 (m, 2H), 1.50 (s, 4H).

4. N-[5-(difluoromethyl)-4-oxo-7-phenyl-5λ4-[1,3]thiazolo[4,5-c]pyridin-2-yl]-8-oxa-2-azaspiro[4.5]decane-2-carboxamide



v N-[4-hydroxy-7-phenyl-[1,3]thiazolo[4,5-c]pyridin-2-yl]-8-oxa-2-azaspiro[4.5]decane-2-carboxamide

20 Into a 25-mL round-bottom flask, was placed N-[4-methoxy-7-phenyl-[1,3]thiazolo[4,5-c]pyridin-2-yl]-8-oxa-2-azaspiro[4.5]decane-2-carboxamide (200 mg, 0.458 mmol, 97%), in dichloromethane (8 mL). BBr₃ (0.138 mL, 0.138 mmol, 1M in dichloromethane) was added dropwise at 0°C and the resulting solution was stirred additional 2 hr at 0°C. The reaction was then stopped by the addition of ice water. The mixture was extracted 3 times with dichloromethane (10 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and evaporated to dryness under reduced pressure. The residue was applied onto a silica gel column with dichloromethane/methanol (0-30%) to result in 150 mg (78%, 98% purity) of N-[4-hydroxy-7-phenyl-[1,3]thiazolo[4,5-c]pyridin-2-yl]-8-oxa-2-azaspiro[4.5]decane-2-carboxamide as a white solid. MS: m/z = 411.2 [M+H]⁺.

w N-[5-(difluoromethyl)-4-oxo-7-phenyl-5lambda4-[1,3]thiazolo[4,5-c]pyridin-2-yl]-8-oxa-2-azaspiro[4.5]decane-2-carboxamide

Into a 50-mL sealed tube purged and maintained with an inert atmosphere of nitrogen was placed N-[4-hydroxy-7-phenyl-[1,3]thiazolo[4,5-c]pyridin-2-yl]-8-oxa-2-azaspiro[4.5]decane-2-carboxamide (100 mg, 0.238 mmol, 98%), anhydrous Na₂SO₄ (3.37 mg, 0.024 mmol, 98%) in acetonitrile (5 mL). To this mixture 2,2-difluoro-2-(fluorosulfonyl)acetic acid (50.8 mg, 0.285 mmol, 98%) was added at room temperature and the resulting solution was stirred additional 3 h at room temperature. The reaction was then stopped by the addition of water (20 mL). The mixture was extracted 3 times with dichloromethane (10 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and evaporated to dryness under reduced pressure. The crude product was purified by preparative HPLC (2#SHIMADZU (HPLC-01): column; Xselect CSH OBD Column 30*150 mm, 5µm, mobile phase: water/acetonitrile; detector: UV). This resulted in N-[5-(difluoromethyl)-4-oxo-7-phenyl-5lambda4-[1,3]thiazolo[4,5-c]pyridin-2-yl]-8-oxa-2-azaspiro[4.5]decane-2-carboxamide (20.0 mg, 17%) as a white solid. Mp = 225-226°C. HPLC: 95.1% purity, RT = 6.27 min. MS: m/z = 461.2 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆, ppm) 11.57 (s, 1H), 8.08 (d, J = 8.6 Hz, 1H), 7.89 (s, 1H), 7.72 (d, J = 7.9 Hz, 2H), 7.54 (dt, J = 32.6, 7.5 Hz, 3H), 3.52 (s, 7H), 3.30 (s, 1H), 1.81 (d, J = 38.2 Hz, 2H), 1.50 (s, 4H).

Example 3: Testing compounds of the present invention for inhibitory activities against human adenosine receptors in recombinant cells.

The functional activities of human A_{2A}, A_{2B}, A₁ and A₃ receptors were determined by quantification of cAMP, being the second messenger for adenosine receptors. For this purpose recombinant HEK293 cells, expressing either human A_{2A} or A_{2B} receptors (both G_s coupled) were seeded into 394-well microtiter plates, test compounds and agonist (NECA) were added. After a 15 min incubation, HTRF reagents (cAMP dynamic 2, Cis Bio) were added and the cellular cAMP levels were determined using the ENVISION (Perkin Elmer) plate reader.

For human A₁ and A₃ receptors, recombinant CHO cells, expressing either A₁ or A₃-receptor, were used. As both receptors couple to Gi proteins, the assay protocol was adapted:

Cells were seeded into 384-well plates, forskolin, test compounds and agonists (CPA for A₁- and IB-MECA for A₃-receptor) were added. After 30 min incubation, HTRF reagents (cAMP dynamic 2, Cis Bio) were added and the cellular cAMP levels were determined using the ENVISION (Perkin Elmer) plate reader. Obtained raw data were normalized against the inhibitor control and the neural control (DMSO) and the normalized data were fitted using GeneData software.

The compounds of the present invention show a high selectivity for adenosine A_{2A} and A_{2B} receptors over adenosine A₁ and A₃ receptors (see e.g. the data of some examples of the compounds of the present invention in table 4)

Particularly, in contrast to the known adenosine A_{2A} receptor antagonist Tozadenant and similar benzothiazole derivatives (see table 5), the compounds of the present invention surprisingly show an A_{2A}/A_{2B} dual activity (see table 4) which is preferred for the treatment and/or prevention of hyperproliferative and infectious diseases and disorders as it is disclosed above or the compounds of the present invention show at least a high A_{2A} inhibitory activity together with the other surprising advantages disclosed herein leading to a high efficacy in the treatment and/or prevention of hyperproliferative and infectious diseases and disorders.

Table 4 – Compounds of the present invention

No.	Functional A _{2A} receptor activity, HEK293, cAMP, IC ₅₀ [μM]	Functional A _{2B} receptor activity, HEK293, cAMP, IC ₅₀ [μM]	Functional A ₁ receptor activity, CHO, cAMP, IC ₅₀ [μM]	Functional A ₃ receptor activity, CHO, cAMP, IC ₅₀ [μM]
1	A	B	D	D
3	A	A	C	D
4	A	A	D	C
6	A	A	D	C
7	A	A	D	D
9	A	B	D	D

5	10	A	B	D	D
	11	A	A	D	D
	12	A	A	C	D
	13	A	A	C	D
	15	A	A	D	D
10	16	A	B	D	D
	17	A	A	C	D
	19	A	B	D	D
	20	A	A	D	D
	22	A	A	C	C
15	23	A	A	C	D
	24	A	B	C	D
	25	A	A	D	D
	26	A	B	D	D
	27	A	A	C	D
20	28	A	B	C	C
	29	A	A	D	D
	31	A	B	D	D
	32	A	A	B	D
	33	A	B	D	D
25	34	A	B	D	D
	35	A	B	D	D
	37	A	B	D	D
	38	A	A	D	D
	39	A	A	D	D
30	40	B	B	D	D
	43	A	B	C	D
	44	B	B	D	D
	45	B	B	D	D
	47	A	A	D	D
	48	A	A	D	D
	50	A	A	D	D
	52	A	A	D	D
	54	A	A	D	D
	59	A	B	C	D
	60	A	A	C	C
	61	A	A	C	D
	62	A	B	D	D
	63	A	B	C	D
	64	A	A	C	D
	65	A	A	B	D
	67	A	B	C	D

128

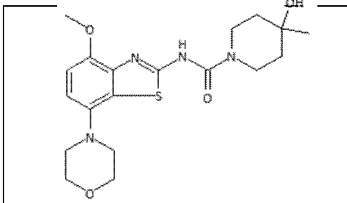
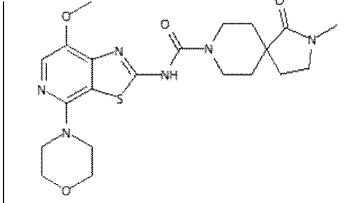
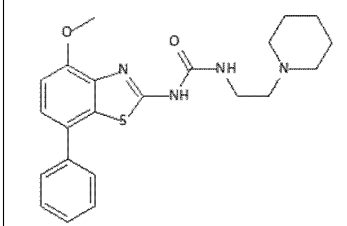
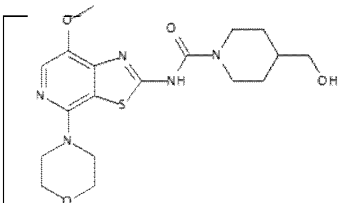
5	68	A	A		D
	69	A	A	B	C
	70	A	C	D	D
	71	A	A	C	D
	72	A	A	C	D
10	73	A	B	D	D
	74	A	B	C	D
	75	A	B	D	D
	76	A	A	B	D
	77	A	C	D	D
15	78	A	C	D	D
	79	A	B	C	D
	80	A	B	D	D
	81	A	A	C	D
	82	A	A	B	D
20	83	A	A	C	D
	84	A	B	B	D
	88	A	B	D	D
	89	A	B	D	D
	90	A	A	D	D
25	91	A	A	D	D
	92	A	A	B	C
	94	A	B	D	D
	95	A	A	C	C
	97	A	B	D	D
30	98	A	B	D	D
	99	A	A	D	D
	100	A	A	C	D
	101	A	B	D	D
	102	A	B	D	D
	103	A	B	C	D
	104	A	B		D
	105	A	B		D
	106	A	B	C	D
	108	A	A	C	D
	109	A	A	D	D
	110	A	B	D	D
	111	A	B	C	D
	112	A	B	D	D
	113	A	B	D	D
	114	A	B	C	D
	115	A	A		C

