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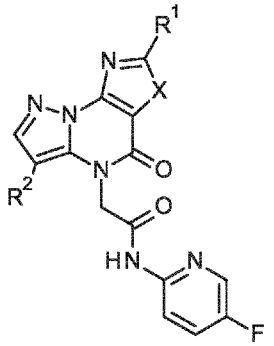

(I)

(57) Abstract: The present invention relates to substituted pyrazolo[1,5-a]pyridine-[3,2-e]pyrimidines compounds of formula (I) wherein X, R^1, and R^2 are as defined in the claims, methods of preparing said compounds, pharmaceutical compositions and combinations comprising said compounds and the compounds for use in the treatment or prophylaxis of diseases, in particular of neurogenic diseases, as a sole agent or in combination with other active ingredients.

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PYRAZOLO[1,5-A]PYRIDO[3,2-E]PYRIMIDINES AND PYRAZOLO[1,5-A][1,3]THIAZOLO[5,4-E]PYRIMIDINES AS P2X3 INHIBITORS FOR THE TREATMENT OF NEUROGENIC DISORDERS

The present invention covers novel substituted pyrazolo[1,5-a]pyridine-[3,2-e]pyrimidines of formula (I) as described and defined herein, methods of preparing said compounds, pharmaceutical compositions and combinations comprising said compounds, and the use of said compounds for manufacturing pharmaceutical compositions for the treatment or prophylaxis of diseases, in particular of neurogenic disorders, as a sole agent or in combination with other active ingredients.

BACKGROUND

P2X purinoceptor 3 is a protein that in humans is encoded by the P2RX3 gene (Garcia-Guzman M, Stuhmer W, Soto F (Sep 1997). "Molecular characterization and pharmacological properties of the human P2X3 purinoceptor". Brain Res Mol Brain Res 47 (1–2): 59–66). The product of this gene belongs to the family of purinoceptors for ATP. This receptor functions as a ligand-gated ion channel and transduces ATP-evoked nociceptor activation.

P2X purinoreceptors are a family of ligand-gated ion channels that are activated by ATP. To date, seven members of this family have been cloned, comprising P2X1-7 [Burnstock 2013, front Cell Neurosci 7:227]. These channels can exist as homomers and heteromers [Saul 2013, front Cell Neurosci 7:250]. Purines, such as ATP, have been recognized as important neurotransmitters and by acting via their respective receptors they have been implicated in various physiological and pathophysiological roles [Burnstock 1993, Drug Dev Res 28:196-206; Burnstock 2011, Prog Neurobiol 95:229-274; Jiang 2012, Cell Health Cytoskeleton 4:83-101].
Among the P2X family members, in particular the P2X3 receptor has been recognized as an important mediator of nociception [Burnstock 2013, Eur J Pharmacol 716:24-40; North 2003, J Phyiol 554:301-308; Chizh 2000, Pharmacol Rev 53:553-568]. It is mainly expressed in dorsal root ganglia in a subset of nociceptive sensory neurons. During inflammation the expression of the P2X3 receptor is increased, and activation of P2X3 receptor has been described to sensitize peripheral nerves [Fabretti 2013, front Cell Neurosci 7:236].
The prominent role of the P2X3 receptor in nociception has been described in various animal models, including mouse and rat models for acute, chronic, and inflammatory pain. P2X3 receptor knock-out mice show a reduced pain response [Cockayne 2000, Nature 407:1011-1015; Souslova 2000, Nature 407:1015-1017]. P2X3 receptor antagonists have been shown to act anti-nociceptive in different models of pain and inflammatory pain [Ford 2012, Purin Signal 8 (Suppl 1): S3-S26]. The P2X3 receptor has also been shown to integrate different nociceptive stimuli. Hyperalgesia induced by PGE2, ET-1 and dopamine have all been shown to be mediated via release of ATP and activation of the P2X3 receptor [Prado 2013, Neuropharm 67:252-258; Joseph 2013, Neurosci 232C: 83-89].

Besides its prominent role in nociception and in pain-related diseases involving both chronic and acute pain, the P2X3 receptor has been shown to be involved in genitourinary, gastrointestinal and respiratory conditions and disorders, including overactive bladder and chronic cough [Ford 2013, front Cell Neurosci 7:267; Burnstock 2014, Purin Signal 10(1):3-50]. ATP-release occurs in these 2 examples from epithelial cells, which in turn activates the P2X3 receptor and induces contraction of bladder and lung muscles respectively leading to premature voiding or cough.

P2X3 subunits do not only form homotrimers but also heterotrimers with P2X2 subunits. P2X3 subunits and P2X2 subunits are also expressed on nerve fibres innervating the tongue, therein taste buds [Kinnamon 2013, front Cell Neurosci 7:264]. In a physiological setting, receptors containing P2X3 and/ or P2X2 subunits are involved in the transmission of taste from the tongue (bitter, sweet, salty, umami and sour). Recent data show that while blocking the P2X3 homomeric receptor alone is important to achieve anti-nociceptive efficacy, non-selective blockade of both the P2X3 homomeric receptor and the P2X2/3 heteromeric receptor leads to changes in taste perception which might limit the therapeutic use of non-selective P2X3 and P2X2/3 receptor antagonists [Ford 2014, purines 2014, abstract book p15]. Therefore, compounds that differentiate between P2X3 and P2X2/3 receptors are highly desirable.

Compounds blocking both the exclusively P2X3 subunit containing ion channel (P2X3 homomer) as well as the ion channel composed of P2X2 and P2X3 subunit (P2X2/3 heterotrimer) are called P2X3 and P2X2/3 nonselective receptor antagonists [Ford, Pain Manag 2012]. Clinical Ph II trials demonstrated that AF-219, a P2X3 antagonist, leads to taste disturbances in treated subjects by affecting taste sensation via the tongue [e.g. Abdulqawi et al, Lancet 2015; Strand et al, 2015 ACR/ARMP Annual Meeting, Abstract 2240]. This side effect has been attributed to the blockade of P2X2/3 channels, i.e. the heterotrimer [A. Ford, London 2015 Pain Therapeutics Conference, congress report]. Both P2X2 and P2X3 subunits are expressed on sensory nerve fibers innervating the tongue. Knock-out animals deficient for P2X2 and P2X3 subunits show reduced taste sensation and even taste loss [Finger et al, Science 2005], whereas P2X3 subunit single knock-outs exhibit a mild or no change in phenotype with respect to taste. Moreover, 2 distinct populations of neurons have been described in the geniculate ganglion expressing either P2X2 and P2X3 subunits or P2X3 subunit alone. In an *in vivo* setting assessing taste preference towards an artificial sweetener via a lickometer, only at very high free plasma levels (> 100 µM) effects on taste were observed, indicating that rather the P2X2 and P2X3 subunits expressing population plays a major role in taste sensation than the P2X3 subunit expressing population [Vandenbeuch et al, J Physiol. 2015]. Hence, as a modified taste perception has profound effects on the quality of life of patients, P2X3-homomeric receptor-selective antagonists are deemed to be superior towards non-selective receptor antagonists and are considered to represent a solution towards the problem of insufficient patient compliance during chronic treatment as indicated by increased drop-out rates during Ph II trials [Strand et al, 2015 ACR/ARMP Annual

Meeting, Abstract 2240 and A. Ford, London 2015 Pain Therapeutics Conference, congress report].

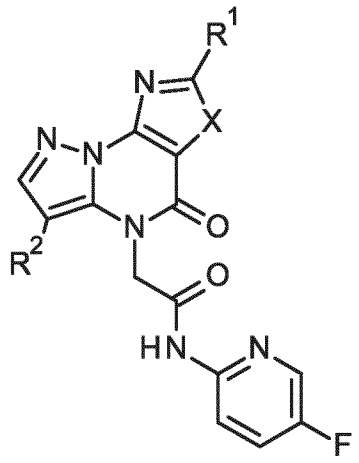
WO 2021/115225 discloses pyrazole-containing polycyclic compounds as P2X3 inhibitors with substitution in 2- and 3-position. Specifically disclosed are 2-substituted and unsubstituted pyrazolo[1,5-a]pyridine-[3,2-e]pyrimidines with a fluoropyridin-acetamide side-chain in position 5. Example 80 is the only one compound with cyano-substitution at position 3. Most of the exemplified compounds are 2-substituted pyrazole-containing polycyclic derivatives have an IC50 at P2X3 from 16 to 385 nM.

The problem of the present invention is to provide further P2X3 inhibitors which show similar or better inhibition of the P2X purinoreceptor 3 compared to the prior art in combination with a good selectivity and oral bioavailability. Oral bioavailability of active ingredients is determined by its solubility in addition to other parameters..

There are now provided novel compounds with surprisingly improved therapeutic efficiency in comparison with the prior art cited above rendering them very suitable for the preparation of a medicine for the treatment of various P2X3-related disorders, in particular of neurogenic disorders. These novel pyrazolo[1,5-a]pyridine-[3,2-e]pyrimidines have only small substituents in position 3 instead of position 2 in comparison to WO 2021/115225. Surprisingly , most of these very potent P2X3 inhibitors show good to superior solubility behavior in kinetic solubility measurements.The more potent the inhibitor the lower the required dose to achieve a pharmacological effect in case that other drug properties are similar. The benefit of such inhibitors is their good pharmaceutical usability because of less to be expected side or toxic effects. The more soluble an oral inhibitor the more increase the chance to good absorption behavior in the gastrointestinal tract. P2X3 inhibitors with better absorption behavior in the gastrointestinal tract increase the chance to improve oral bioavailability and thereby decreasing the required dose to achieve a pharmacological effect.

DESCRIPTION OF THE INVENTION

The present invention covers compounds of formula (I)



(I)

wherein:

R^1 represents C_1-C_3 alkyl, optionally substituted with one ore more halogen, cyclopropyl, or cyano

R^2 represents C_1-C_3 alkyl, optionally substituted with one ore more halogen, cyclopropyl, or halogen

X represents -CH=CH- or -S-;

or an N-oxide thereof.

DEFINITIONS

The term “substituted” means that one or more hydrogen atoms on the designated atom or group are replaced with a selection from the indicated group, provided that the designated atom's normal valency under the existing circumstances is not exceeded. Combinations of substituents and/or variables are permissible.

The term “optionally substituted” means that the number of substituents can be equal to or different from zero. Unless otherwise indicated, it is possible that optionally substituted groups are substituted with as many optional substituents as can be accommodated by replacing a hydrogen atom with a non-hydrogen substituent on any available carbon or nitrogen or oxygen atom. Commonly, it is possible for the number of optional substituents, when present, to be 1, 2, 3, 4 or 5, in particular 1 or 2.

As used herein, the term "one or more", *e.g.,* in the definition of the substituents of the compounds of formula (I) of the present invention, means 1, 2, 3, 4 or 5, particularly 1, 2, 3 or 4, more particularly 1, 2 or 3, even more particularly 1 or 2.

Should a composite substituent be composed of more than one parts, *e.g.* (C_1-C_4-alkoxy)-(C_1-C_4-alkyl)-, it is possible for the position of a given part to be at any suitable position of said composite substituent, *i.e.* the C_1-C_4-alkoxy part can be attached to any carbon atom of the C_1-C_4-alkyl part of said (C_1-C_4-alkoxy)-(C_1-C_4-alkyl)- group. A hyphen at the beginning or at the end of such a composite substituent indicates the point of attachment of said composite substituent to the rest of the molecule. Unless otherwise indicated, should a ring, comprising carbon atoms and optionally one or more heteroatoms, such as nitrogen, oxygen or sulfur atoms for example, be substituted with a substituent, it is possible for said substituent to be bound at any suitable position of said ring, be it bound to a suitable carbon atom and/or to a suitable heteroatom.

The term "comprising" when used in the specification includes "consisting of".

The terms as mentioned in the present text have the following meanings:

The term "C_1-C_4-alkyl" means a linear or branched, saturated, monovalent hydrocarbon group having 1, 2, 3, or 4 carbon atoms, *e.g.* a methyl, ethyl, propyl, isopropyl, butyl, *sec*-butyl, isobutyl, or *tert*-butyl group, or an isomer thereof. Particularly, said group has 1, 2 or 3 carbon atoms ("C_1-C_3-alkyl"), *e.g.* a methyl, ethyl, *n*-propyl or isopropyl group.

The term "five-membered heterocyclic ring containing 2 to 3 nitrogen atoms" means a monocyclic, saturated, partially unsaturated, or aromatic heterocycle with 5 ring atoms in total, which contains two or three ring nitrogen atoms.

Said five-membered heterocyclic ring, without being limited thereto, can be imidazolidin, pyrazolidin, dihydroimidazol, imidazol, pyrazol, or triazol, for example.

The term "C_1-C_6", as used in the present text, *e.g.* in the context of the definition of "C_1-C_6-alkyl" means an alkyl group having a finite number of carbon atoms of 1 to 6, *i.e.* 1, 2, 3, 4, 5 or 6 carbon atoms.

Further, as used herein, the term "C_3-C_7", as used in the present text, *e.g.* in the context of the definition of "C_3-C_7-cycloalkyl", means a cycloalkyl group having a finite number of carbon atoms of 3 to 7, *i.e.* 3, 4, 5, 6 or 7 carbon atoms.

When a range of values is given, said range encompasses each value and sub-range within said range.

For example:

"C_1-C" encompasses C_1, C_2, C_3, C_4, C_5, C_6, C_1-C_6, C_1-C_5, C_1-C_4, C_1-C_3, C_1-C_2, C_2-C_6, C_2-C_5, C_2-C_4, C_2-C_3, C_3-C_6, C_3-C_5, C_3-C_4, C_4-C_6, C_4-C_5, and C_5-C_6;

"C_1-C_3" encompasses C_1, C_2, C_3, C_1-C_3, C_1-C_2, C_2-C_3;"C_2-C_6" encompasses C_2, C_3, C_4, C_5, C_6, C_2-C_6, C_2-C_5, C_2-C_4, C_2-C_3, C_3-C_6, C_3-C_5, C_3-C_4, C_4-C_6, C_4-C_5, and C_5-C_6;

"C_3-C_{10}" encompasses C_3, C_4, C_5, C_6, C_7, C_8, C_9, C_{10}, C_3-C_{10}, C_3-C_9, C_3-C_8, C_3-C_7, C_3-C_6, C_3-C_5, C_3-C_4, C_4-C_{10}, C_4-C_9, C_4-C_8, C_4-C_7, C_4-C_6, C_4-C_5, C_5-C_{10}, C_5-C_9, C_5-C_8, C_5-C_7, C_5-C_6, C_6-C_{10}, C_6-C_9, C_6-C_8, C_6-C_7, C_7-C_{10}, C_7-C_9, C_7-C_8, C_8-C_{10}, C_8-C_9 and C_9-C_{10};

"C_3-C_8" encompasses C_3, C_4, C_5, C_6, C_7, C_8, C_3-C_8, C_3-C_7, C_3-C_6, C_3-C_5, C_3-C_4, C_4-C_8, C_4-C_7, C_4-C_6, C_4-C_5, C_5-C_8, C_5-C_7, C_5-C_6, C_6-C_8, C_6-C_7 and C_7-C_8;

"C_3-C_6" encompasses C_3, C_4, C_5, C_6, C_3-C_6, C_3-C_5, C_3-C_4, C_4-C_6, C_4-C_5, and C_5-C_6;

"C_4-C_8" encompasses C_4, C_5, C_6, C_7, C_8, C_4-C_8, C_4-C_7, C_4-C_6, C_4-C_5, C_5-C_8, C_5-C_7, C_5-C_6, C_6-C_8, C_6-C_7 and C_7-C_8;

"C_4-C_7" encompasses C_4, C_5, C_6, C_7, C_4-C_7, C_4-C_6, C_4-C_5, C_5-C_7, C_5-C_6 and C_6-C_7;

"C_4-C_6" encompasses C_4, C_5, C_6, C_4-C_6, C_4-C_5 and C_5-C_6;

"C_5-C_{10}" encompasses C_5, C_6, C_7, C_8, C_9, C_{10}, C_5-C_{10}, C_5-C_9, C_5-C_8, C_5-C_7, C_5-C_6, C_6-C_{10}, C_6-C_9, C_6-C_8, C_6-C_7, C_7-C_{10}, C_7-C_9, C_7-C_8, C_8-C_{10}, C_8-C_9 and C_9-C_{10};

"C_6-C_{10}" encompasses C_6, C_7, C_8, C_9, C_{10}, C_6-C_{10}, C_6-C_9, C_6-C_8, C_6-C_7, C_7-C_{10}, C_7-C_9, C_7-C_8, C_8-C_{10}, C_8-C_9 and C_9-C_{10}.

The term “halogen” or “halogen atom” means a fluorine, chlorine, bromine or iodine atom, particularly a fluorine, chlorine or bromine atom.

As used herein, the term “leaving group” means an atom or a group of atoms that is displaced in a chemical reaction as stable species taking with it the bonding electrons. In particular, such a leaving group is selected from the group comprising: halide, in particular fluoride, chloride, bromide or iodide, (methylsulfonyl)oxy, [(trifluoromethyl)sulfonyl]oxy, [(nonafluorobutyl)-sulfonyl]oxy, (phenylsulfonyl)oxy, [(4-methylphenyl)sulfonyl]oxy, [(4-bromophenyl)sulfonyl]oxy, [(4-nitrophenyl)sulfonyl]oxy, [(2-nitrophenyl)sulfonyl]oxy, [(4-isopropylphenyl)sulfonyl]oxy, [(2,4,6-triisopropylphenyl)sulfonyl]oxy, [(2,4,6-trimethylphenyl)sulfonyl]oxy, [(4-*tert*-butyl-phenyl)sulfonyl]oxy and [(4-methoxyphenyl)sulfonyl]oxy.

It is possible for the compounds of formula (I) to exist as isotopic variants. The invention therefore includes one or more isotopic variant(s) of the compounds of formula (I), particularly deuterium-containing compounds of formula (I).

The term "Isotopic variant" of a compound or a reagent is defined as a compound exhibiting an unnatural proportion of one or more of the isotopes that constitute such a compound.

The term "Isotopic variant of the compound of formula (I)" is defined as a compound of formula (I) exhibiting an unnatural proportion of one or more of the isotopes that constitute such a compound.

The expression "unnatural proportion" means a proportion of such isotope which is higher than its natural abundance. The natural abundances of isotopes to be applied in this context are described in "Isotopic Compositions of the Elements 1997", Pure Appl. Chem., 70(1), 217-235, 1998.

Examples of such isotopes include stable and radioactive isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, sulfur, fluorine, chlorine, bromine and iodine, such as ^{2}H (deuterium), ^{3}H (tritium), ^{11}C, ^{13}C, ^{14}C, ^{15}N, ^{17}O, ^{18}O, ^{32}P, ^{33}P, ^{33}S, ^{34}S, ^{35}S, ^{36}S, ^{18}F, ^{36}Cl, ^{82}Br, ^{123}I, ^{124}I, ^{125}I, ^{129}I and ^{131}I, respectively.

With respect to the treatment and/or prophylaxis of the disorders specified herein the isotopic variant(s) of the compounds of formula (I) preferably contain deuterium ("deuterium-containing compounds of formula (I)"). Isotopic variants of the compounds of formula (I) in which one or more radioactive isotopes, such as ^{3}H or ^{14}C, are incorporated are useful e.g., in drug and/or substrate tissue distribution studies. These isotopes are particularly preferred for the ease of their incorporation and detectability. Positron emitting isotopes such as ^{18}F or ^{11}C may be incorporated into a compound of formula (I). These isotopic variants of the compounds of formula (I) are useful for in vivo imaging applications. Deuterium-containing and ^{13}C-containing compounds of formula (I) can be used in mass spectrometry analyses in the context of preclinical or clinical studies.

Isotopic variants of the compounds of formula (I) can generally be prepared by methods known to a person skilled in the art, such as those described in the schemes and/or examples herein, by substituting a reagent for an isotopic variant of said reagent, preferably for a deuterium-containing reagent. Depending on the desired sites of deuteration, in some cases deuterium from D_2O can be incorporated either directly into the compounds or into reagents that are useful for synthesizing such compounds. Deuterium gas is also a useful reagent for incorporating deuterium into molecules. Catalytic deuteration of olefinic bonds and acetylenic bonds is a rapid route for incorporation of deuterium. Metal catalysts (i.e. Pd, Pt, and Rh) in the presence of deuterium gas can be used to directly exchange deuterium for hydrogen in functional groups containing hydrocarbons. A variety of deuterated reagents and synthetic building blocks are commercially available from companies such as for example C/D/N Isotopes, Quebec, Canada; Cambridge Isotope Laboratories Inc., Andover, MA, USA; and CombiPhos Catalysts, Inc., Princeton, NJ, USA.

The term "deuterium-containing compound of formula (I)" is defined as a compound of formula (I), in which one or more hydrogen atom(s) is/are replaced by one or more deuterium atom(s) and in which the abundance of deuterium at each deuterated position of the compound of formula (I) is higher than the natural abundance of deuterium, which is about 0.015%. Particularly, in a deuterium-containing compound of formula (I) the abundance of deuterium at each deuterated position of the compound of formula (I) is higher than 10%, 20%, 30%, 40%, 50%, 60%, 70% or 80%, preferably higher than 90%, 95%, 96% or 97%, even more preferably higher than 98% or 99% at said position(s). It is understood that the abundance of deuterium at each deuterated position is independent of the abundance of deuterium at other deuterated position(s).

The selective incorporation of one or more deuterium atom(s) into a compound of formula (I) may alter the physicochemical properties (such as for example acidity [C. L. Perrin, et al., J. Am. Chem. Soc., 2007, 129, 4490], basicity [C. L. Perrin et al., J. Am. Chem. Soc., 2005, 127, 9641], lipophilicity [B. Testa et al., Int. J. Pharm., 1984, 19(3), 271]) and/or the metabolic profile of the molecule and may result in changes in the ratio of parent compound to metabolites or in the amounts of metabolites formed. Such changes may result in certain therapeutic advantages and hence may be preferred in some circumstances. Reduced rates of metabolism and metabolic switching, where the ratio of metabolites is changed, have been reported (A. E. Mutlib et al., Toxicol. Appl. Pharmacol., 2000, 169, 102). These changes in the exposure to parent drug and metabolites can have important consequences with respect to the pharmacodynamics, tolerability and efficacy of a deuterium-containing compound of formula (I). In some cases deuterium substitution reduces or eliminates the formation of an undesired or toxic metabolite and enhances the formation of a desired metabolite (e.g. Nevirapine: A. M. Sharma et al., Chem. Res. Toxicol., 2013, 26, 410; Efavirenz: A. E. Mutlib et al., Toxicol. Appl. Pharmacol., 2000, 169, 102). In other cases the major effect of deuteration is to reduce the rate of systemic clearance. As a result, the biological half-life of the compound is increased. The potential clinical benefits would include the ability to maintain similar systemic exposure with decreased peak levels and increased trough levels. This could result in lower side effects and enhanced efficacy, depending on the particular compound's pharmacokinetic/ pharmacodynamic relationship. ML-337 (C. J. Wenthur et al., J. Med. Chem., 2013, 56, 5208) and Odanacatib (K. Kassahun et al., WO2012/112363) are examples for this deuterium effect. Still other cases have been reported in which reduced rates of metabolism result in an increase in exposure of the drug without changing the rate of systemic clearance (e.g. Rofecoxib: F. Schneider et al., Arzneim. Forsch. / Drug. Res., 2006, 56, 295; Telaprevir: F. Maltais et al., J. Med. Chem., 2009, 52, 7993). Deuterated drugs showing this effect may have reduced dosing requirements (e.g. lower number of doses or lower dosage to achieve the desired effect) and/or may produce lower metabolite loads.

A compound of formula (I) may have multiple potential sites of attack for metabolism. To optimize the above-described effects on physicochemical properties and metabolic profile, deuterium-containing compounds of formula (I) having a certain pattern of one or more deuterium-hydrogen exchange(s) can be selected. Particularly, the deuterium atom(s) of deuterium-containing compound(s) of formula (I) is/are attached to a carbon atom and/or is/are located at those positions of the compound of formula (I), which are sites of attack for metabolizing enzymes such as e.g., cytochrome P_{450}.

Where the plural form of the word compounds, salts, polymorphs, hydrates, solvates and the like, is used herein, this is taken to mean also a single compound, salt, polymorph, isomer, hydrate, solvate or the like.

By "stable compound' or "stable structure" is meant a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

The compounds of the present invention optionally contain one or more asymmetric centres, depending upon the location and nature of the various substituents desired. It is possible that one or more asymmetric carbon atoms are present in the (R) or (S) configuration, which can result in racemic mixtures in the case of a single asymmetric centre, and in diastereomeric mixtures in the case of multiple asymmetric centres. In certain instances, it is possible that asymmetry also be present due to restricted rotation about a given bond, for example, the central bond adjoining two substituted aromatic rings of the specified compounds.