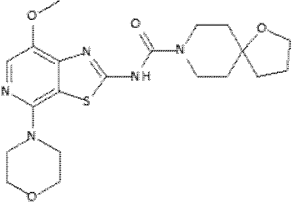
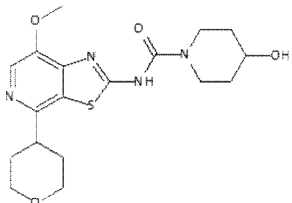
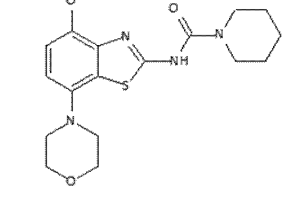
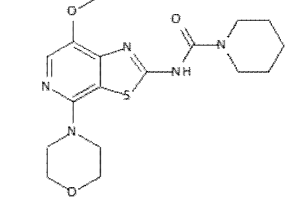
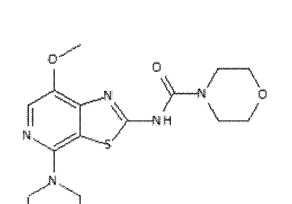
129

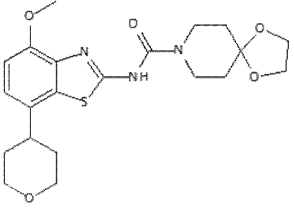
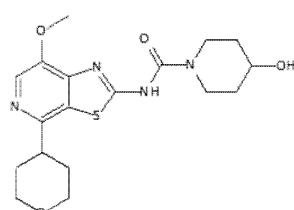
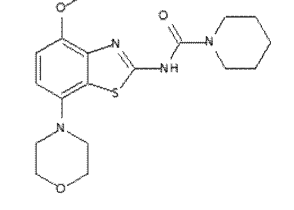
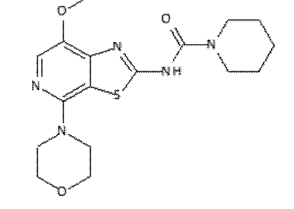
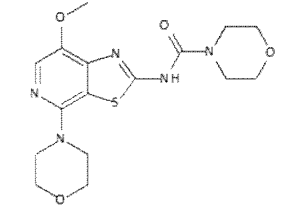
5	116	A	A		C
	117	A	A		C
	118	A	B		D
	119	A	B		D
	120	B		D	D
10	121	A	B	D	D
	122	A	B	D	D
	123	A	B	D	D
	124	A	A	D	D
	125	A	A	C	D
15	129	A	B	C	D
	131	A	A	C	D
	135	A	A	C	C
	137	A	A	C	D
	139	A	B		D
20	140	A	B	C	D
	147	A	A	D	C
	149	A	A	C	D
	150	A	B	D	D
	153	A	A	C	D
25	156	A	A	C	D
	157	A	A	C	D
	158	A	A		D
	160	A	A	C	D
	161	A	B	D	D
30	162	A	A	C	D
	163	A	B		D
	164	A	A	D	D
	165	A	A		D
	166	A	B	D	D
	167	A	A		D
	168	A	B		D
	169	A	B	D	D
	170	A	B	D	D
	171	B	B	D	D
	173	A	A	C	D
	174	A	B	D	D

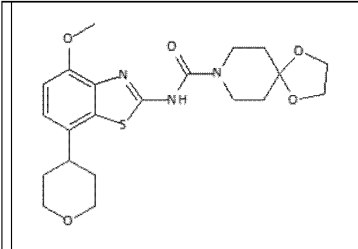
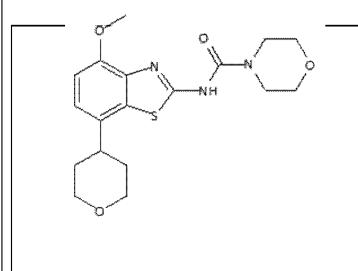
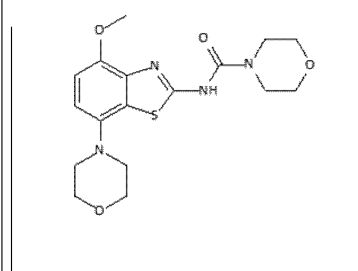
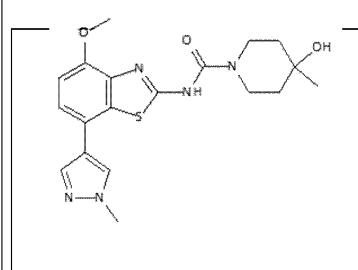
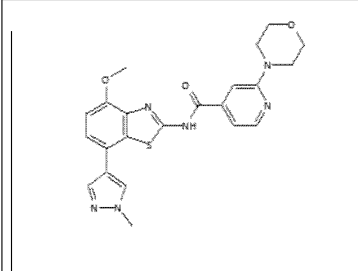
A means IC₅₀ value is < 10 nM, B means IC₅₀ value is < 100 nM, C means IC₅₀ value is < 1 µM, D means IC₅₀ value is > 1 µM.

Table 5 - Prior art compounds specifically disclosed in WO2005/028484 and WO2005/000842

5	No.	Functional A2A receptor activity, HEK293, cAMP, IC50 [μ M]	Functional A2B receptor activity, HEK293, cAMP, IC50 [μ M]	Functional A1 receptor activity, CHO, cAMP, IC50 [μ M]	Functional A3 receptor activity, CHO, cAMP, IC50 [μ M]
10	Tozadenant 	B	D	D	D
15		B	D		D
20		B	D	D	D
25		A	C	D	D
30		A	C	D	D

5					
10		B	C	D	C
15		A	C	D	C
20		A	C	D	B
25		A	C	D	C
30		A	C	D	D

5					
10		B	C	D	C
15		A	C	D	C
20		A	C	D	B
25		A	C	D	C
30		A	C	D	D

5					
10		A	C	C	D
15		A	C	D	D
20		A	C	C	C
25		A	C	C	C

30

A means IC_{50} value is < 10 nM, B means IC_{50} value is < 100 nM, C means IC_{50} value is < 1 μ M, D means IC_{50} value is > 1 μ M.

Example 4: Testing the effects of the compounds of the present invention against endogenous human A_{2A} receptor

5 The endogenous functional activity of the Gs-coupled human A_{2A} receptor was measured in T cells, where this receptor is highly expressed. Determination of receptor activity was done by quantification of cAMP, which is a second messenger for adenosine receptors.

10 In short, human pan T cells were isolated from human PBMC (MACS Pan T Cell Isolation Kit, Miltenyi Biotec) that have been derived from fresh whole blood. The T cells were seeded in 384-well microtiter plates and treated with test compounds. After 10min incubation at room temperature, the A_{2A} adenosine receptor agonist CGS-21680 was added, and the plates were incubated for another 45min. Finally, HTRF reagents (cAMP Femto Kit, CisBio) were added to the wells, and after 1h
15 cellular cAMP levels were determined using the ENVISION (Perkin Elmer) plate reader.

The obtained raw data were normalized against the inhibitor control and the neutral control (DMSO) and the normalized data were fitted using Genedata Screener
20 software.

The compounds of the present invention show that they are able to inhibit the A_{2A} receptor expressed in human T cells which incubated with the A_{2A} adenosine receptor agonist CGS-21680 (as measured by quantification of cAMP), which is preferred for the treatment and/or prevention of hyperproliferative and infectious
25 diseases and disorders as it is disclosed above. Therefore, the compounds of the present invention surprisingly are able to prevent immunosuppression and thus are able to support anti-tumor T cell induced inhibition of tumor growth, reduction or destruction of metastases and prevention of neovascularization.

30 **Example 5: Testing the pharmacokinetic properties of the compounds of the present invention in rat and mouse**

The objective of the study was to obtain information on the pharmacokinetic properties of the compounds of the present invention in female Wistar rats/mice following single intravenous and oral administration.

5 Material and Methods:

Animal Experiments (In-Life Phase)

Female Wistar rats/mice (n=6) received either a single intravenous (bolus) injection or an oral administration (by gavage) of the tested compound. Doses of 0,2 and 10 mg/kg (per compound) were given intravenously and per os, respectively, as a solution in DMSO (0,2%)/PEG 200 (40%)/water for iv administration and as a
10 suspension in Methocel (0,5%)/Tween 20 (0,25%) in water for oral dosing. Consecutive blood samples were taken sub-lingually under isoflurane inhalation from 3 animals per route of administration after 0.1 (only iv), 0.25 (only po), 0.5, 1, 2, 4, 6 and 24 h and were further processed to obtain plasma. Also, urine and feces samples of 3 rats per route of administration were collected over the time interval
15 from 0-24 h and were pooled for analysis.

Bioanalytics:

The concentrations of the compounds in plasma, feces were quantified using an UPLC method with tandem mass spectrometric detection (LC-MS/MS) previously developed at the 'Institute of Drug Metabolism and Pharmacokinetics'. The LC-
20 MS/MS system consisted of a Waters Acquity UPLC coupled to an AB Sciex mass spectrometer API 5500 Q-trap. The UPLC separation was carried out on a reversed phase column (HSS T3, 1.8 μ M, 2.1 $\times$ 50 mm) using a mobile phase gradient with 0.1% formic acid and acetonitrile as eluents. The detection of the compounds was performed using multiple reaction monitoring in the positive ionization mode.

25 Plasma samples were spiked with internal standard (20 μ l) and the analyte was extracted from the matrix using tertiary-butyl methyl ether (tBME). The organic phase was evaporated to dryness under a stream of nitrogen. The residue was dissolved in acetonitrile/0.1% formic acid for LC-MS/MS analysis. Feces samples were homogenized with 4-times their volume of an ethanol/water mixture (4:1, v/v).

30 Aliquots of the aqueous-ethanolic extracts were spiked with internal standard, diluted with acetonitrile/water (1:1, v/v) and directly injected into the LC-MS/MS system.