Preferred compounds are those which produce the more desirable biological activity. Separated, pure or partially purified isomers and stereoisomers or racemic or diastereomeric mixtures of the compounds of the present invention are also included within the scope of the present invention. The purification and the separation of such materials can be accomplished by standard techniques known in the art.

The optical isomers can be obtained by resolution of the racemic mixtures according to conventional processes, for example, by the formation of diastereoisomeric salts using an optically active acid or base or formation of covalent diastereomers. Examples of appropriate acids are tartaric, diacetyltartaric, ditoluoyltartaric and camphorsulfonic acid. Mixtures of diastereoisomers can be separated into their individual diastereomers on the basis of their physical and/or chemical differences by methods known in the art, for example, by chromatography or fractional crystallisation. The optically active bases or acids are then liberated from the separated diastereomeric salts. A different process for separation of optical isomers involves the use of chiral chromatography (*e.g.*, HPLC columns using a chiral phase), with or without conventional derivatisation, optimally chosen to maximise the separation of the enantiomers. Suitable HPLC columns using a chiral phase are commercially available, such as those manufactured by Daicel, *e.g.*, Chiracel OD and Chiracel OJ, for example, among many

others, which are all routinely selectable. Enzymatic separations, with or without derivatisation, are also useful. The optically active compounds of the present invention can likewise be obtained by chiral syntheses utilizing optically active starting materials.

In order to distinguish different types of isomers from each other reference is made to IUPAC Rules Section E (Pure Appl Chem 45, 11-30, 1976).

The present invention includes all possible stereoisomers of the compounds of the present invention as single stereoisomers, or as any mixture of said stereoisomers, *e.g.* (R)- or (S)-isomers, in any ratio. Isolation of a single stereoisomer, *e.g.* a single enantiomer or a single diastereomer, of a compound of the present invention is achieved by any suitable state of the art method, such as chromatography, especially chiral chromatography, for example.

Further, the compounds of the present invention can exist as N-oxides, which are defined in that at least one nitrogen of the compounds of the present invention is oxidised. The present invention includes all such possible N-oxides.

The present invention also covers useful forms of the compounds of the present invention, such as metabolites, hydrates, solvates, prodrugs, salts, in particular pharmaceutically acceptable salts, and/or co-precipitates.

The compounds of the present invention can exist as a hydrate, or as a solvate, wherein the compounds of the present invention contain polar solvents, in particular water, methanol or ethanol for example, as structural element of the crystal lattice of the compounds. It is possible for the amount of polar solvents, in particular water, to exist in a stoichiometric or non-stoichiometric ratio. In the case of stoichiometric solvates, *e.g.* a hydrate, hemi-, (semi-), mono-, sesqui-, di-, tri-, tetra-, penta- *etc.* solvates or hydrates, respectively, are possible. The present invention includes all such hydrates or solvates.

Further, it is possible for the compounds of the present invention to exist in free form, *e.g.* as a free base, or as a free acid, or as a zwitterion, or to exist in the form of a salt. Said salt may be any salt, either an organic or inorganic addition salt, particularly any pharmaceutically acceptable organic or inorganic addition salt, which is customarily used in pharmacy, or which is used, for example, for isolating or purifying the compounds of the present invention.

The term “pharmaceutically acceptable salt" refers to an inorganic or organic acid addition salt of a compound of the present invention. For example, see S. M. Berge, *et al.* “Pharmaceutical Salts,” J. Pharm. Sci. 1977, 66, 1-19.

A suitable pharmaceutically acceptable salt of the compounds of the present invention may be, for example, an acid-addition salt of a compound of the present invention bearing a nitrogen atom, in a chain or in a ring, for example, which is sufficiently basic, such as an acid-addition

salt with an inorganic acid, or "mineral acid", such as hydrochloric, hydrobromic, hydroiodic, sulfuric, sulfamic, bisulfuric, phosphoric, or nitric acid, for example, or with an organic acid, such as formic, acetic, acetoacetic, pyruvic, trifluoroacetic, propionic, butyric, hexanoic, heptanoic, undecanoic, lauric, benzoic, salicylic, 2-(4-hydroxybenzoyl)-benzoic, camphoric, cinnamic, cyclopentanepropionic, digluconic, 3-hydroxy-2-naphthoic, nicotinic, pamoic, pectinic, 3-phenylpropionic, pivalic, 2-hydroxyethanesulfonic, itaconic, trifluoromethanesulfonic, dodecylsulfuric, ethanesulfonic, benzenesulfonic, para-toluenesulfonic, methanesulfonic, 2-naphthalenesulfonic, naphthalinedisulfonic, camphorsulfonic, citric, tartaric, stearic, lactic, oxalic, malonic, succinic, malic, adipic, alginic, maleic, fumaric, D-gluconic, mandelic, ascorbic, glucoheptanoic, glycerophosphoric, aspartic, sulfosalicylic, or thiocyanic acid, for example.

Further, another suitably pharmaceutically acceptable salt of a compound of the present invention which is sufficiently acidic, is an alkali metal salt, for example a sodium or potassium salt, an alkaline earth metal salt, for example a calcium, magnesium or strontium salt, or an aluminium or a zinc salt, or an ammonium salt derived from ammonia or from an organic primary, secondary or tertiary amine having 1 to 20 carbon atoms, such as ethylamine, diethylamine, triethylamine, ethyldiisopropylamine, monoethanolamine, diethanolamine, triethanolamine, dicyclohexylamine, dimethylaminoethanol, diethylaminoethanol, tris(hydroxymethyl)amino-methane, procaine, dibenzylamine, *N*-methylmorpholine, arginine, lysine, 1,2-ethylenediamine, *N*-methylpiperidine, *N*-methyl-glucamine, *N,N*-dimethyl-glucamine, *N*-ethyl-glucamine, 1,6-hexanediamine, glucosamine, sarcosine, serinol, 2-amino-1,3-propanediol, 3-amino-1,2-propanediol, 4-amino-1,2,3-butanetriol, or a salt with a quarternary ammonium ion having 1 to 20 carbon atoms, such as tetramethylammonium, tetraethylammonium, tetra(*n*-propyl)-ammonium, tetra(*n*-butyl)ammonium, *N*-benzyl-*N,N,N*-trimethylammonium, choline or benzalkonium.

Those skilled in the art will further recognise that it is possible for acid addition salts of the claimed compounds to be prepared by reaction of the compounds with the appropriate inorganic or organic acid via any of a number of known methods. Alternatively, alkali and alkaline earth metal salts of acidic compounds of the present invention are prepared by reacting the compounds of the present invention with the appropriate base via a variety of known methods.

The present invention includes all possible salts of the compounds of the present invention as single salts, or as any mixture of said salts, in any ratio.

In the present text, in particular in the Experimental Section, for the synthesis of intermediates and of examples of the present invention, when a compound is mentioned as a salt form with the corresponding base or acid, the exact stoichiometric composition of said salt form, as obtained by the respective preparation and/or purification process, is, in most cases, unknown.

Unless specified otherwise, suffixes to chemical names or structural formulae relating to salts, such as "hydrochloride", "trifluoroacetate", "sodium salt", or "x HCl", "x CF_3COOH", "x Na^+", for example, mean a salt form, the stoichiometry of which salt form not being specified.

This applies analogously to cases in which synthesis intermediates or example compounds or salts thereof have been obtained, by the preparation and/or purification processes described, as solvates, such as hydrates, with (if defined) unknown stoichiometric composition.

Furthermore, the present invention includes all possible crystalline forms, or polymorphs, of the compounds of the present invention, either as single polymorph, or as a mixture of more than one polymorph, in any ratio.

Moreover, the present invention also includes prodrugs of the compounds according to the invention. The term “prodrugs” here designates compounds which themselves can be biologically active or inactive, but are converted (for example metabolically or hydrolytically) into compounds according to the invention during their residence time in the body.

DETAILED DESCRIPTION OF THE INVENTION

In one embodiment, the present invention relates to compounds of formula (I), wherein:

R^1 represents methyl, isopropyl, cyclopropyl, difluoromethyl, trifluoromethyl, or cyano;

R^2 represents methyl, ethyl, isopropyl, cyclopropyl, trifluoromethyl, chloro, or bromo;

X represents -CH=CH- or -S-;

or an N-oxide thereof.

In another embodiment, the present invention relates to compounds of formula (I), wherein:

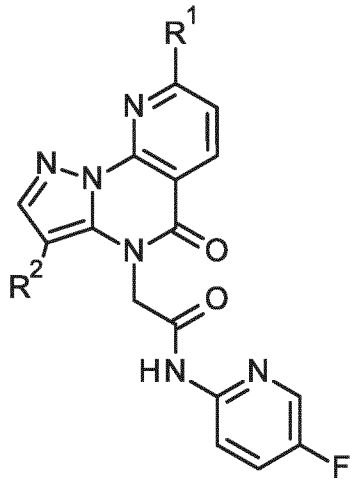
R^1 represents methyl, difluoromethyl, or trifluoromethyl;

R^2 represents methyl, ethyl, or cyclopropyl;

X represents -CH=CH- or -S- ;

or an N-oxide thereof.

In a further embodiment, the present invention relates to compounds of formula (II):



(II)

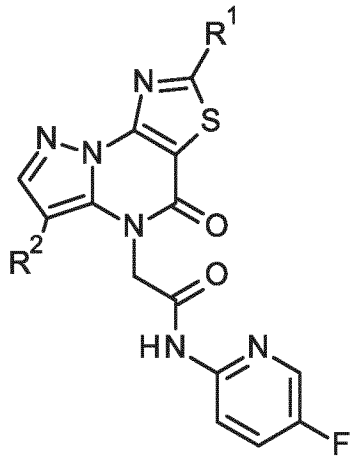
in which:

R^1 represents methyl, difluoromethyl, or trifluoromethyl;

R^2 represents methyl, ethyl, or cyclopropyl;

or an N-oxide thereof.

In a further embodiment, the present invention relates to compounds of formula (III)



(III)

in which:

R^1 represents methyl, difluoromethyl, or trifluoromethyl;

R^2 represents methyl, ethyl, i-propyl, or cyclopropyl;

or an N-oxide thereof.

In a preferred embodiment, the present invention relates to compounds of formula (II):

N-(5-fluoropyridin-2-yl)-2-[3-methyl-5-oxo-8-(trifluoromethyl)pyrazolo[1,5-a]pyrido[3,2-e]pyrimidin-4(5H)-yl]acetamide,

2-[3-chloro-5-oxo-8-(trifluoromethyl)pyrazolo[1,5-a]pyrido[3,2-e]pyrimidin-4(5H)-yl]-N-(5-fluoropyridin-2-yl)acetamide,

2-[3-cyclopropyl-5-oxo-8-(trifluoromethyl)pyrazolo[1,5-a]pyrido[3,2-e]pyrimidin-4(5H)-yl]-N-(5-fluoropyridin-2-yl)acetamide,

2-[3-cyclopropyl-8-(difluoromethyl)-5-oxopyrazolo[1,5-a]pyrido[3,2-e]pyrimidin-4(5H)-yl]-N-(5-fluoropyridin-2-yl)acetamide,

2-[3-cyclopropyl-5-oxo-8-(propan-2-yl)pyrazolo[1,5-a]pyrido[3,2-e]pyrimidin-4(5H)-yl]-N-(5-fluoropyridin-2-yl)acetamide,

2-(3-cyclopropyl-8-methyl-5-oxopyrazolo[1,5-a]pyrido[3,2-e]pyrimidin-4(5H)-yl)-N-(5-fluoropyridin-2-yl)acetamide,

2-(3-chloro-8-cyclopropyl-5-oxopyrazolo[1,5-a]pyrido[3,2-e]pyrimidin-4(5H)-yl)-N-(5-fluoropyridin-2-yl)acetamide,

2-(3,8-dicyclopropyl-5-oxopyrazolo[1,5-a]pyrido[3,2-e]pyrimidin-4(5H)-yl)-N-(5-fluoropyridin-2-yl)acetamide,

2-(8-cyano-3-cyclopropyl-5-oxopyrazolo[1,5-a]pyrido[3,2-e]pyrimidin-4(5H)-yl)-N-(5-fluoropyridin-2-yl)acetamide,

2-[3-ethyl-5-oxo-8-(trifluoromethyl)pyrazolo[1,5-a]pyrido[3,2-e]pyrimidin-4(5H)-yl]-N-(5-fluoropyridin-2-yl)acetamide,

2-[3-ethyl-5-oxo-8-(propan-2-yl)pyrazolo[1,5-a]pyrido[3,2-e]pyrimidin-4(5H)-yl]-N-(5-fluoropyridin-2-yl)acetamide,

N-(5-fluoropyridin-2-yl)-2-[5-oxo-3-(propan-2-yl)-8-(trifluoromethyl)pyrazolo[1,5-a]pyrido[3,2-e]pyrimidin-4(5H)-yl]acetamide,

2-[3-bromo-5-oxo-8-(trifluoromethyl)pyrazolo[1,5-a]pyrido[3,2-e]pyrimidin-4(5H)-yl]-N-(5-fluoropyridin-2-yl)acetamide,

N-(5-fluoropyridin-2-yl)-2-[5-oxo-3,8-bis(trifluoromethyl)pyrazolo[1,5-a]pyrido[3,2-e]pyrimidin-4(5H)-yl]acetamide, and

2-[8-cyclopropyl-5-oxo-3-(trifluoromethyl)pyrazolo[1,5-a]pyrido[3,2-e]pyrimidin-4(5H)-yl]-N-(5-fluoropyridin-2-yl)acetamide.

In a preferred embodiment, the present invention relates to compounds of formula (III):

2-(2,6-dicyclopropyl-4-oxopyrazolo[1,5-a][1,3]thiazolo[5,4-e]pyrimidin-5(4H)-yl)-N-(5-fluoropyridin-2-yl)acetamide, and

2-[6-cyclopropyl-4-oxo-2-(trifluoromethyl)pyrazolo[1,5-a][1,3]thiazolo[5,4-e]pyrimidin-5(4H)-yl]-N-(5-fluoropyridin-2-yl)acetamide.

Most preferred are the following compounds of formula (II):

N-(5-fluoropyridin-2-yl)-2-[3-methyl-5-oxo-8-(trifluoromethyl)pyrazolo[1,5-a]pyrido[3,2-e]pyrimidin-4(5H)-yl]acetamide,

2-[3-chloro-5-oxo-8-(trifluoromethyl)pyrazolo[1,5-a]pyrido[3,2-e]pyrimidin-4(5H)-yl]-N-(5-fluoropyridin-2-yl)acetamide, and

2-[3-cyclopropyl-5-oxo-8-(trifluoromethyl)pyrazolo[1,5-a]pyrido[3,2-e]pyrimidin-4(5H)-yl]-N-(5-fluoropyridin-2-yl)acetamide

N-(5-fluoropyridin-2-yl)-2-[5-oxo-3-(propan-2-yl)-8-(trifluoromethyl)pyrazolo[1,5-a]pyrido[3,2-e]pyrimidin-4(5H)-yl]acetamide.

The present invention covers any sub-combination within any embodiment or aspect of the present invention of compounds of formula (I), *supra*.

The present invention covers methods of preparing compounds of the present invention of formula (I), said methods comprising the steps as described in the Experimental Section herein.

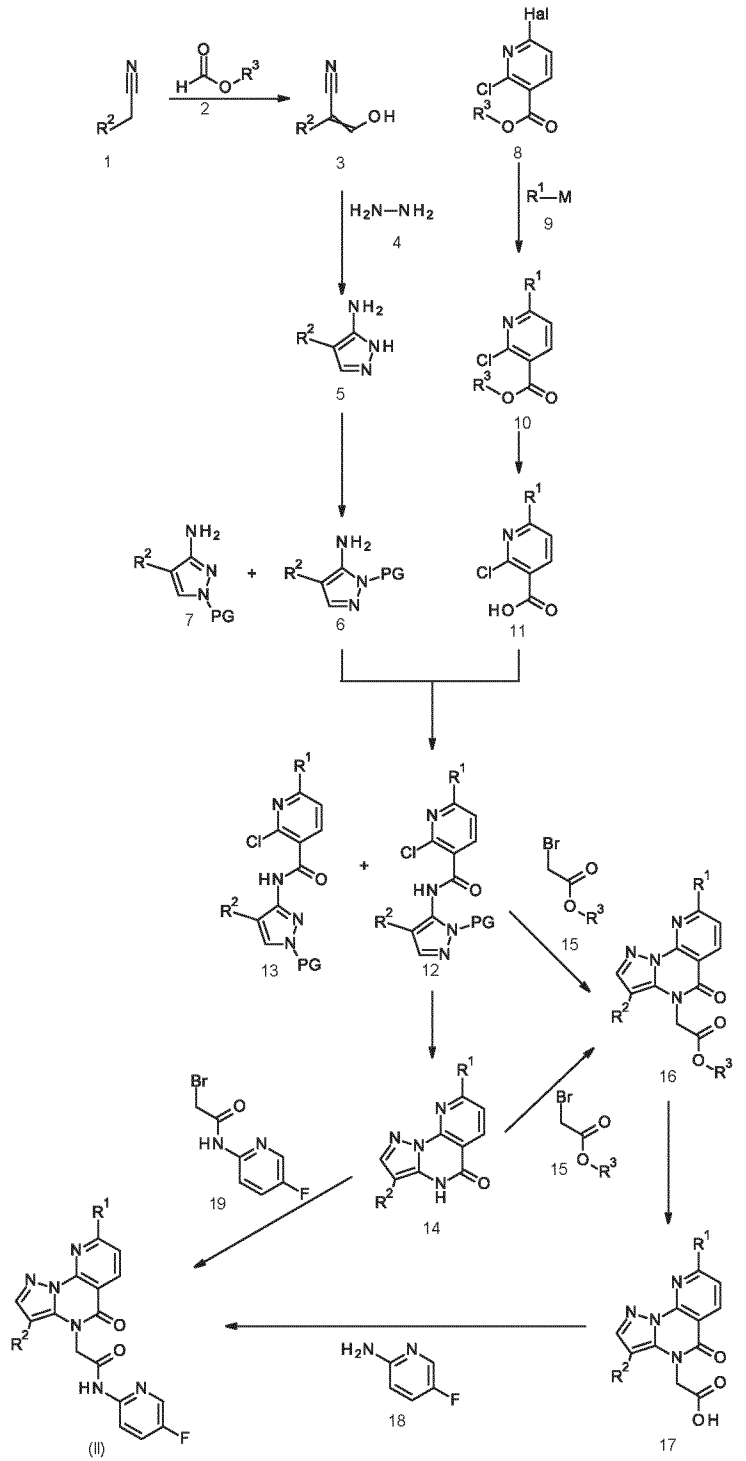
The compounds according to the invention of formula (I) are prepared according to the following schemes 1 to 6. The schemes and procedures described below illustrate synthetic routes to the compounds of formulae (III), (IV), (V), (VI), (VII), and (VIII) of the invention and are not intended to be limiting. It is clear to the person skilled in the art that the order of transformations as exemplified in schemes 1 to 6 can be modified in various ways. The order of transformations exemplified in these schemes is therefore not intended to be limiting. Appropriate protecting groups and their introduction and cleavage are well-known to the person skilled in the art. Specific examples are described in the subsequent paragraphs.

The starting materials are either commercially available or can be prepared according to procedures available from the public domain, as understandable to the person skilled in the art. Specific examples are described in the Experimental Section.

Six routes for the preparation of compounds of formulae (III) – (VIII) are described in schemes 1 to 6.

Synthesis of compounds of general formula (I) of the present invention

Scheme 1



Compounds of general formula (II) can be synthesised according to the routes depicted in Scheme 1 wherein R^1 and R^2 have the same meaning as defined for formula (I)–(III), R^3

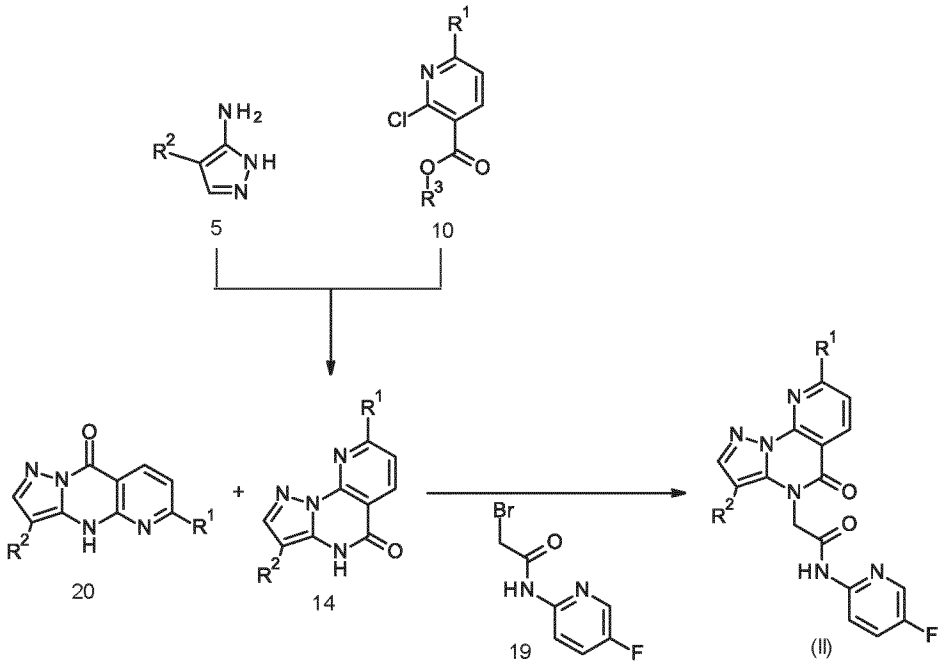
represents C_1-C_4-alkyl, preferably methyl, ethyl or *tert*-butyl, and PG represents a protecting group for example *tert*-butoxycarbonyl (Boc), *p*-methoxybenzyl (PMB), or tetrahydropyran-2-yl (THP).

For the construction of the 3,8-disubstituted pyrazolo[1,5-a]pyrido[3,2-e]pyrimidin-5(4H)-one cores of general formula 14 two building blocks are necessary, namely 4-substituted pyrazol-5-amines of general formula 6 and 7, protected at one pyrazole nitrogen, and 6-substituted 2-chloro-nicotinic acids of formula 11. The 4-substituted pyrazol-5-amines of formula 6 and 7 can be synthesized from commercially available 1-substituted acetonitriles of formula 1. These substituted acetonitriles of formula 1 are formylated with formic esters of general formula 2, wherein R^3 represents C_1-C_4-alkyl, preferably methyl, ethyl or *tert*-butyl. This formylation is performed under basic conditions, using a strong base like for example lithium diisopropylamide, lithium bis(trimethylsilyl)amide, or potassium *tert*-butoxide in etheral or polar aprotic solvents like for example THF, CPME, 2-MeTHF, MTBE, DMF, or DMSO at temperatures from -78°C to 0°C. After subsequent addition of the formic esters of general formula 2 the reaction temperature can be raised to room temperature. The formed 3-hydroxyacrylonitriles of formula 3 can be cyclized to the corresponding 5-aminopyrazoles of formula 5 using for example hydrazine monohydrate or salts of hydrazine in an alcoholic solvent like ethanol at temperatures between 40°C and 80°C. Acetic acid can also be added to the reaction mixture. The 5-aminopyarzoles of formula 5 can be protected at position 1 or 2 at the pyrazole by various methods known to the person skilled in the art. The protection groups can be for example *tert*-butoxycarbonyl (Boc), *p*-methoxybenzyl (PMB), or tetrahydropyran-2-yl (THP), but are not limited to the cited ones. The preferred protection group is tert-butoxycarbonyl (Boc). The protection group like *tert*-butoxycarbonyl (Boc), or *p*-methoxybenzyl (PMB) is introduced under basic conditions using an organic or inorganic base like *N*,*N*-diisopropylethylamine or potassium carbonate in polar aprotic or halogenated solvents at temperatures ranging from 25°C to 40°C. A protection group like tetrahydropyran-2-yl (THP) can be installed under acidic conditions using for example 4-toluenesulfonic acid as catalyst in ethereal solvents like THF, or CPME at temperatures from 40°C to 80°C. Under basic conditions the protection is usually regioselective with the 1-protected aminopyrazoles of general formula 6 as the major regioisomer. The minor regioisomer of general formula 7 is anyhow formed with ratios ranging from 2% to 15%. This minor isomer does not need to be separated as under cyclization conditions to the tricyclic core the pyrazole is deprotected beforehand. The 6-substituted 2-chloro-nicotinic acids of formula 11 can be obtained from commercially available 6-halogenated 2-chloronicotinates of formula 8, wherein R^3 again represents C_1-C_4-alkyl, preferably methyl, ethyl or *tert*-butyl. The substituent at position 6 can be introduced using a nucleophilic organometallic species, like for example a magnesium organyl (Grignard reagent), a zinc organyl (Reformatzky reagent), or a boron organyl (boronic acid, pinacol ester of boronic acid, *N*-methylimidodiacetic boronic acid esters (MIDA boronates)). The introduction of the substituent R^1 can for example be done under Suzuki-Miyaura cross-