Pharmacokinetic Evaluation:

Pharmacokinetic parameters $C_{\max}$ and $t_{\max}$ were taken from the observed data. Area under the curve (AUC), clearance (CL), volume (V), half-life ($t_{1/2}$), F and all dose-normalized values were calculated using the custom-made software 'DDS-TOX'. 'DDS-TOX' values were evaluated for several compounds and shown comparable to the values given by the validated software WinNonLin. AUC values were calculated by non-compartmental analysis using the linear up/log down method. Numerical data for mean plasma concentrations and derived pharmacokinetic parameters were rounded to 3 significant digits for presentation. Oral bioavailability and excretion data – expressed as % of dose – are displayed using 2 significant digits.

In comparison with the known adenosine A_{2A} receptor antagonist Tozadenant and similar benzothiazole derivatives, the compounds of the present invention surprisingly show better pharmacokinetic properties in mouse as the animal model relevant for cancer (see table 6), which is preferred for the treatment and/or prevention of hyperproliferative and infectious diseases and disorders as it is disclosed above.

Table 6

No.	Name	CL [L/h/kg]	$t_{1/2}$ [h]	Vss [L/kg]	Feces iv [%]	CMax (iv)@1 mg/kg [ng/ml]
	Tozadenant	8,68	0,184	2,03	23@0.2	337
25	(S)-7-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide	4.65	0.91	3.16	22@0.2	500

Example 6: Testing the effect of the compounds of the present invention on mouse T cells

Background:

5 Adenosine (Ado) in tumor microenvironment can inhibit T cell activity by signaling through A_{2A} receptors and suppress cytokine secretion by T cells. A_{2A} specific agonists like NECA does similar job of inhibition of T cell cytokine secretion in vitro and in vivo. Potential A_{2A} antagonists or A_{2A}/A_{2B} dual antagonists can rescue T cells from this inhibition. Herein, we describe the in vitro system we established using Pan T cells from mouse spleens to screen potential A_{2A} antagonists or A_{2A}/A_{2B} dual
10 antagonists for their activity. The method described involves the use of CD3/CD28 pre-coated beads to stimulate Pan T cells purified from mouse splenocytes, combined with the addition of A_{2A} agonist along with potential A_{2A} or A_{2A}/A_{2B} dual antagonists to evaluate potentiation of T cell cytokine production.

15 mTcell assay, cAMP, assay description:

Pan T-cells are isolated from black 6 mice by manual dissociation and purified using a Miltenyi Pan T-cell isolation kit. The isolated T-cells are activated in 96 well plates for 48 hours using anti-CD3/CD28 beads in T-cell proliferation media. After 48 hours, the T-cells are pooled, counted and suspended in serum free media containing 0.1% BSA. The cells are plated at 50,000 cells per well in 10 ul of media
20 and incubated for 2 hours at 37 °C. Test compounds are dispensed into the wells at a 10-point dose response, starting at a concentration of 10 uM. Following the compound addition, the agonist, NECA, is added to all wells at a 1 uM concentration. The plates are incubated for 30 minutes at 37 °C and assayed for cAMP levels using the Cisbio cAMP Dynamic2 reagent kit by adding 10 ul of the kit
25 reagents to each well. The plates are incubated for 1 hour at room temperature and the HTRF signal is read on an Envision plate reader. The raw data is analyzed in Genedata Screener and the resulting data is loaded into the database.

mTcell assay, IL-2, assay description:

30 Briefly, mouse Pan T cells are purified from spleens of BALB/c mice using Pan T cell isolation kit Mouse II (MACS Miltenyi biotech Cat# Order no. 130-095-130) according to manufacturer's protocol. The purified T cells are seeded in Nunc™ 96-Well Polystyrene Round Bottom Microwell Plates in RPMI medium with 10% heat

inactivated fetal bovine serum. The cells are rested at 37°C for 1 h before activating with CD3/CD28 pre-coated beads (Dynabeads™ Mouse T-Activator CD3/CD28; Cat# 11456D). After 30 min the cells are treated with varying doses of test antagonist(s). The cells are incubated for additional 30 min at 37°C before treating with A_{2A} agonist NECA (1 µM) or neutral control (DMSO). After 24 h incubation IL-2 levels in the supernatants are measured by ELISAs according to manufacturer's protocol (R&D systems Cat# DY402 (IL-2)). Once the concentrations are calculated, the difference of cytokine concentration of DMSO control and agonist alone control is calculated and the percentage of rescue by each concentration of antagonist is calculated by using Microsoft Excel. These percentages of cytokine rescue in a dose dependent manner of antagonist is plotted in GraphPad Prism software and IC₅₀ is calculated.

In contrast to the known adenosine A_{2A} receptor antagonist Tozadenant and similar compounds (see table 8), the compounds of the present invention show that they are able to rescue T cells from inhibition and are able to prevent the suppression of cytokine secretion as induced by adenosine or A_{2A} specific agonists like NECA (see table 7), which is preferred for the treatment and/or prevention of hyperproliferative and infectious diseases and disorders as it is disclosed above. Therefore, the compounds of the present invention surprisingly are able to prevent immunosuppression and thus are able to support anti-tumor T cell induced inhibition of tumor growth, reduction or destruction of metastases and prevention of neovascularization.

Table 7 – Compounds of the present invention

No.	Name / IUPAC	mTcell data, cAMP, IC ₅₀ [µM]	mTcell data IL-2, IC ₅₀ (µM)
1	(R)-3-Aminomethyl-pyrrolidine-1-carboxylic acid (4-methoxy-7-phenyl-thiazolo[4,5-c]pyridin-2-yl)-amide	B	
3	(S)-3-Aminomethyl-pyrrolidine-1-carboxylic acid (4-methoxy-7-phenyl-thiazolo[4,5-c]pyridin-2-yl)-amide	A	

5	6	N-(6-Fluoro-4-methoxy-7-morpholin-4-yl-thiazolo[4,5-c]pyridin-2-yl)-4-(1H-tetrazol-5-yl)-benzamide	B	
	7	7-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid (6-fluoro-4-methoxy-7-morpholin-4-yl-thiazolo[4,5-c]pyridin-2-yl)-amide	A	
	10	(R)-7-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid (6-fluoro-4-methoxy-7-morpholin-4-yl-thiazolo[4,5-c]pyridin-2-yl)-amide	A	
10	11	(5S)-N-[6-fluoro-4-methoxy-7-(morpholin-4-yl)-[1,3]thiazolo[4,5-c]pyridin-2-yl]-7-oxa-2-azaspiro[4.5]decane-2-carboxamide		B
	12	(R)-7-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid (6-fluoro-4-methoxy-7-phenyl-thiazolo[4,5-c]pyridin-2-yl)-amide	A	A
	13	(5S)-N-{6-fluoro-4-methoxy-7-phenyl-[1,3]thiazolo[4,5-c]pyridin-2-yl}-7-oxa-2-azaspiro[4.5]decane-2-carboxamide	A	
15	15	7-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide		B
	19	(5S)-N-[6-fluoro-4-methoxy-7-(morpholin-4-yl)-[1,3]thiazolo[4,5-c]pyridin-2-yl]-2-oxa-7-azaspiro[4.4]nonane-7-carboxamide	B	B
	20	N-[6-Fluoro-4-methoxy-7-(tetrahydro-pyran-4-yl)-thiazolo[4,5-c]pyridin-2-yl]-N',N'-dimethyl-terephthalamide	B	B

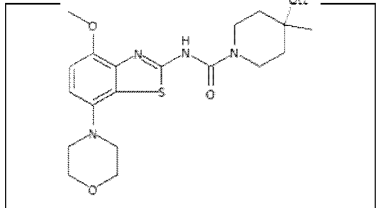
5	24	(R)-7-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide	B	
	25	(S)-7-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide	A	A
	26	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [6-fluoro-4-methoxy-7-(tetrahydro-pyran-4-yl)-thiazolo[4,5-c]pyridin-2-yl]-amide	A	A
10	29	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [6-fluoro-7-(4-fluoro-phenyl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide	A	A
15	31	7-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [6-fluoro-4-methoxy-7-(tetrahydro-pyran-4-yl)-thiazolo[4,5-c]pyridin-2-yl]-amide	A	
	35	(5S)-N-[6-fluoro-4-methoxy-7-(oxan-4-yl)-[1,3]thiazolo[4,5-c]pyridin-2-yl]-7-oxa-2-azaspiro[4.5]decane-2-carboxamide	A	A
20	38	(5S)-N-[6-fluoro-4-methoxy-7-(oxan-4-yl)-[1,3]thiazolo[4,5-c]pyridin-2-yl]-2-oxa-7-azaspiro[4.4]nonane-7-carboxamide	A	B
25	39	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [7-(3-amino-phenyl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide	A	A
30	47	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid (4-methoxy-7-thiophen-2-yl-thiazolo[4,5-c]pyridin-2-yl)-amide	B	B

5	48	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid (7-furan-2-yl-4-methoxy-thiazolo[4,5-c]pyridin-2-yl)-amide	B	
	50	N-[6-Fluoro-4-methoxy-7-(tetrahydro-pyran-4-yl)-thiazolo[4,5-c]pyridin-2-yl]-N'-(2-hydroxy-ethyl)-N'-methyl-terephthalamide	B	
	52	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid (7-furan-3-yl-4-methoxy-thiazolo[4,5-c]pyridin-2-yl)-amide	B	
10	54	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [4-methoxy-7-(3-methoxy-phenyl)-thiazolo[4,5-c]pyridin-2-yl]-amide	A	B
15	61	N4-[7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-[1,3]thiazolo[4,5-c]pyridin-2-yl]-N1,N1-dimethylbenzene-1,4-dicarboxamide		B
20	98	2,8-Diaza-spiro[4.5]decane-2-carboxylic acid [7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide	B	
	99	4-(2,5-Dioxo-pyrrolidin-1-yl)-piperidine-1-carboxylic acid (4-methoxy-7-phenyl-thiazolo[4,5-c]pyridin-2-yl)-amide	B	
25	100	4-(2,5-Dioxo-pyrrolidin-1-yl)-piperidine-1-carboxylic acid [7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide	B	
30	102	2,7-Diaza-spiro[4.5]decane-2-carboxylic acid [7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide	A	
	112	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [4-methoxy-7-(3-methylamino-phenyl)-	A	