coupling reaction conditions between 6-halogenated 2-chloronicotinates of formula 8 and organometallic species of general formula 9, wherein M stands for a boronic acid or an ester of a boronic acid. The different Suzuki-Miyaura cross-coupling methods very well known to those skilled in the art can be employed using a Pd catalyst (like palladium(II)diacetate), a ligand (like tricyclohexylphosphine) and a base (like potassium carbonate) in an aprotic solvent (such as toluene) at temperatures between 70°C and 120°C to get the 6-substituted nicotinates of general formula 10. In case a zinc organyl is used as the organometallic species of general formula 9, typically a nickel- or palladium-catalyzed Negishi cross-coupling using a catalyst (like tris(dibenzylideneacetone)dipalladium(0)), a ligand (like triphenylphospoine) in an aprotic solvent (such as THF) at temperatures between 25°C and 100°C can be employed. For magnesium organyls as organometallic species of general formula 9 a nickel- or palladium-catalyzed Kumada coupling can be done using a catalyst (like dichloro-bis-(triphenylphosphine)-nickel(II)) and a ligand (like triphenylphospoine) in an aprotic solvent (such as MTBE) at temperatures between 0°C and 80°C. After formation of 6-substituted nicotinates of general formula 10, the ester can be saponified under basic conditions in case R^3 represents for example a methyl or ethyl or under acidic conditions in case R^3 represents for example a *tert*-butyl. Under basic conditions for example lithium hydroxide can be used as base in aqueous THF and for acidic ester hydrolysis e.g. HCl in dioxane or TFA optionally in an appropriate solvent like CH_2Cl_2 are possible reaction conditions. In the next step, the formed nicotinic acid compounds of general formula 11 are coupled with the aminopyrazoles of general formula 6 and 7 under classical amide coupling reaction conditions. Therefore the acids of general formula 11 are activated using a well known coupling reagent like for example HATU, T_3P, CDI, or EDC or by intermediate formation of an acyl chloride (not shown) using for example thionyl chloride ($SOCl_2$), phosphoryl chloride ($POCl_3$), or 1-chlor-1-dimethylamino-2-methyl-1-propen (Ghosez reagent). Subsequent reaction with the aminopyrazoles of general formula 6 and 7 in presence of an organic base like *N*,*N*-diisopropylethylamine or *N*,*N*-dicyclohexylmethylamine in aprotic solvents like toluene, THF, or CH_2Cl_2 at temperatures from 20°C to 80°C lead to the amides of formula 12 and 13. These amides can be cyclized to the 3,8-disubstituted pyrazolo[1,5-a]pyrido[3,2-e]pyrimidin-5(4H)-one core of general formula 14 under acidic or basic deprotection conditions. In case of acidic conditions HCl in dioxane or TFA optionally in an appropriate solvent like CH_2Cl_2 case be employed at temperatures from 0°C to 40°C and for the basic deprotection inorganic bases like potassium carbonate or potassium tert-butoxide in polar aprotic solvents like e.g. DMSO or NMP at temperatures from 80°C to 150°C are applicable. For protection groups like p-methoxybenzyl (PMB) also oxidative cleavage with e.g. ceric ammonium nitrate (CAN) in aqueous polar aprotic solvents like acetonitrile from 0°C to 40°C might be an option for deprotection. The tricyclic core of general formula 14 can then be alkylated using esters of bromoacetate of formula 15 wherein R^3 again represents C_1-C_4-alkyl, preferably methyl, ethyl or *tert*-butyl. Using potassium carbonate as base in polar aprotic solvents like DMSO or NMP leads to the regioselective

formation of the *N*-alkylated products of general formula 16 at temperatures from 20°C to 40°C. The corresponding *O*-alkylated side products (not shown in Scheme 1) are only formed in less than 5% under these reaction conditions. As the cyclization to compounds of general formula 14 and the subsequent *N*-alkylation to products of formula 16 can be done with the same base in the same solvent these two reactions can also be performed one pot without isolation of intermediate 14. The acetates of general formula 16 can be hydrolyzed to the corresponding acids of general formula 17 using the same conditions as described for the hydrolysis of the nicotinate esters of formula 10. The final coupling of acids of general formula 17 with 5-fluoropyridin-2-amine of formula 18 can be done using an appropriate activating agent, like for example T_3P, CDI, HATU, EDC or thionyl chloride optionally in presence of a base like *N,N*-diisopropylethylamine in an appropriate solvent like CH_2Cl_2, DMF, or pyridine at temperatures ranging from 0°C to 60°C. The obtained final compounds of general formula (II) are also directly accessible from the non-alkylated tricyclic core compounds of general formula 14 using 2-bromo-N-(5-fluoropyridin-2-yl)acetamide of formula 19 as electrophile. Typical reaction conditions include for example the presence of a base like sodium carbonate in a polar aprotic solvent like NMP or DMF at temperatures from 20°C to 50°C. The usage of 2-bromo-N-(5-fluoropyridin-2-yl)acetamide of formula 19 as electrophile usually results in higher percentage of the *O*-alkyated side product (up to 50% possible) next the desired *N*-alkylated final products of general formula (II).

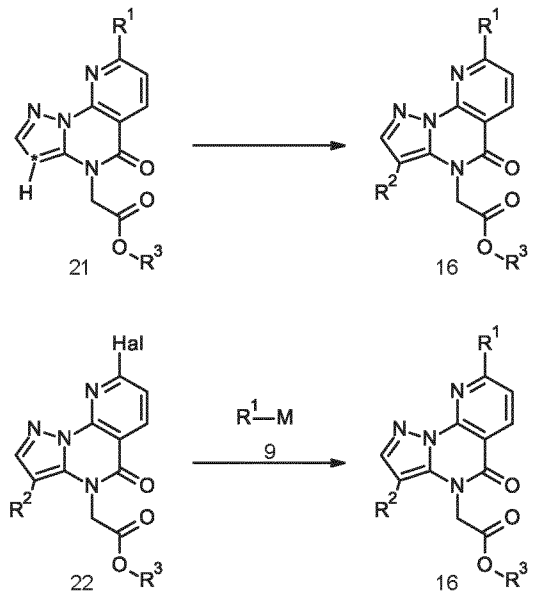
Scheme 2



Compounds of general formula (II) can be synthesised according to the route depicted in Scheme 2, wherein R^1 and R^2 have the same meaning as defined for formula (I) – (III), and R^3 and PG have the same meaning as described under Scheme 1.

The non protected aminopyrazoles of general formula 5 can also be employed to directly form the 3,8-disubstituted pyrazolo[1,5-a]pyrido[3,2-e]pyrimidin-5(4H)-one cores of general formula 14. Therefore the aminopyrazoles of formula 5 are reacted with 6-substituted 2-chloro-nicotinate esters of formula 10, wherein R^3 represents again C_1-C_4-alkyl, preferably methyl, ethyl or *tert*-butyl, under strong acidic conditions using polyphosphoric acid directly as solvent to mainly form the kinked tricyclic core of general formula 14. Up to 5% of the linear core of general formula 20 might be observed as side product under the strongly acidic reaction conditions. If a weaker acid like acetic acid is used as solvent the linear core of formula 20 is formed as the major product and by employment of an alcoholic solvent like ethanol or *n*-butanol the liner core of formula 20 is formed exclusively. Having separated the kinked core intermediate of general formula 14 the electrophile 2-bromo-N-(5-fluoropyridin-2-yl)acetamide of formula 19 can be used to directly *N*-alkylate the kinked core to get the desired final products of general formula (II). As already described for Scheme 1 e.g. sodium carbonate might be added as base in a polar aprotic solvent like NMP or DMF at temperatures from 20°C to 50°C to perform this *N*-alkylation. Also here, the *O*-alkylated side product might be observed and needs to be separated from the desired *N*-alkylated product of general formula (II).

Scheme 3

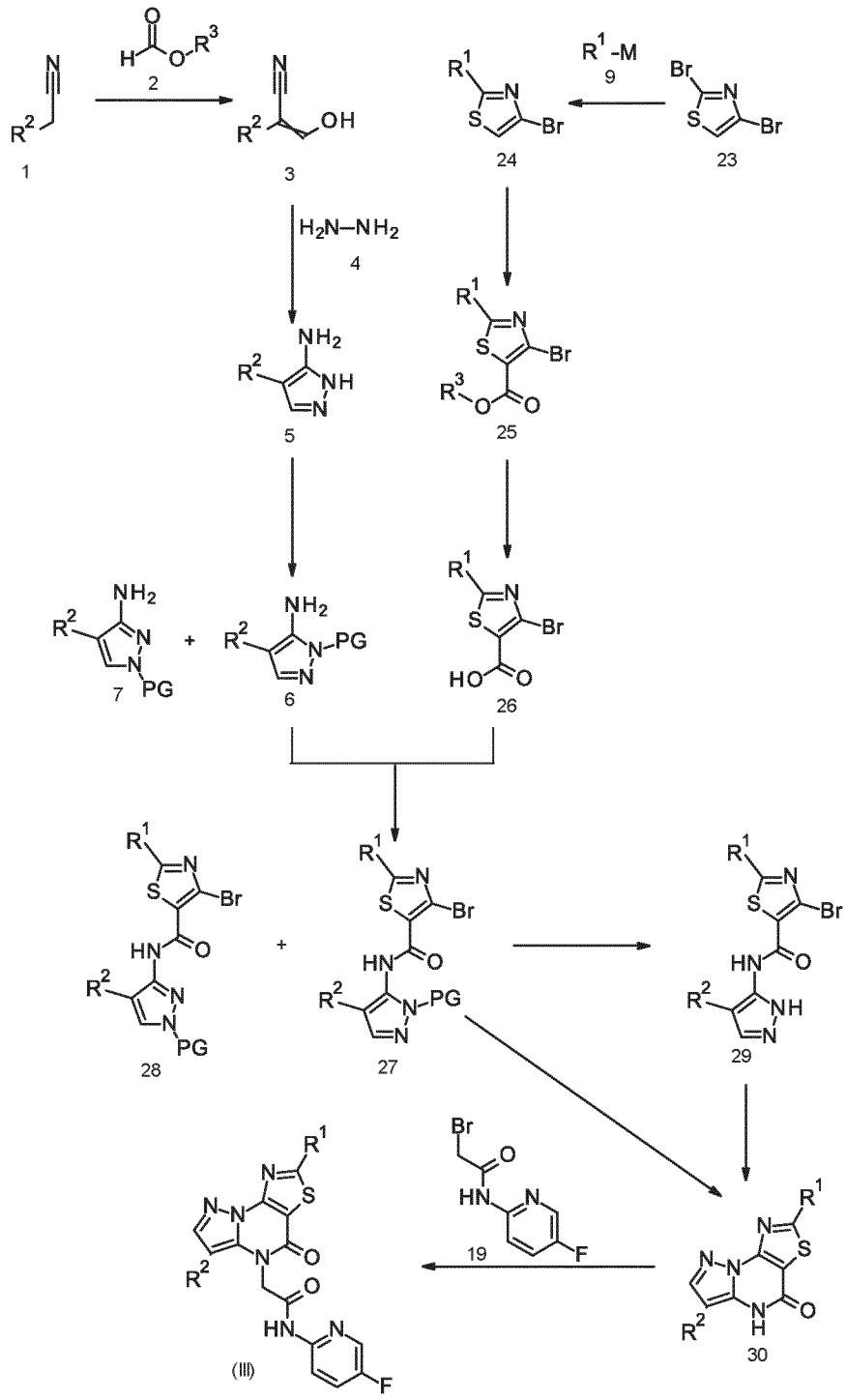


Intermediates of general formula 16 can be synthesised according to the route depicted in Scheme 3, wherein R^1 and R^2 have the same meaning as defined for formula (I) – (III), and R^3 and PG have the same meaning as described under Scheme 1.

The substituents R^1 and R^2 included in the final products of general formula (II) don't need to be present already from the beginning in the corresponding aminopyrazoles of general formula 5 and the 6-substituted 2-chloro-nicotinic acids of formula 11, but can also be introduced later on at appropriate states of intermediates. One such appropriate intermediate state is depicted in

Scheme 3 for the compounds of formula 21, where substituent R^2 at the pyrazole is still missing. As the position 4 at the pyrazole, depicted with an asterisk (*), is electron-rich it can be attacked by an appropriate electrophile. For example this position at the pyrazole can be chlorinated using *N*-chlorosuccinimide (NCS) in an appropriate polar solvent like ethyl acetate at temperatures from 20°C to 60°C. The chlorination step might be accelerated using an acidic additive like sulfuric acid. Brominations can also be performed using *N*-bromosuccinimide (NBS) or bromine (Br_2) as electrophile source. Fluorination at the 4 position of the pyrazole can be done using 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (Selectfluor) in polar aprotic solvents like acetonitrile including an acidic additive like trifluoroacetic acid (TFA). The substituent R^2, in *ortho*-position to the pyridine nitrogen, can be introduced using a nucleophilic organometallic species of general formula 9, already described in Scheme 1, like for example a magnesium organyl (Grignard reagent), a zinc organyl (Reformatzky reagent), or a boron organyl (boronic acid, pinacol ester of boronic acid, *N*-methylimidodiacetic boronic acid esters (MIDA boronates)). Using *ortho*-halogenated pyridines of general formula 22, as depicted in Scheme 3, a nickel- or palladium-catalyzed cross-coupling reaction with an organometallic species of general formula 9 might lead to the desired intermediates of general formula 16. As already described under Scheme 1 and also known to a person skilled in the art, a Suzuki-Miyaura, a Negishi, or a Kumada cross-coupling reaction might be used to build the intermediates of general formula 16.

Scheme 4



Compounds of general formula (III) can be synthesised according to the route depicted in Scheme 4, wherein R^1 and R^2 have the same meaning as defined for formula (I) – (III), and R^3 and PG have the same meaning as described under Scheme 1.

For the synthesis of 2,6-disubstituted pyrazolo[1,5-a][1,3]thiazolo[5,4-e]pyrimidin-4(5H)-one cores of general formula 30 according to Scheme 4 two building blocks are necessary, namely 4-substituted pyrazol-5-amines of formula 6 and 7, protected at one pyrazole nitrogen, and 2-substituted 4-bromo-1,3-thiazole-5-carboxylic acids of formula 26. The 4-substituted pyrazol-5-

amines of formula 6 and 7 can be obtained as described under Scheme 1. For the construction of 2-substituted 4-bromo-1,3-thiazole-5-carboxylic acids of formula 26 the commercially available 2,4-dibromo-1,3-thiazole of formula 23 can be used as starting material. The substituent R^1 in 4-bromo-1,3-thiazoles of general formula 24 can be introduced using a nucleophilic organometallic species of general formula 9, already described in Scheme 1, like for example a magnesium organyl (Grignard reagent), a zinc organyl (Reformatzky reagent), or a boron organyl (boronic acid, pinacol ester of boronic acid, *N*-methylimidodiacetic boronic acid esters (MIDA boronates)). Using 2,4-dibromo-1,3-thiazole of formula 23, as depicted in Scheme 4, a nickel- or palladium-catalyzed cross-coupling reaction with an organometallic species of general formula 9 can lead to the desired intermediates of general formula 24. As already described under Scheme 1 and also known to a person skilled in the art, a Suzuki-Miyaura, a Negishi, or a Kumada cross-coupling reaction might be used to build the intermediates of general formula 24. The subsequent ester hydrolysis to reach the acids of general formula 26 can be done under basic conditions in case R^3 represents for example a methyl or ethyl or under acidic conditions in case R^3 represents for example a *tert*-butyl. As reaction procedures the same conditions as exemplified for the synthesis of acids of general formula 11 depicted in Scheme 1 can be employed. In the next step the formed 2-substituted 4-bromo-1,3-thiazole-5-carboxylic acids of general formula 26 are coupled with the aminopyrazoles of general formula 6 and 7 under classical amide coupling reaction conditions. Therefore the acids of general formula 26 are activated using a well known coupling reagent like for example HATU, T_3P, CDI, or EDC, by intermediate formation of an acyl chloride (not shown) using for example thionyl chloride ($SOCl_2$), oxalyl chloride ($(COCl)_2$), or 1-chlor-1-dimethylamino-2-methyl-1-propen (Ghosez reagent), or by intermediate formation of a mixed anhydride using for example methanesulfonyl chloride (MsCl). Subsequent reaction with the aminopyrazoles of general formula 6 and 7 in presence of an organic base like *N*,*N*-diisopropylethylamine, *N*,*N*-dicyclohexylmethylamine, or pyridine in aprotic solvents like toluene, THF, or CH_2Cl_2 at temperatures from 20°C to 80°C lead to the amides of formula 28 and 27. These amides can be deproteced to the amides of general formula 29 under acidic or basic deprotection conditions. In case of acidic conditions HCl in dioxane or TFA optionally in an appropriate solvent like dichloromethane case be employed at temperatures from 0°C to 40°C and for the basic deprotection inorganic bases like potassium carbonate or potassium *tert*-butoxide in polar aprotic solvents like e.g. DMSO or NMP at temperatures from 80°C to 150°C are applicable to obtain the deprotected amides of general formula 29. The subsequent cyclization to the 2,6-disubstituted pyrazolo[1,5-a][1,3]thiazolo[5,4-e]pyrimidin-4(5H)-one cores of general formula 30 can for example be performed under Buchwald-Hartwig cross-coupling conditions, that are well known to a person skilled in the art. For example a Pd catalyst (like tris-(dibenzylidenaceton)-dipalladium(0)), a ligand (like 4,5-bis-(diphenyl-phosphino)-9,9-dimethylxanthen (Xantphos)) and a base (like caesium carbonate or sodium tert-butoxide) in an aprotic solvent (like toluene, diglyme) at temperatures between 70°C and 140°C

can be used to get the 2,6-disubstituted pyrazolo[1,5-a][1,3]thiazolo[5,4-e]pyrimidin-4(5H)-one cores of general formula 30. As medium to strong bases are usually used in the Buchwald-Hartwig cross-coupling reactions the deprotection and subsequent cyclization to the tricyclic cores of general formula 30 can also be performed in one pot without intermediate isolation of compounds of general formula 29. The final *N*-alkylation of the 2,6-disubstituted pyrazolo[1,5-a][1,3]thiazolo[5,4-e]pyrimidin-4(5H)-ones can be done with 2-bromo-*N*-(5-fluoropyridin-2-yl)acetamide of formula 19 as electrophile. As already described for Scheme 1 e.g. sodium carbonate might be added as base in a polar aprotic solvent like NMP or DMF at temperatures from 20°C to 50°C to perform this *N*-alkylation. Also here, the *O*-alkylated side product might be observed and needs to be separated from the desired *N*-alkylated product of general formula (III).

Compounds of formula (I) of the present invention demonstrate a valuable pharmacological spectrum of action and pharmacokinetic profile if supported by data, both of which could not have been predicted. Compounds of the present invention have surprisingly been found to effectively and selectively inhibit P2X3 and it is possible therefore that said compounds be used for the treatment or prophylaxis of diseases, preferably neurogenic disorders in humans and animals.

These novel pyrazolo[1,5-a]pyridine-[3,2-e]pyrimidines have only small substituents in position 3 instead of position 2 in comparison to WO 2021/115225. Surprisingly , most of these very potent P2X3 inhibitors show good to superior solubility behavior in kinetic solubility measurements. Said 3-substitution makes the compounds of the present invention to very potent P2X3 inhibitors in a range of 5-fold to 15-fold compared to WO 2021/115225.

In addition to that, more preferred compounds of the present invention show further advantageous properties that are beneficial for their use as medicaments, such as desirable pharmacokinetic profiles that provide suitable oral bioavailability. Asuitable oral bioavailability can be predicted byseveral parameters like solubility and metabolic stability. The compounds of formula (I) of the present invention show a solubility which is between 3-fold and over 100-fold better as it was found for compounds with the same substituents at position 2 in WO 2021/115225.

Method for treatment

The present invention also relates to a method for using a compound of formula (I) and compositions thereof, to treat mammalian neurogenic diseases and disorders. This method comprises administering to a mammal in need thereof, including a human, an amount of a compound of formula (I) or composition thereof, which is effective to treat the disease or disorder. Neurogenic diseases and disorders include but are not limited to genitourinary, gastrointestinal,

respiratory diseases, cardiovascular disease associated with autonomic imbalance caused by increased chemoreceptor sensitivity, and pain as such as well as pain-related diseases, conditions and disorders, gynecological diseases, urinary tract disease states, pain-related diseases and disorders, pain-associated diseases and disorders, neurological diseases and disorders, neurodegenerative diseases and disorders and dermatological diseases and disorders.

Gynecological diseases include but are not limited to dysmenorrhea (primary and secondary dysmenorrhea), dyspareunia, endometriosis, and adenomyosis; endometriosis-associated pain; endometriosis-associated symptoms, wherein said symptoms are in particular dysmenorrhea, dyspareunia, dysuria, or dyschezia; endometriosis-associated proliferation; pelvic hypersensitivity.

Preference is given to endometriosis and to moderate to severe pain associated with endometriosis in women of reproductive age.

Urinary tract disease states include, but are not limited to those associated with the bladder outlet obstruction; urinary incontinence conditions such as reduced bladder capacity, increased frequency of micturition, urge incontinence, stress incontinence, or bladder hyperreactivity; benign prostatic hypertrophy; prostatic hyperplasia; prostatitis; detrusor hyperreflexia; overactive urinary bladder and symptoms related to overactive urinary bladder wherein said symptoms are in particular increased urinary frequency, nocturia, urinary urgency or urge incontinence; pelvic hypersensitivity; urethritis; prostatitis; prostatodynia; cystitis, in particular Interstitial cystitis; idiopathic bladder hypersensitivity and bladder pain syndrome,.

Preference is given to overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency, urinary frequency and nocturia. Furthermore, preference is given to interstitial cystitis and bladder pain syndrome as well.

Neurological diseases and disorders include, but are not limited to epilepsy, partial and generalized seizures.

Respiratory diseases and disorders include, but are not limited to asthma, chronic obstructive pulmonary disease (COPD), pulmonary fibrosis, acute cough, chronic cough including chronic idiopathic and refractory and/ or unexplained chronic cough, bronchospasm and interstitial lung disease (including idiopathic pulmonary fibrosis).

Preference is given to refractory and/ or unexplained chronic cough.

Cardiovascular diseases and disorders include, but are not limited to those associated with nerve fiber sensitization, and/or other pathological conditions associated with autonomic imbalance

caused by increased chemoreceptor sensitivity, in particular for the treatment of breathing disorders, Cheyne Stokes respiration, central and obstructive sleep apnea, cardiovascular disease, hypertension, resistant hypertension, and heart failure, which are related to increased activity of P2X3 receptors.

Gastrointestinal dieases and disorders include, but are not limited to irritable bowel syndrome (IBS), epigastric pain syndrome (functional dyspepsia syndrome), functional abdominal bloating with distension, inflammatory bowel disease (IBD), biliary colic and other biliary disorders, renal colic, diarrhea-dominant IBS; gastroesophageal reflux, gastrointestinal distension, ulcerative colitis (Crohn's disease).

Preference is given to irritable bowel syndrome (IBS) and inflammatory bowel disease (IBD). Furthermore, irritable bowel syndrome with diarrhea (IBS D) is preferred.

Neurodegenerative diseases and disorders include, but are not limited to Alzheimer's disease, Multiple Sclerosis, Parkinson's disease, Brain ischemia and traumatic brain injury.

Dermatological diseases and disorders include, but are not limited to Prurigo nodularis, chronic pruritus of unknown origin, pruritus due to kidney or liver disease, Brachioradial pruritus, Rosacea, Chronic hand eczema, Dyshidrotic eczema, Atopic dermatitis and Psoriasis.

Pain-related diseases and disorders include, but are not limited to acute, chronic, inflammatory and neuropathic pain syndromes.