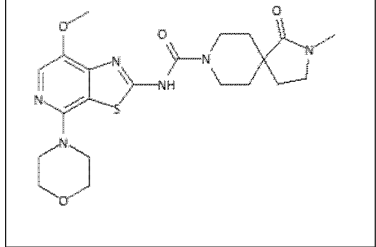
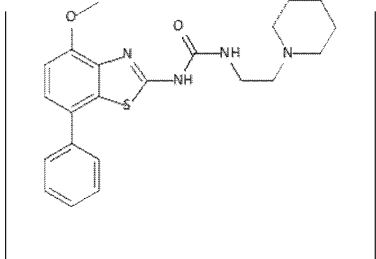
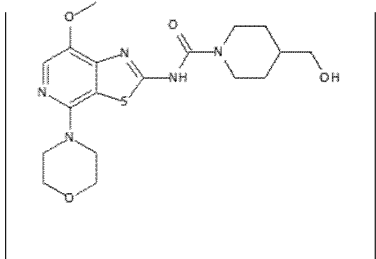
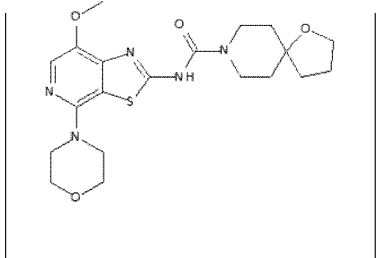
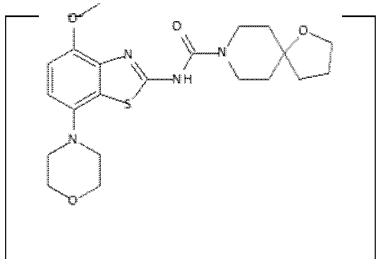
		thiazolo[4,5-c]pyridin-2-yl]-amide		
5	131	4-(2,5-Dioxo-imidazolidin-1-yl)-piperidine-1-carboxylic acid [7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide	B	
	137	4-(2,5-Dioxo-imidazolidin-1-yl)-piperidine-1-carboxylic acid (4-methoxy-7-phenyl-thiazolo[4,5-c]pyridin-2-yl)-amide	A	
10	147	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid {4-methoxy-7-[3-(1-methyl-1H-pyrazol-4-yloxy)-phenyl]-thiazolo[4,5-c]pyridin-2-yl}-amide	A	
15	152	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid ((S)-7-[1,4]dioxan-2-yl-4-methoxy-thiazolo[4,5-c]pyridin-2-yl)-amide	B	

A means IC₅₀ value is < 10 nM, B means IC₅₀ value is < 100 nM, C means IC₅₀ value is < 1 µM, D means IC₅₀ value is > 1 µM.

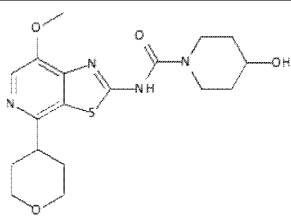
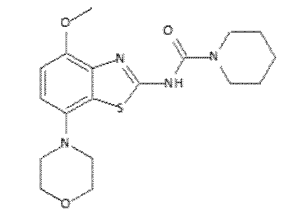
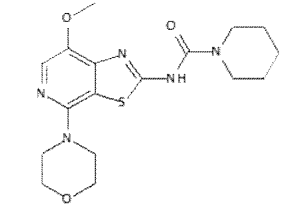
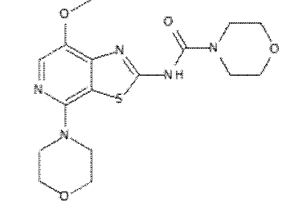
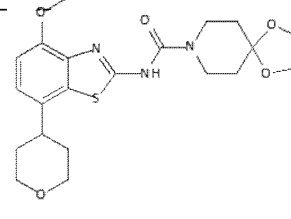
20 **Table 8 - Prior art compounds specifically disclosed in WO2005/028484 and WO2005/000842**

	Name / Structure	mTcell data, cAMP, IC₅₀ [µM]	mTcell data IL-2, IC₅₀ (µM)
25	Tozadenant		
30		C	NA

143

5		D	NA
10		D	NA
15		C	
20		D	
25		C	NA
30		C	

144

5			
10		C	NA
15		C	NA
20		D	NA
25			NA

30

A means IC_{50} value is < 10 nM, B means IC_{50} value is < 100 nM, C means IC_{50} value is < 1 μ M, D means IC_{50} value is > 1 μ M.

Example 7: Testing the effect of the compounds of the present invention on human T cells

5 The endogenous functional activity of the Gs-coupled human A_{2A} receptor was measured in T cells, where this receptor is highly expressed. Determination of receptor activity was done by quantification of cAMP, which is a second messenger for adenosine receptors.

Assay description

10 In short, human pan T cells were isolated from human PBMC (MACS Pan T Cell Isolation Kit, Miltenyi Biotec) that have been derived from fresh whole blood. The T cells were seeded in 384-well microtiter plates and treated with test compounds. After 10min incubation at room temperature, the A_{2A} adenosine receptor agonist NECA was added, and the plates were incubated for another 45min. Finally, HTRF reagents (cAMP Femto Kit, CisBio) were added to the wells, and after 1h cellular
15 cAMP levels were determined using the ENVISION (Perkin Elmer) plate reader.

The obtained raw data were normalized against the inhibitor control and the neutral control (DMSO) and the normalized data were fitted using Genedata Screener
20 software.

The compounds of the present invention show that they are able to inhibit the A_{2A} receptor expressed in human T cells which incubated with the A_{2A} adenosine receptor agonist NECA (as measured by quantification of cAMP), which is preferred for the treatment and/or prevention of hyperproliferative and infectious diseases and disorders as it is disclosed above. Therefore, the compounds of the present
25 invention surprisingly are able to prevent immunosuppression and thus are able to support anti-tumor T cell induced inhibition of tumor growth, reduction or destruction of metastases and prevention of neovascularization.

Table 9 – Compounds of the present invention

30

No.	Name/ IUPAC	hTcell data, cAMP, IC50 [μM]	hTcell data, IL-2, IC50 [μM]
1	(R)-3-Aminomethyl-pyrrolidine-	A	

		1-carboxylic acid (4-methoxy-7-phenyl-thiazolo[4,5-c]pyridin-2-yl)-amide		
5	3	(S)-3-Aminomethyl-pyrrolidine-1-carboxylic acid (4-methoxy-7-phenyl-thiazolo[4,5-c]pyridin-2-yl)-amide	A	
	6	N-(6-Fluoro-4-methoxy-7-morpholin-4-yl-thiazolo[4,5-c]pyridin-2-yl)-4-(1H-tetrazol-5-yl)-benzamide	B	A
10	7	7-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid (6-fluoro-4-methoxy-7-morpholin-4-yl-thiazolo[4,5-c]pyridin-2-yl)-amide	A	
15	10	(R)-7-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid (6-fluoro-4-methoxy-7-morpholin-4-yl-thiazolo[4,5-c]pyridin-2-yl)-amide	A	
20	11	(5S)-N-[6-fluoro-4-methoxy-7-(morpholin-4-yl)-[1,3]thiazolo[4,5-c]pyridin-2-yl]-7-oxa-2-azaspiro[4.5]decane-2-carboxamide	A	A
	12	(R)-7-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid (6-fluoro-4-methoxy-7-phenyl-thiazolo[4,5-c]pyridin-2-yl)-amide	A	A
25	13	(5S)-N-[6-fluoro-4-methoxy-7-phenyl-[1,3]thiazolo[4,5-c]pyridin-2-yl]-7-oxa-2-azaspiro[4.5]decane-2-carboxamide	A	
30	15	7-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide		A
	19	(5S)-N-[6-fluoro-4-methoxy-7-(morpholin-4-yl)-	A	B

		[1,3]thiazolo[4,5-c]pyridin-2-yl]-2-oxa-7-azaspiro[4.4]nonane-7-carboxamide		
5	20	N-[6-Fluoro-4-methoxy-7-(tetrahydro-pyran-4-yl)-thiazolo[4,5-c]pyridin-2-yl]-N',N'-dimethyl-terephthalamide	A	A
	24	(R)-7-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide	A	A
10	25	(S)-7-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide	A	A
15	26	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [6-fluoro-4-methoxy-7-(tetrahydro-pyran-4-yl)-thiazolo[4,5-c]pyridin-2-yl]-amide	A	B
	29	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [6-fluoro-7-(4-fluoro-phenyl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide	A	A
20	31	7-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [6-fluoro-4-methoxy-7-(tetrahydro-pyran-4-yl)-thiazolo[4,5-c]pyridin-2-yl]-amide	A	
25	35	(5S)-N-[6-fluoro-4-methoxy-7-(oxan-4-yl)-[1,3]thiazolo[4,5-c]pyridin-2-yl]-7-oxa-2-azaspiro[4.5]decane-2-carboxamide	A	B
30	37	(R)-2-Oxa-7-aza-spiro[4.4]nonane-7-carboxylic acid [6-fluoro-4-methoxy-7-(tetrahydro-pyran-4-yl)-thiazolo[4,5-c]pyridin-2-yl]-amide	A	

5	38	(5S)-N-[6-fluoro-4-methoxy-7-(oxan-4-yl)-[1,3]thiazolo[4,5-c]pyridin-2-yl]-2-oxa-7-azaspiro[4.4]nonane-7-carboxamide	A	
	39	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [7-(3-amino-phenyl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide	A	B
10	47	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid (4-methoxy-7-thiophen-2-yl-thiazolo[4,5-c]pyridin-2-yl)-amide	A	
	48	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid (7-furan-2-yl-4-methoxy-thiazolo[4,5-c]pyridin-2-yl)-amide	B	
15	50	N-[6-Fluoro-4-methoxy-7-(tetrahydro-pyran-4-yl)-thiazolo[4,5-c]pyridin-2-yl]-N'-(2-hydroxy-ethyl)-N'-methyl-terephthalamide	A	
	54	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [4-methoxy-7-(3-methoxy-phenyl)-thiazolo[4,5-c]pyridin-2-yl]-amide	A	
20	59	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid (7-cyclohex-1-enyl-4-methoxy-thiazolo[4,5-c]pyridin-2-yl)-amide	A	
	61	N4-[7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-[1,3]thiazolo[4,5-c]pyridin-2-yl]-N1,N1-dimethylbenzene-1,4-dicarboxamide	A	
25	63	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [7-(4,4-difluoro-cyclohex-1-enyl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide	A	
	65	1H-Imidazole-4-carboxylic acid [7-(3,6-dihydro-2H-pyran-4-yl)-	A	

		4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide		
5	68	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [4-methoxy-7-(1-pyridin-3-ylmethyl-1H-pyrazol-4-yl)-thiazolo[4,5-c]pyridin-2-yl]-amide	A	
	69	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [4-methoxy-7-(1-pyridin-2-ylmethyl-1H-pyrazol-4-yl)-thiazolo[4,5-c]pyridin-2-yl]-amide	A	
10	71	N-[7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-[1,3]thiazolo[4,5-c]pyridin-2-yl]-4-(1H-1,2,3-triazol-1-yl)benzamide	A	
15	72	4-{[7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-[1,3]thiazolo[4,5-c]pyridin-2-yl]carbonyl}benzoic acid	B	
	74	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid {7-[1-(2,2-difluoro-ethyl)-1H-pyrazol-4-yl]-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide	B	
20	89	3-[7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-[1,3]thiazolo[4,5-c]pyridin-2-yl]-1-[4-(2-oxopyrrolidin-1-yl)phenyl]urea	A	
25	91	N-[7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-[1,3]thiazolo[4,5-c]pyridin-2-yl]-4-(2,4-dioxo-1,3-thiazolidin-3-yl)piperidine-1-carboxamide	A	
	97	[4-(4-Methoxy-7-phenyl-thiazolo[4,5-c]pyridin-2-ylcarbonyl)-benzyl]-methyl-carbamic acid methyl ester	B	
30	98	2,8-Diaza-spiro[4.5]decane-2-carboxylic acid [7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide	A	

5	99	4-(2,5-Dioxo-pyrrolidin-1-yl)-piperidine-1-carboxylic acid (4-methoxy-7-phenyl-thiazolo[4,5-c]pyridin-2-yl)-amide	B	
	100	4-(2,5-Dioxo-pyrrolidin-1-yl)-piperidine-1-carboxylic acid [7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide	A	
	102	2,7-Diaza-spiro[4.5]decane-2-carboxylic acid [7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide	A	
10	112	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [4-methoxy-7-(3-methylamino-phenyl)-thiazolo[4,5-c]pyridin-2-yl]-amide	A	
15	131	4-(2,5-Dioxo-imidazolidin-1-yl)-piperidine-1-carboxylic acid [7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide	A	
20	137	4-(2,5-Dioxo-imidazolidin-1-yl)-piperidine-1-carboxylic acid (4-methoxy-7-phenyl-thiazolo[4,5-c]pyridin-2-yl)-amide	A	
25	152	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid ((S)-7-[1,4]dioxan-2-yl-4-methoxy-thiazolo[4,5-c]pyridin-2-yl)-amide	A	
30	161	N-(7-[1,4]Dioxan-2-yl-4-methoxy-thiazolo[4,5-c]pyridin-2-yl)-terephthalamic acid	B	
	164	N-(7-[1,4]Dioxan-2-yl-4-methoxy-thiazolo[4,5-c]pyridin-2-yl)-4-(1H-tetrazol-5-yl)-benzamide	B	
	165	2-Pyridin-4-yl-1H-imidazole-4-carboxylic acid [7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-	A	

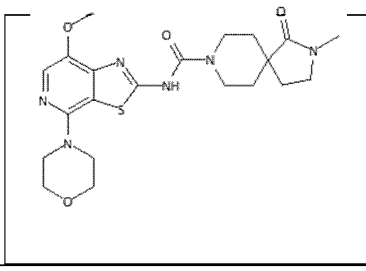
151

	thiazolo[4,5-c]pyridin-2-yl]-amide		
5	168	5-[7-(3,6-Dihydro-2H-pyran-4-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-ylcarbamoyl]-1H-imidazole-2-carboxylic acid	B
	170	N-((S)-7-[1,4]Dioxan-2-yl-4-methoxy-thiazolo[4,5-c]pyridin-2-yl)-terephthalamic acid	A
10	173	(5R)-N-[7-(3,6-dihydro-2H-pyran-4-yl)-4-(2H3)methoxy-[1,3]thiazolo[4,5-c]pyridin-2-yl]-7-oxa-2-azaspiro[4.5]decane-2-carboxamide	A
15	174	(5S)-N-[7-(3,6-dihydro-2H-pyran-4-yl)-4-(2H3)methoxy-[1,3]thiazolo[4,5-c]pyridin-2-yl]-7-oxa-2-azaspiro[4.5]decane-2-carboxamide	A

A means IC₅₀ value is < 10 nM, B means IC₅₀ value is < 100 nM, C means IC₅₀ value is < 1 μM, D means IC₅₀ value is > 1 μM.

Table 10 - Prior art compounds specifically disclosed in WO2005/028484 and WO2005/000842

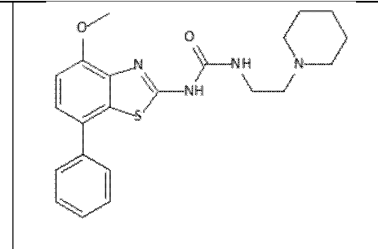
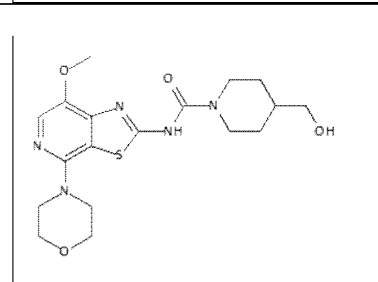
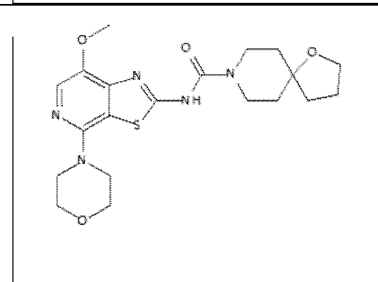
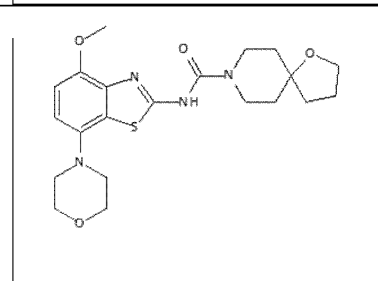
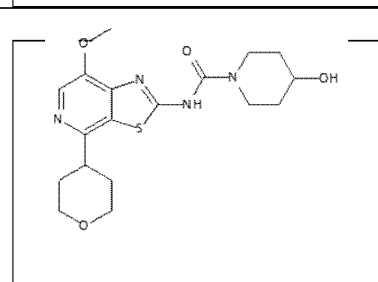
20

Name/ Structure	hTcell data, cAMP, IC50 [μM]	hTcell data, IL-2, IC50 [μM]
	C	NA
	C	NA

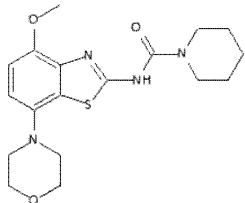
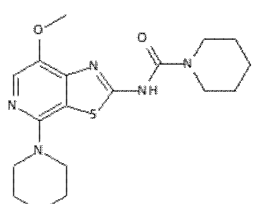
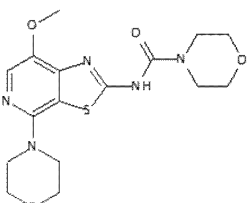
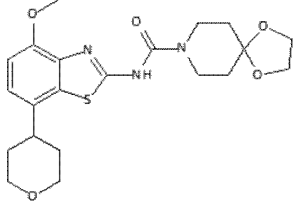
25

30

152

5			
10		C	
15		C	
20		C	
25		C	
30		C	

153

5			
10		C	
15		C	
20			NA

25 A means IC_{50} value is < 10 nM, B means IC_{50} value is < 100 nM, C means IC_{50} value is < 1 μ M, D means IC_{50} value is > 1 μ M.

Example 8: Injection vials

30 A solution of 100 g of a compound of the present invention and 5 g of disodium hydrogenphosphate in 3 l of bidistilled water is adjusted to pH 6.5 using 2 N hydrochloric acid, filtered under sterile conditions, transferred into injection vials,

lyophilised under sterile conditions and sealed under sterile conditions. Each injection vial contains 5 mg of a compound of the present invention.