Pain-related diseases and disorders include, but are not limited to pain syndromes selected from the group consisting of acute, chronic, inflammatory and neuropathic pain, preferably inflammatory pain, low back pain, surgical pain, postsurgical neuropathic pain, posttraumatic neuropathic pain, visceral pain, dental pain, periodontitis, premenstrual pain, endometriosis-associated pain, pain associated with fibrotic diseases, central pain, pain due to burning mouth syndrome, pain due to burns, pain due to migraine, cluster headaches, pain due to nerve injury, pain due to neuritis, neuralgias, pain due to poisoning, pain due to ischemic injury, pain due to interstitial cystitis, cancer-related neuropathic pain, chemotherapy-related neuropathic pain, pain due to viral, parasitic or bacterial infections, pain due to traumatic nerve-injury, pain due to post-traumatic injuries (including fractures and sport injuries), pain due to trigeminal neuralgia, pain associated with small fiber neuropathy, pain associated with diabetic neuropathy, postherpetic neuralgia, chronic lower back pain, neck pain phantom limb pain, pelvic pain syndrome, chronic pelvic pain, neuroma pain, complex regional pain syndrome, bladder pain syndrome, pain associated with gastrointestinal distension, chronic arthritic pain and related neuralgias, and pain associated with cancer, Morphine-resistant pain, pain associated with chemotherapy, HIV and HIV treatment-induced neuropathy; and pain associated with diseases or disorders selected

from the group consisting of hyperalgesia, allodynia, functional bowel disorders (such as irritable bowel syndrome) and arthritis (such as osteoarthritis, rheumatoid arthritis and ankylosing spondylitis).

Pain-associated diseases and disorders include, but are not limited to hyperalgesia, allodynia, functional bowel disorders (such as irritable bowel syndrome), gout, arthritis (such as osteoarthritis, rheumatoid arthritis and ankylosing spondylitis), burning mouth syndrome, burns, migraine or cluster headaches, nerve injury, traumatic nerve injury, post-traumatic injuries (including fractures and sport injuries), neuritis, neuralgias, poisoning, ischemic injury, interstitial cystitis, cancer, trigeminal neuralgia, small fiber neuropathy, diabetic neuropathy, chronic arthritis and related neuralgias, HIV and HIV treatment-induced neuropathy, pruritus; impaired wound healing and disease of the skeleton like degeneration of the joints.

Preference is given to peripheral neuropathic pain. In particular, preference is given to neuropathic pain associated with diabetic peripheral neuropathy (NP-DPN).
Furthermore, preference is given to cancer and/ or chemotherapy related neuropathic pain, to postherpetic neuralgia and to postsurgical and/ or posttraumatic neuropathic pain.

The present invention relates to a method for using the compounds of the present and compositions thereof to treat inflammation, in particular neurogenic inflammation. The term "inflammation" is also understood to include any inflammatory disease, disorder or condition per se, any condition that has an inflammatory component associated with it, and/or any condition characterized by inflammation as a symptom, including, inter alia, acute, chronic, ulcerative, specific, allergic, infection by pathogens, immune reactions due to hypersensitivity, entering foreign bodies, physical injury, and necrotic inflammation, and other forms of inflammation known to those skilled in the art. The term thus also includes, for the purposes of this invention, inflammatory pain, pain generally and/or fever.

The present invention relates to a method for using the compounds of the present invention and compositions thereof to treat fibromyalgia, myofascial disorders, viral infections (e.g. influenza, common cold, herpes zoster, hepatitis C and AIDS), bacterial infections, fungal infections, surgical or dental procedures, arthritis, osteoarthritis, juvenile arthritis, rheumatoid arthritis, juvenile onset rheumatoid arthritis, rheumatic fever, ankylosing spondylitis, Hodgkin's disease, systemic lupus erythematosus, vasculitis, pancreatitis, nephritis, bursitis, conjunctivitis, iritis, scleritis, uveitis, wound healing, dermatitis, eczema, stroke, autoimmune diseases, allergic disorders, rhinitis, ulcers, mild to moderately active ulcerative colitis, familial adenomatous polyposis, coronary heart disease, sarcoidosis and any other disease with an inflammatory component. The present invention relates to a method for using the compounds of the present invention and compositions thereof to treat mammalian, including human disorders and diseases which are not linked to inflammatory mechanisms, such as in the reduction of bone loss in a

subject. Diseases that may be mentioned in this regard include osteoporosis, osteoarthritis, Paget's disease and/or periodontal diseases.

The inventive compounds can therefore be used in medicaments for treatment and/or prophylaxis of the above-mentioned diseases.

These diseases and/ or disorders have been well characterized in humans, but also exist with a similar etiology in other mammals and can be treated by administering pharmaceutical compositions of the present invention.

The term “treating” or “treatment” as used in the present text is used conventionally, e.g., the management or care of a subject for the purpose of combating, alleviating, reducing, relieving, improving the condition of a disease or disorder, such as neurogenic disorders or diseases.

The compounds of the present invention can be used in therapy and prevention, i.e. prophylaxis, of neurogenic diseases, conditions and disorders.

In accordance with a further aspect, the present invention covers pharmaceutical compositions, in particular a medicament, comprising a compound of formula (I), as described *supra*, or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, a salt thereof, particularly a pharmaceutically acceptable salt, or a mixture of same, and one or more excipients), in particular one or more pharmaceutically acceptable excipient(s). Conventional procedures for preparing such pharmaceutical compositions in appropriate dosage forms can be utilized.

The present invention furthermore covers pharmaceutical compositions, in particular medicaments, which comprise at least one compound according to the invention, conventionally together with one or more pharmaceutically suitable excipients, and to their use for the above mentioned purposes.

It is possible for the compounds according to the invention to have systemic and/or local activity. For this purpose, they can be administered in a suitable manner, such as, for example, via the oral, parenteral, pulmonary, nasal, sublingual, lingual, buccal, rectal, vaginal, dermal, transdermal, conjunctival, otic route or as an implant or stent.

For these administration routes, it is possible for the compounds according to the invention to be administered in suitable administration forms.

For oral administration, it is possible to formulate the compounds according to the invention to dosage forms known in the art that deliver the compounds of the invention rapidly and/or in a modified manner, such as, for example, tablets (uncoated or coated tablets, for example with

enteric or controlled release coatings that dissolve with a delay or are insoluble), orally-disintegrating tablets, films/wafers, films/lyophylisates, capsules (for example hard or soft gelatine capsules), sugar-coated tablets, granules, pellets, powders, emulsions, suspensions, aerosols or solutions. It is possible to incorporate the compounds according to the invention in crystalline and/or amorphised and/or dissolved form into said dosage forms.

Parenteral administration can be effected with avoidance of an absorption step (for example intravenous, intraarterial, intracardial, intraspinal or intralumbal) or with inclusion of absorption (for example intramuscular, subcutaneous, intracutaneous, percutaneous or intraperitoneal). Administration forms which are suitable for parenteral administration are, inter alia, preparations for injection and infusion in the form of solutions, suspensions, emulsions, lyophylisates or sterile powders.

Examples which are suitable for other administration routes are pharmaceutical forms for inhalation [inter alia powder inhalers, nebulizers], nasal drops, nasal solutions, nasal sprays; tablets/films/wafers/capsules for lingual, sublingual or buccal administration; suppositories; eye drops, eye ointments, eye baths, ocular inserts, ear drops, ear sprays, ear powders, ear-rinses, ear tampons; vaginal capsules, aqueous suspensions (lotions, mixturae agitandae), lipophilic suspensions, emulsions, ointments, creams, transdermal therapeutic systems (such as, for example, patches), milk, pastes, foams, dusting powders, implants or stents.

The compounds according to the invention can be incorporated into the stated administration forms. This can be effected in a manner known per se by mixing with pharmaceutically suitable excipients. Pharmaceutically suitable excipients include, inter alia,

- fillers and carriers (for example cellulose, microcrystalline cellulose (such as, for example, Avicel®), lactose, mannitol, starch, calcium phosphate (such as, for example, Di-Cafos®)),
- ointment bases (for example petroleum jelly, paraffins, triglycerides, waxes, wool wax, wool wax alcohols, lanolin, hydrophilic ointment, polyethylene glycols),
- bases for suppositories (for example polyethylene glycols, cacao butter, hard fat),
- solvents (for example water, ethanol, isopropanol, glycerol, propylene glycol, medium chain-length triglycerides fatty oils, liquid polyethylene glycols, paraffins),
- surfactants, emulsifiers, dispersants or wetters (for example sodium dodecyl sulfate), lecithin, phospholipids, fatty alcohols (such as, for example, Lanette®), sorbitan fatty acid esters (such as, for example, Span®), polyoxyethylene sorbitan fatty acid esters (such as, for example, Tween®), polyoxyethylene fatty acid glycerides (such as, for example,

Cremophor®), polyoxethylene fatty acid esters, polyoxyethylene fatty alcohol ethers, glycerol fatty acid esters, poloxamers (such as, for example, Pluronic®),

- buffers, acids and bases (for example phosphates, carbonates, citric acid, acetic acid, hydrochloric acid, sodium hydroxide solution, ammonium carbonate, trometamol, triethanolamine),
- isotonicity agents (for example glucose, sodium chloride),
- adsorbents (for example highly-disperse silicas),
- viscosity-increasing agents, gel formers, thickeners and/or binders (for example polyvinylpyrrolidone, methylcellulose, hydroxypropylmethylcellulose, hydroxypropyl-cellulose, carboxymethylcellulose-sodium, starch, carbomers, polyacrylic acids (such as, for example, Carbopol®); alginates, gelatine),
- disintegrants (for example modified starch, carboxymethylcellulose-sodium, sodium starch glycolate (such as, for example, Explotab®), cross- linked polyvinylpyrrolidone, croscarmellose-sodium (such as, for example, AcDiSol®)),
- flow regulators, lubricants, glidants and mould release agents (for example magnesium stearate, stearic acid, talc, highly-disperse silicas (such as, for example, Aerosil®)),
- coating materials (for example sugar, shellac) and film formers for films or diffusion membranes which dissolve rapidly or in a modified manner (for example polyvinylpyrrolidones (such as, for example, Kollidon®), polyvinyl alcohol, hydroxypropylmethylcellulose, hydroxypropylcellulose, ethylcellulose, hydroxypropyl-methylcellulose phthalate, cellulose acetate, cellulose acetate phthalate, polyacrylates, polymethacrylates such as, for example, Eudragit®)),
- capsule materials (for example gelatine, hydroxypropylmethylcellulose),
- synthetic polymers (for example polylactides, polyglycolides, polyacrylates, polymethacrylates (such as, for example, Eudragit®), polyvinylpyrrolidones (such as, for example, Kollidon®), polyvinyl alcohols, polyvinyl acetates, polyethylene oxides, polyethylene glycols and their copolymers and blockcopolymers),
- plasticizers (for example polyethylene glycols, propylene glycol, glycerol, triacetine, triacetyl citrate, dibutyl phthalate),
- penetration enhancers,
- stabilisers (for example antioxidants such as, for example, ascorbic acid, ascorbyl palmitate, sodium ascorbate, butylhydroxyanisole, butylhydroxytoluene, propyl gallate),

- preservatives (for example parabens, sorbic acid, thiomersal, benzalkonium chloride, chlorhexidine acetate, sodium benzoate),
- colourants (for example inorganic pigments such as, for example, iron oxides, titanium dioxide),
- flavourings, sweeteners, flavour- and/or odour-masking agents.

The present invention furthermore relates to a pharmaceutical composition which comprise at least one compound according to the invention, conventionally together with one or more pharmaceutically suitable excipient(s), and to their use according to the present invention.

In accordance with another aspect, the present invention covers pharmaceutical combinations, in particular medicaments, comprising at least one compound of formula (I) of the present invention and at least one or more further active ingredients, in particular for the treatment and/or prophylaxis of neurogenic disorders, in particular of genitourinary, gastrointestinal, respiratory, cardiovascular disease associated with autonomic imbalance caused by increased chemoreceptor sensitivity, and pain-related diseases, conditions and disorders.

Particularly, the present invention covers a pharmaceutical combination, which comprises:

- one or more first active ingredients, in particular compounds of formula (I) as defined *supra,* and
- one or more further active ingredients, suitable for the treatment of neurogenic disorders, genitourinary, gastrointestinal, respiratory, cardiovascular disease associated with autonomic imbalance caused by increased chemoreceptor sensitivity, and pain-related diseases, conditions and disorders.

The term “combination” in the present invention is used as known to persons skilled in the art, it being possible for said combination to be a fixed combination, a non-fixed combination or a kit-of-parts.

A “fixed combination” in the present invention is used as known to persons skilled in the art and is defined as a combination wherein, for example, a first active ingredient, such as one or more compounds of formula (I) of the present invention, and a further active ingredient are present together in one unit dosage or in one single entity. One example of a “fixed combination” is a pharmaceutical composition wherein a first active ingredient and a further active ingredient are present in admixture for simultaneous administration, such as in a formulation. Another example of a “fixed combination” is a pharmaceutical combination wherein a first active ingredient and a further active ingredient are present in one unit without being in admixture.