5

Example 9: Solution

A solution is prepared from 1 g of a compound of the present invention, 9.38 g of $\text{NaH}_2\text{PO}_4 \cdot 2 \text{H}_2\text{O}$, 28.48 g of $\text{Na}_2\text{HPO}_4 \cdot 12 \text{H}_2\text{O}$ and 0.1 g of benzalkonium chloride in 940 ml of bidistilled water. The pH is adjusted to 6.8, and the solution is made up to 1 l and sterilised by irradiation.

10

Example 10: Ampoules

A solution of 1 kg of a compound of the present invention in 60 l of bidistilled water is filtered under sterile conditions, transferred into ampoules, lyophilised under sterile conditions and sealed under sterile conditions. Each ampoule contains 10 mg of a compound of the present invention.

15

20

25

30

Claims

1. Compound selected from the group consisting of:

1	(R)-3-Aminomethyl-pyrrolidine-1-carboxylic acid (4-methoxy-7-phenyl-thiazolo[4,5-c]pyridin-2-yl)-amide
2	N-{4-methoxy-7-[4-(oxan-4-yloxy)phenyl]-[1,3]thiazolo[4,5-c]pyridin-2-yl}-8-oxa-2-azaspiro[4.5]decane-2-carboxamide
3	(S)-3-Aminomethyl-pyrrolidine-1-carboxylic acid (4-methoxy-7-phenyl-thiazolo[4,5-c]pyridin-2-yl)-amide
4	Cyclopropanecarboxylic acid (6-fluoro-4-methoxy-7-morpholin-4-yl-thiazolo[4,5-c]pyridin-2-yl)-amide
6	N-(6-Fluoro-4-methoxy-7-morpholin-4-yl-thiazolo[4,5-c]pyridin-2-yl)-4-(1H-tetrazol-5-yl)-benzamide
7	7-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid (6-fluoro-4-methoxy-7-morpholin-4-yl-thiazolo[4,5-c]pyridin-2-yl)-amide
9	N-[7-(1H-indol-6-yl)-4-methoxy-[1,3]thiazolo[4,5-c]pyridin-2-yl]-8-oxa-2-azaspiro[4.5]decane-2-carboxamide
10	(R)-7-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid (6-fluoro-4-methoxy-7-morpholin-4-yl-thiazolo[4,5-c]pyridin-2-yl)-amide
11	(5S)-N-[6-fluoro-4-methoxy-7-(morpholin-4-yl)-[1,3]thiazolo[4,5-c]pyridin-2-yl]-7-oxa-2-azaspiro[4.5]decane-2-carboxamide
12	(R)-7-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid (6-fluoro-4-methoxy-7-phenyl-thiazolo[4,5-c]pyridin-2-yl)-amide
13	(5S)-N-{6-fluoro-4-methoxy-7-phenyl-[1,3]thiazolo[4,5-c]pyridin-2-yl}-7-oxa-2-azaspiro[4.5]decane-2-carboxamide
14	3-Dimethylaminomethyl-bicyclo[1.1.1]pentane-1-carboxylic acid (4-methoxy-7-morpholin-4-yl-thiazolo[4,5-c]pyridin-2-yl)-amide
15	7-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide
16	N-[6-fluoro-4-methoxy-7-(morpholin-4-yl)-[1,3]thiazolo[4,5-c]pyridin-2-yl]-2-oxa-7-azaspiro[4.4]nonane-7-carboxamide

17	N-[4-methoxy-7-(oxan-4-yl)-[1,3]thiazolo[4,5-c]pyridin-2-yl]-2-[(2-methoxyethyl)amino]-1,3-thiazole-5-carboxamide
18	(R)-2-Oxa-7-aza-spiro[4.4]nonane-7-carboxylic acid (6-fluoro-4-methoxy-7-morpholin-4-yl-thiazolo[4,5-c]pyridin-2-yl)-amide
19	(5S)-N-[6-fluoro-4-methoxy-7-(morpholin-4-yl)-[1,3]thiazolo[4,5-c]pyridin-2-yl]-2-oxa-7-azaspiro[4.4]nonane-7-carboxamide
20	N-[6-Fluoro-4-methoxy-7-(tetrahydro-pyran-4-yl)-thiazolo[4,5-c]pyridin-2-yl]-N',N'-dimethyl-terephthalamide
21	1-Imidazol-1-ylmethyl-cyclopropanecarboxylic acid [6-fluoro-4-methoxy-7-(tetrahydro-pyran-4-yl)-thiazolo[4,5-c]pyridin-2-yl]-amide
22	N-[6-fluoro-4-methoxy-7-(oxan-4-yl)-[1,3]thiazolo[4,5-c]pyridin-2-yl]-1-(2-methoxyethyl)-1H-pyrazole-4-carboxamide
23	N-[6-fluoro-4-methoxy-7-(oxan-4-yl)-[1,3]thiazolo[4,5-c]pyridin-2-yl]-1-methyl-1H-pyrazole-4-carboxamide
24	(R)-7-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide
25	(S)-7-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide
26	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [6-fluoro-4-methoxy-7-(tetrahydro-pyran-4-yl)-thiazolo[4,5-c]pyridin-2-yl]-amide
27	4-Hydroxy-4-methyl-piperidine-1-carboxylic acid [6-fluoro-7-(4-fluoro-phenyl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide
28	Cyclopropanecarboxylic acid [6-fluoro-4-methoxy-7-(tetrahydro-pyran-4-yl)-thiazolo[4,5-c]pyridin-2-yl]-amide
29	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [6-fluoro-7-(4-fluoro-phenyl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide
30	Cyclopropanecarboxylic acid [7-(3-ethylaminomethyl-phenyl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide
31	7-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [6-fluoro-4-methoxy-7-(tetrahydro-pyran-4-yl)-thiazolo[4,5-c]pyridin-2-yl]-amide
32	1H-Imidazole-4-carboxylic acid (6-fluoro-4-methoxy-7-phenyl-thiazolo[4,5-c]pyridin-2-yl)-amide
33	N-[6-fluoro-4-methoxy-7-(oxan-4-yl)-[1,3]thiazolo[4,5-c]pyridin-2-yl]-2-oxa-7-azaspiro[4.4]nonane-7-carboxamide
34	(R)-7-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [6-fluoro-4-methoxy-7-(tetrahydro-pyran-4-yl)-thiazolo[4,5-c]pyridin-2-yl]-amide

35	(5S)-N-[6-fluoro-4-methoxy-7-(oxan-4-yl)-[1,3]thiazolo[4,5-c]pyridin-2-yl]-7-oxa-2-azaspiro[4.5]decane-2-carboxamide
37	(R)-2-Oxa-7-aza-spiro[4.4]nonane-7-carboxylic acid [6-fluoro-4-methoxy-7-(tetrahydro-pyran-4-yl)-thiazolo[4,5-c]pyridin-2-yl]-amide
38	(5S)-N-[6-fluoro-4-methoxy-7-(oxan-4-yl)-[1,3]thiazolo[4,5-c]pyridin-2-yl]-2-oxa-7-azaspiro[4.4]nonane-7-carboxamide
39	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [7-(3-amino-phenyl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide
40	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [4-methoxy-7-(3-oxo-cyclopent-1-enyl)-thiazolo[4,5-c]pyridin-2-yl]-amide
41	Bicyclo[1.1.1]pentane-1,3-dicarboxylic acid [6-fluoro-4-methoxy-7-(tetrahydro-pyran-4-yl)-thiazolo[4,5-c]pyridin-2-yl]-amide (2-hydroxy-ethyl)-methyl-amide
42	N-[7-(2,5-dihydrofuran-3-yl)-4-methoxy-[1,3]thiazolo[4,5-c]pyridin-2-yl]cyclopropanecarboxamide
43	N-[7-(2,5-dihydrofuran-3-yl)-4-methoxy-[1,3]thiazolo[4,5-c]pyridin-2-yl]-1H-imidazole-4-carboxamide
44	N-[7-(2,5-dihydrofuran-3-yl)-4-methoxy-[1,3]thiazolo[4,5-c]pyridin-2-yl]-8-oxa-2-azaspiro[4.5]decane-2-carboxamide
45	N-[7-(2,5-dihydrofuran-3-yl)-4-methoxy-[1,3]thiazolo[4,5-c]pyridin-2-yl]-7-oxa-2-azaspiro[4.5]decane-2-carboxamide
46	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [7-(1-acetyl-1,2,3,6-tetrahydro-pyridin-4-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide
47	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid (4-methoxy-7-thiophen-2-yl-thiazolo[4,5-c]pyridin-2-yl)-amide
48	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid (7-furan-2-yl-4-methoxy-thiazolo[4,5-c]pyridin-2-yl)-amide
49	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [7-(3-ethylaminomethyl-phenyl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide
50	N-[6-Fluoro-4-methoxy-7-(tetrahydro-pyran-4-yl)-thiazolo[4,5-c]pyridin-2-yl]-N'-(2-hydroxy-ethyl)-N'-methyl-terephthalamide
51	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid (4-methoxy-7-piperidin-1-yl-thiazolo[4,5-c]pyridin-2-yl)-amide

52	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid (7-furan-3-yl-4-methoxy-thiazolo[4,5-c]pyridin-2-yl)-amide
53	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [4-methoxy-7-(4-methyl-piperazin-1-yl)-thiazolo[4,5-c]pyridin-2-yl]-amide
54	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [4-methoxy-7-(3-methoxy-phenyl)-thiazolo[4,5-c]pyridin-2-yl]-amide
56	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [4-methoxy-7-(6-methyl-pyridazin-3-yl)-thiazolo[4,5-c]pyridin-2-yl]-amide
57	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid (7-azetidin-1-yl-4-methoxy-thiazolo[4,5-c]pyridin-2-yl)-amide
58	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [7-(3-hydroxy-azetidin-1-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide
59	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid (7-cyclohex-1-enyl-4-methoxy-thiazolo[4,5-c]pyridin-2-yl)-amide
60	1H-Imidazole-4-carboxylic acid (4-methoxy-7-phenyl-thiazolo[4,5-c]pyridin-2-yl)-amide
61	N4-[7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-[1,3]thiazolo[4,5-c]pyridin-2-yl]-N1,N1-dimethylbenzene-1,4-dicarboxamide
62	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid (7-cyclohexyl-4-methoxy-thiazolo[4,5-c]pyridin-2-yl)-amide
63	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [7-(4,4-difluoro-cyclohex-1-enyl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide
64	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [7-(3,6-dihydro-2H-thiopyran-4-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide
65	1H-Imidazole-4-carboxylic acid [7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide
66	N-[4-methoxy-7-(4-methoxycyclohex-1-en-1-yl)-[1,3]thiazolo[4,5-c]pyridin-2-yl]-8-oxa-2-azaspiro[4.5]decane-2-carboxamide
67	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [4-methoxy-7-(2-methyl-thiazol-4-yl)-thiazolo[4,5-c]pyridin-2-yl]-amide
68	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [4-methoxy-7-(1-pyridin-3-ylmethyl-1H-pyrazol-4-yl)-thiazolo[4,5-c]pyridin-2-yl]-amide

69	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [4-methoxy-7-(1-pyridin-2-ylmethyl-1H-pyrazol-4-yl)-thiazolo[4,5-c]pyridin-2-yl]-amide
71	N-[7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-[1,3]thiazolo[4,5-c]pyridin-2-yl]-4-(1H-1,2,3-triazol-1-yl)benzamide
72	4-[[7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-[1,3]thiazolo[4,5-c]pyridin-2-yl]carbonyl]benzoic acid
73	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid (7-[1,4]dioxan-2-yl-4-methoxy-thiazolo[4,5-c]pyridin-2-yl)-amide
74	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid {7-[1-(2,2-difluoroethyl)-1H-pyrazol-4-yl]-4-methoxy-thiazolo[4,5-c]pyridin-2-yl}-amide
75	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [4-methoxy-7-(1-pyridin-4-ylmethyl-1H-pyrazol-4-yl)-thiazolo[4,5-c]pyridin-2-yl]-amide
76	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [7-(1-benzyl-1H-pyrazol-4-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide
79	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [7-(1-difluoromethyl-1H-pyrazol-4-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide
80	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid (4-difluoromethoxy-7-phenyl-thiazolo[4,5-c]pyridin-2-yl)-amide
81	N-[7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-[1,3]thiazolo[4,5-c]pyridin-2-yl]-2-[(2-methoxyethyl)amino]-1,3-thiazole-5-carboxamide
82	N-[7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-[1,3]thiazolo[4,5-c]pyridin-2-yl]-4-[(1H-imidazol-1-yl)methyl]benzamide
83	N-[7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-[1,3]thiazolo[4,5-c]pyridin-2-yl]-4-[(1R)-1-acetamidoethyl]benzamide

84	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid {4-methoxy-7-[1-(tetrahydro-pyran-2-ylmethyl)-1H-pyrazol-4-yl]-thiazolo[4,5-c]pyridin-2-yl}-amide
85	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid {4-methoxy-7-[1-(tetrahydro-pyran-4-ylmethyl)-1H-pyrazol-4-yl]-thiazolo[4,5-c]pyridin-2-yl}-amide
86	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [7-(1,1-dioxo-hexahydro-1H-thiopyran-4-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide
87	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid {4-methoxy-7-[1-(tetrahydro-pyran-3-ylmethyl)-1H-pyrazol-4-yl]-thiazolo[4,5-c]pyridin-2-yl}-amide
88	N-[7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-[1,3]thiazolo[4,5-c]pyridin-2-yl]-4-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)piperidine-1-carboxamide
89	3-[7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-[1,3]thiazolo[4,5-c]pyridin-2-yl]-1-[4-(2-oxopyrrolidin-1-yl)phenyl]urea
90	N-[4-({[7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-[1,3]thiazolo[4,5-c]pyridin-2-yl]carbamoyl}amino)phenyl]-2-(dimethylamino)acetamide
91	N-[7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-[1,3]thiazolo[4,5-c]pyridin-2-yl]-4-(2,4-dioxo-1,3-thiazolidin-3-yl)piperidine-1-carboxamide
92	N-[4-({[7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-[1,3]thiazolo[4,5-c]pyridin-2-yl]carbamoyl}amino)-2-methylphenyl]acetamide
93	N4-[7-(3,6-dihydro-2H-pyran-4-yl)-4-hydroxy-[1,3]thiazolo[4,5-c]pyridin-2-yl]-N1-(2-hydroxyethyl)-N1-methylbenzene-1,4-dicarboxamide
94	3-[7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-[1,3]thiazolo[4,5-c]pyridin-2-yl]-1-[4-(3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-1-yl)phenyl]urea
95	3-[7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-[1,3]thiazolo[4,5-c]pyridin-2-yl]-1-[4-(2-oxo-1,3-oxazolidin-3-yl)phenyl]urea
96	N1-[7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-[1,3]thiazolo[4,5-c]pyridin-2-yl]-N4,N4-dimethylpiperidine-1,4-dicarboxamide
97	[4-(4-Methoxy-7-phenyl-thiazolo[4,5-c]pyridin-2-ylcarbamoyl)-benzyl]-methyl-carbamic acid methyl ester

98	2,8-Diaza-spiro[4.5]decane-2-carboxylic acid [7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide
99	4-(2,5-Dioxo-pyrrolidin-1-yl)-piperidine-1-carboxylic acid (4-methoxy-7-phenyl-thiazolo[4,5-c]pyridin-2-yl)-amide
100	4-(2,5-Dioxo-pyrrolidin-1-yl)-piperidine-1-carboxylic acid [7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide
101	Bicyclo[1.1.1]pentane-1,3-dicarboxylic acid (6-fluoro-4-methoxy-7-phenyl-thiazolo[4,5-c]pyridin-2-yl)-amide (2-hydroxy-ethyl)-methylamide
102	2,7-Diaza-spiro[4.5]decane-2-carboxylic acid [7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide
103	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid (4-methoxy-7-{1-[2-(2-methoxy-ethoxy)-ethyl]-1H-pyrazol-4-yl}-thiazolo[4,5-c]pyridin-2-yl)-amide
104	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid (4-methoxy-7-{1-[(R)-1-(tetrahydro-pyran-3-yl)methyl]-1H-pyrazol-4-yl}-thiazolo[4,5-c]pyridin-2-yl)-amide
105	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid (4-methoxy-7-{1-[(S)-1-(tetrahydro-pyran-3-yl)methyl]-1H-pyrazol-4-yl}-thiazolo[4,5-c]pyridin-2-yl)-amide
106	N1-[7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-[1,3]thiazolo[4,5-c]pyridin-2-yl]piperidine-1,4-dicarboxamide
107	N-[7-(3,6-dihydro-2H-pyran-4-yl)-4-hydroxy-[1,3]thiazolo[4,5-c]pyridin-2-yl]-2-oxa-7-azaspiro[4.4]nonane-7-carboxamide
108	N-[7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-[1,3]thiazolo[4,5-c]pyridin-2-yl]-2-oxa-7-azaspiro[4.4]nonane-7-carboxamide
109	4-({4-methoxy-7-phenyl-[1,3]thiazolo[4,5-c]pyridin-2-yl}carbamoyl)benzoic acid
110	N-{4-methoxy-7-phenyl-[1,3]thiazolo[4,5-c]pyridin-2-yl}-4-(1H-1,2,3,4-tetrazol-5-yl)benzamide
111	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [7-(4,4-difluorocyclohexyl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide

112	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [4-methoxy-7-(3-methylamino-phenyl)-thiazolo[4,5-c]pyridin-2-yl]-amide
113	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [4-methoxy-7-(5-methyl-thiophen-2-yl)-thiazolo[4,5-c]pyridin-2-yl]-amide
114	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [4-methoxy-7-(5-methyl-furan-2-yl)-thiazolo[4,5-c]pyridin-2-yl]-amide
115	4-[(4-methoxy-7-{1-[(pyridin-3-yl)methyl]-1H-pyrazol-4-yl}-[1,3]thiazolo[4,5-c]pyridin-2-yl)carbonyl]benzoic acid
116	N-[7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-[1,3]thiazolo[4,5-c]pyridin-2-yl]-1H-pyrazole-4-carboxamide
117	N-{4-methoxy-7-phenyl-[1,3]thiazolo[4,5-c]pyridin-2-yl}-1H-pyrazole-4-carboxamide
118	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid (4-methoxy-7-{1-[(S)-1-(tetrahydro-pyran-2-yl)methyl]-1H-pyrazol-4-yl}-thiazolo[4,5-c]pyridin-2-yl)-amide
119	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid (4-methoxy-7-{1-[(R)-1-(tetrahydro-pyran-2-yl)methyl]-1H-pyrazol-4-yl}-thiazolo[4,5-c]pyridin-2-yl)-amide
121	(R)-2,7-Diaza-spiro[4.5]decane-2-carboxylic acid [7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide
122	(S)-2,7-Diaza-spiro[4.5]decane-2-carboxylic acid [7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide
123	Piperidine-1,4-dicarboxylic acid 4-dimethylamide 1-[(4-methoxy-7-phenyl-thiazolo[4,5-c]pyridin-2-yl)-amide]
124	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [7-(2-amino-pyridin-4-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide
125	N-[7-(3,6-Dihydro-2H-pyran-4-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-4-(4-methyl-piperazine-1-carbonyl)-benzamide
126	N-[7-(3,6-Dihydro-2H-pyran-4-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-N'-(2-piperidin-1-yl-ethyl)-terephthalamide
127	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [4-methoxy-7-(2-methylamino-pyridin-4-yl)-thiazolo[4,5-c]pyridin-2-yl]-amide
128	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [4-methoxy-7-(5-methyl-cyclohex-1-enyl)-thiazolo[4,5-c]pyridin-2-yl]-amide

129	N-[7-(3,6-Dihydro-2H-pyran-4-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-4-(4-hydroxy-4-methyl-piperidine-1-carbonyl)-benzamide
130	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [7-(3-fluoro-5-methanesulfonylamino-phenyl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide
131	4-(2,5-Dioxo-imidazolidin-1-yl)-piperidine-1-carboxylic acid [7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide
132	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [4-methoxy-7-(3-methyl-3,6-dihydro-2H-pyran-4-yl)-thiazolo[4,5-c]pyridin-2-yl]-amide
133	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [4-methoxy-7-(3-trifluoromethyl-piperidin-1-yl)-thiazolo[4,5-c]pyridin-2-yl]-amide
134	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [4-methoxy-7-(3-methoxy-piperidin-1-yl)-thiazolo[4,5-c]pyridin-2-yl]-amide
135	Imidazo[1,2-a]pyridine-3-carboxylic acid [7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide
136	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [4-methoxy-7-(5-oxo-2,5-dihydro-1H-pyrrol-3-yl)-thiazolo[4,5-c]pyridin-2-yl]-amide
137	4-(2,5-Dioxo-imidazolidin-1-yl)-piperidine-1-carboxylic acid (4-methoxy-7-phenyl-thiazolo[4,5-c]pyridin-2-yl)-amide
138	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [7-(5-amino-2-fluoro-pyridin-3-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide
139	N-(2-Azetidin-1-yl-ethyl)-N'-[7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-terephthalamide
140	2-Pyridin-3-yl-1H-imidazole-4-carboxylic acid [7-(3,6-dihydro-2H-pyran-4-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide
141	N-{4-methoxy-7-[3-(trifluoromethyl)phenyl]-[1,3]thiazolo[4,5-c]pyridin-2-yl}-8-oxa-2-azaspiro[4.5]decane-2-carboxamide
142	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [7-(5-amino-6-fluoro-pyridin-3-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide
143	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [7-(5-amino-pyridin-3-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]-amide
144	{4-[7-(3,6-Dihydro-2H-pyran-4-yl)-4-methoxy-thiazolo[4,5-c]pyridin-2-yl]carbamoyl}-phenyl}-acetic acid
145	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [4-methoxy-7-((S)-3-methyl-cyclohex-1-enyl)-thiazolo[4,5-c]pyridin-2-yl]-amide
146	8-Oxa-2-aza-spiro[4.5]decane-2-carboxylic acid [4-methoxy-7-((R)-3-methyl-cyclohex-1-enyl)-thiazolo[4,5-c]pyridin-2-yl]-amide

and physiologically acceptable salts, solvates and stereoisomers thereof, including mixtures thereof in all ratios

2. Pharmaceutical preparation comprising at least one compound according to Claim 1 and/or physiologically acceptable salts, solvates and stereoisomers thereof, including mixtures thereof in all ratios.
3. Pharmaceutical preparation according to Claim 2 comprising further excipients and/or adjuvants.
4. Pharmaceutical preparation comprising at least one compound according to Claim 1 and/or physiologically acceptable salts, solvates and stereoisomers thereof, including mixtures thereof in all ratios, and at least one further medicament active compound.
5. Process for the preparation of a pharmaceutical preparation, characterised in that a compound according to Claim 1 and/or one of its physiologically acceptable salts, solvates and stereoisomers, including mixtures thereof in all ratios, is brought into a suitable dosage form together with a solid, liquid or semi-liquid excipient or adjuvant.
6. Medicament comprising at least one compound according to Claim 1 and/or one of its physiologically acceptable salts, solvates and stereoisomers, including mixtures thereof in all ratios, for use in the treatment and/or prophylaxis of pathophysiological states.
7. Medicament comprising at least one compound according to Claim 1 and/or one of its physiologically acceptable salts, solvates and stereoisomers, including mixtures thereof in all ratios, for use in the treatment and/or prophylaxis of pathophysiological states, selected from the group consisting of hyperproliferative and infectious diseases and disorders.
8. Medicament for use according to Claim 7, wherein the hyperproliferative disease or disorder is cancer.
9. Medicament for use according to Claim 8, wherein the cancer is selected from the group consisting of acute and chronic lymphocytic leukemia, acute granulocytic leukemia, adrenal cortex cancer, bladder cancer, brain cancer, breast cancer, cervical cancer, cervical hyperplasia, chorio cancer, chronic granulocytic leukemia, chronic lymphocytic leukemia, colon cancer,

endometrial cancer, esophageal cancer, essential thrombocytosis, genitourinary carcinoma, glioma, glioblastoma, hairy cell leukemia, head and neck carcinoma, Hodgkin's disease, Kaposi's sarcoma, lung carcinoma, lymphoma, malignant carcinoid carcinoma, malignant hypercalcemia, malignant melanoma, malignant pancreatic insulinoma, medullary thyroid carcinoma, melanoma, multiple myeloma, mycosis fungoides, myeloid and lymphocytic leukemia, neuroblastoma, non-Hodgkin's lymphoma, non-small cell lung cancer, osteogenic sarcoma, ovarian carcinoma, pancreatic carcinoma, polycythemia vera, primary brain carcinoma, primary macroglobulinemia, prostatic cancer, renal cell cancer, rhabdomyosarcoma, skin cancer, small-cell lung cancer, soft-tissue sarcoma, squamous cell cancer, stomach cancer, testicular cancer, thyroid cancer and Wilms' tumor.

10. Medicament for use according to Claim 7, wherein the hyperproliferative disease or disorder is selected from the group consisting of age-related macular degeneration, Crohn's disease, cirrhosis, chronic inflammatory-related disorders, proliferative diabetic retinopathy, proliferative vitreoretinopathy, retinopathy of prematurity, granulomatosis, immune hyperproliferation associated with organ or tissue transplantation and an immunoproliferative disease or disorder selected from the group consisting of inflammatory bowel disease, psoriasis, rheumatoid arthritis, systemic lupus erythematosus (SLE), vascular hyperproliferation secondary to retinal hypoxia and vasculitis.
11. Medicament for use according to Claim 7, wherein the infectious disease or disorder is selected from the group consisting of
 - i. virally induced infectious diseases which are caused by retroviruses, hepadnaviruses, herpesviruses, flaviviridae and/or adenoviruses wherein the retroviruses are selected from lentiviruses or oncoretroviruses, wherein the lentivirus is selected from the group consisting of HIV-1, HIV-2, FIV, BIV, SIVs, SHIV, CAEV, VMV and EIAV and the oncoretrovirus is selected from the group consisting of HTLV-I, HTLV-II and BLV, the hepadnavirus is selected from the group consisting of HBV, GSHV and WHV, the herpesvirus is selected from the group from the group consisting of HSV I, HSV II, EBV, VZV, HCMV or HHV 8 and the flaviviridae is selected from the group consisting of HCV, West nile and Yellow Fever,
 - ii. bacterial infectious diseases which are caused by Gram-positive bacteria wherein the Gram-positive bacteria are selected from the group consisting

- of methicillin-susceptible and methicillin-resistant staphylococci (including *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Staphylococcus haemolyticus*, *Staphylococcus hominis*, *Staphylococcus saprophyticus*, and coagulase-negative staphylococci), glycopeptides-intermediate susceptible *Staphylococcus aureus* (GISA), penicillin-susceptible and penicillin-resistant streptococci (including *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus avium*, *Streptococcus bovis*, *Streptococcus lactis*, *Streptococcus sanguis* and Streptococci Group C (GCS), Streptococci Group G (GGS) and viridans streptococci), enterococci (including vancomycin-susceptible and vancomycin-resistant strains such as *Enterococcus faecalis* and *Enterococcus faecium*), *Clostridium difficile*, *Listeria monocytogenes*, *Corynebacterium jeikeium*, *Chlamydia* spp (including *C. pneumoniae*) and *Mycobacterium tuberculosis*,
- iii. bacterial infectious diseases which are caused by Gram-negative bacteria wherein the Gram-negative bacteria are selected from the group consisting of the Genus Enterobacteriaceae, including *Escherichia* spp. (including *Escherichia coli*), *Klebsiella* spp., *Enterobacter* spp., *Citrobacter* spp., *Serratia* spp., *Proteus* spp., *Providencia* spp., *Salmonella* spp., *Shigella* spp., the genus *Pseudomonas* (including *P. aeruginosa*), *Moraxella* spp. (including *M. catarrhalis*), *Haemophilus* spp. and *Neisseria* spp.,
 - iv. infectious diseases induced by intracellular active parasites selected from the group consisting of phylum Apicomplexa, or Sarcodistigophora (including *Trypanosoma*, *Plasmodia*, *Leishmania*, *Babesia* or *Theileria*), Cryptosporidia, Sarcocystida, Amoebia, Coccidia and Trichomonadia.

12. Set (kit) consisting of separate packs of

- a) an effective amount of a compound according to one or more of Claim 1 and/or physiologically acceptable salts, solvates and stereoisomers thereof, including mixtures thereof in all ratios, and
- b) an effective amount of a further medicament active compound.