A non-fixed combination or "kit-of-parts" in the present invention is used as known to persons skilled in the art and is defined as a combination wherein a first active ingredient and a further active ingredient are present in more than one unit. One example of a non-fixed combination or kit-of-parts is a combination wherein the first active ingredient and the further active ingredient are present separately. It is possible for the components of the non-fixed combination or kit-of-parts to be administered separately, sequentially, simultaneously, concurrently or chronologically staggered.

The compounds of the present invention can be administered as the sole pharmaceutical agent or in combination with one or more other pharmaceutically active ingredients where the combination causes no unacceptable adverse effects. The present invention also covers such pharmaceutical combinations. For example, the compounds of the present invention can be combined with known hormonal therapeutic agents.

The compounds of the present invention can be combined with therapeutic agents or active ingredients, that are already approved or that are still under development for the treatment and/ or prophylaxis of diseases, which are related to or mediated by P2X3 receptor. Such therapeutic agents or active ingredients are for example, but not limited, to 5-(2,4-Diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-benzenesulfonamide (Gefapixant/ MK-7264/AF-219), (5-(5-iodo-2-isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine (AF-353), 5-[2-isopropyl-4-methoxy-5-(methylsulfonyl)phenoxy]pyrimidine-2,4-diamine (AF-130), 2-[[4-amino-5-(5-iodo-4-methoxy-2-propan-2-ylphenoxy)-pyrimidin-2-yl]amino]propane-1,3-diol (AF-906), and (S)-methyl 2-((2-(2,6-difluoro-4-(methylcarbamoyl)-phenyl)-5-methyl-1H-benzo[d]imidazol-1-yl)methyl)morpholine-4-carboxylate (BLU-5937/ NEO 5937).

The compounds of the present invention can be combined with therapeutic agents or active ingredients, that are already approved or that are still under development for the treatment and/ or prophylaxis of diseases, which are related to other targets like NK1 inhibitors, for example 2-(R)-(4-Fluoro-2-methyl-phenyl)-4-(S)-((8aS)-6-oxohexahydro-pyrrolo[1,2-a]-pyrazin-2-yl)-piperidine-1-carboxylic acid [1-(R)-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide (Orvepitant), 3-[(3aR,4R,5S,7aS)-5-{(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy}-4-(4-fluorophenyl)octahydro-2H-isoindol-2-yl]cyclopent-2-en-1-one (Serlopitant), 5-[((2S,3R)-2- 5-[(2R,3S)-2-((R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy)-3-(4-fluorophenyl)-morpholino]methyl)-1H-1,2,4-triazol-3(2H)-one (Aprepitant), [2-[1-[[3,5-bis(trifluoromethyl)-phenyl]methyl]-5-pyridin-4-yltriazol-4-yl]pyridin-3-yl]-(2-chlorophenyl)methanone (Tradipitant), (2R,4S)-4-(4-Acetylpiperazin-1-yl)-N--2-(4-fluoro-2-methylphenyl)-N-methylpiperidine-1-carboxamide (Casopitant), 2-[3,5-bis(trifluoromethyl)phenyl]-N,2-dimethyl-N-[4-(2-methyl-phenyl)-6-(4-methyl-piperazin-1-yl)pyridin-3-yl]propanamide (Netupitant), [3-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoro-methyl)phenyl]ethoxy]-3-(4-fluorophenyl)morpholin-4-yl]methyl]-5-oxo-4H-1,2,4-triazol-1-yl]phosphonic acid (Fosaprepitant), (5S,8S)-8-[[(1R)-1-[3,5-bis(trifluoromethyl)-

phenyl]ethoxy]methyl]-8-phenyl-1,9-diazaspiro[4.5]decan-2-one (Rolapitant), (2S)-N-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethyl]-2-(4-fluoro-2-methylphenyl)-N-methylpiperazine-1-carboxamide (Vestipitant), 2-[1-[2-[(2R)-4-[2-[3,5-bis(trifluoromethyl)phenyl]acetyl]-2-(3,4-dichlorophenyl)morpholin-2-yl]ethyl]piperidin-4-yl]-2-methylpropanamide (Burapitant), [4-[5-[[2-[3,5-bis(trifluoromethyl)phenyl]-2-methylpropanoyl]-methylamino]-4-(2-methylphenyl)pyridin-2-yl]-1-methylpiperazin-1-ium-1-yl]methyl hydrogen phosphate (Fosnetupitant), or NK1/ NK3 inhibiotrs, for example N-[6-[(7S,9alphaS)-7-(hydroxymethyl)-3,4,6,7,9,9alpha-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-4-(4-fluoro-2-methylphenyl)pyridin-3-yl]-2-[3,5-bis(trifluoro-methyl)phenyl]-N,2-dimethylpropanamide (Elinzanetant), or nicotinic Acetylcholine modulators, for example N-(2-((3-pyridinyl)Methyl)-1-azabicyclo[2.2.2]oct-3-yl)benzofuran-2-carboxamide (Bradanicline/ ATA-101).

The compounds of the present invention can be administered as the sole pharmaceutical agent or in combination with one or more other pharmaceutically active ingredients where the combination causes no unacceptable adverse effects. The present invention also covers such pharmaceutical combinations. For example, the compounds of the present invention can be combined with known indication agents.

For example, the compounds of the present invention can be combined with known hormonal therapeutic agents.

In particular, the compounds of the present invention can be administered in combination or as comedication with Selective Progesterone Receptor Modulators (SPRMs) or hormonal contraceptives. SPRMs and hormonal contraceptives can be administered via oral, subcutan, transdermal, intrauterine or intravaginal route, for example as Combined Oral Contraceptives (COCs), or Progestin-Only-Pills (POPs) or hormone-containing devices like implants, patches or intravaginal rings.

COCs include but are not limited to birth control pills or a birth control method that includes a combination of an estrogen (estradiol) and a progestogen (progestin). The estrogenic part is in most of the COCs ethinyl estradiol. Some COCs contain estradiol or estradiol valerate.

Said COCs contain the progestins norethynodrel, norethindrone, norethindrone acetate, ethynodiol acetate, norgestrel, levonorgestrel, norgestimate, desogestrel, gestodene, drospirenone, dienogest, or nomegestrol acetate.

Birth control pills include for example but are not limited to Yasmin, Yaz, both containing ethinyl estradiol and drospirenone; Microgynon or Miranova containing levonorgestrel and ethinyl estradiol; Marvelon containing ethinyl estradiol and desogestrel; Valette containing ethinyl estradiol and dienogest; Belara and Enriqa containing ethinyl estradiol and

chlormadinonacetate; Qlaira containing estradiol valerate and dienogest as active ingredients; and Zoely containing estradiol and normegestrol.

POPs are contraceptive pills that contain only synthetic progestogens (progestins) and do not contain estrogen. They are colloquially known as mini pills.

POPs include but are not limited to Cerazette containing desogestrel; Microlut containing levonorgestrel and Micronor containing norethindrone.

Other Progeston-Only forms are intrauterine devices (IUDs), for example Mirena containing levonorgestrel or injectables, for example Depo-Provera containing medroxyprogesterone acetate, or implants, for example Implanon containing etonogestrel.

Other hormone-containing devices with contraceptive effect which are suitable for a combination with the compounds of the present invention are vaginal rings like Nuvaring containing ethinyl estradiol and etonogestrel or transdermal systems like a contraceptive patch, for example Ortho-Evra or Apleek (Lisvy) containing ethinyl estradiol and gestodene.

A preferred embodiment of the present invention is the administration of a compound of formula (I) in combination with a COC or a POP or other Progestin-Only forms as well as vaginal rings or contraceptive patches as mentioned above.

The compounds of the present invention can be combined with therapeutic agents or active ingredients, that are already approved or that are still under development for the treatment and/ or prophylaxis of diseases which are related to or mediated by P2X3 receptor.

For the treatment and/ or prophylaxis of urinary tract diseases, the compounds of the present invention can be administered in combination or as comedication with any substance that can be applied as therapeutic agent in the following indications:

Urinary tract disease states associated with the bladder outlet obstruction; urinary incontinence conditions such as reduced bladder capacity, increased frequency of micturition, urge incontinence, stress incontinence, or bladder hyperreactivity; benign prostatic hypertrophy; prostatic hyperplasia; prostatitis; detrusor hyperreflexia; overactive bladder and symptoms related to overactive bladder wherein said symptoms are in particular increased urinary frequency, nocturia, urinary urgency or urge incontinence; pelvic hypersensitivity; urethritis; prostatitis; prostatodynia; cystitis, in particular interstitial cystitis; idiopathic bladder hypersensitivity.

For the treatment and/ or prophylaxis of overactive bladder and symptoms related to overactive bladder, the compounds of the present invention can be administered in combination or as comedication, independently or in addition to behavioral therapy like diet, lifestyle or bladder training, with anticholinergics like oxybutynin, tolterodine, propiverine, solifenacin, darifenacin, trospium, fesoterdine; ß-3 agonists like mirabegron; neurotoxins like onabutolinumtoxin A; or antidepressants like imipramine, duloxetine.

For the treatment and/ or prophylaxis of interstitial cystitis, the compounds of the present invention can be administered in combination or as comedication, independently or in addition to behavioral therapy like diet, lifestyle or bladder training, with pentosans like elmiron; NSAIDS (Non-Steroidal Antiinflammatory Drugs), either unselective NSAIDS like ibuprofen, diclofenac, aspirin, naproxen, ketoprofen, indomethacin; as well as Cox-2 selective NSAIDS like Parecoxib, Etoricoxib, Celecoxib; antidepressants like amitriptyline, imipramine; or antihistamines like loratadine.

For the treatment and/ or prophylaxis of gynaecological diseases, the compounds of the present invention can be administered in combination or as comedication with any substance that can be applied as therapeutic agent in the following indications:

dysmenorrhea, including primary and secondary dysmenorrhea; dyspareunia; endometriosis; endometriosis-associated pain; endometriosis-associated symptoms, wherein said symptoms are in particular dysmenorrhea, dyspareunia, dysuria, or dyschezia.

For the treatment and/ or prophylaxis of dysmenorrhea, including primary and secondary dysmenorrhea; dyspareunia; endometriosis and endometriosis-associated pain, the compounds of the present invention can be administered in combination or as comedication with pain medicaments, in particular NSAIDS like ibuprofen, diclofenac, aspirin, naproxen, ketoprofen, indomethacin; as well as Cox-2 selective NSAIDS like Parecoxib, Etoricoxib, Celecoxib; or in combination with ovulation inhibiting treatment, in particular COCs as mentioned above or contraceptive patches like Ortho-Evra or Apleek (Lisvy); or with progestogenes like dienogest (Visanne); or with GnRH analogous, in particular GnRH agonists and antagonists, for example leuprorelin, nafarelin, goserelin, cetrorelix, abarelix, ganirelix, degarelix; or with androgens: danazol.

For the treatment and/ or prophylaxis of endometriosis and endometriosis-associated pain, the compounds of the present invention can be administered in combination or as comedication with GnRH antagonists like Elagolix, Linzagolix, or Relugolix.

For the treatment and/ or prophylaxis of endometriosis and endometriosis-associated pain, the compounds of the present invention can be administered in combination or as comedication

with Selective Progesterone Receptor Modulators (SPRMs) or Progesterone antagonists like Vilaprisan, Ulipristal acetate, Telapristone, or Mifepristone.

For the treatment and/ or prophylaxis of diseases which are associated with pain, or pain syndromes, the compounds of the present invention can be administered in combination or as comedication with any substance that can be applied as therapeutic agent in the following indications:

pain-associated diseases or disorders like hyperalgesia, allodynia, functional bowel disorders (such as irritable bowel syndrome) and arthritis (such as osteoarthritis, rheumatoid arthritis and ankylosing spondylitis), burning mouth syndrome, burns, migraine or cluster headache, nerve injury, traumatic nerve injury, post-traumatic injuries (including fractures and sport injuries), neuritis, neuralgia, poisoning, ischemic injury, interstitial cystitis, trigeminal neuralgia, small fiber neuropathy, diabetic neuropathy, chronic arthritis and related neuralgias, HIV and HIV treatment-induced neuropathy.

The compounds of the present invention can be combined with other pharmacological agents and compounds that are intended to treat inflammatory diseases, inflammatory pain or general pain conditions.

In addition to well-known medicaments which are already approved and on the market, the compounds of the present invention can be administered in combination with inhibitors of PTGES (prostaglandin E synthase), with inhibitors of IRAK4 (interleukin-1 receptor-associated kinase 4) and with antagonists of the prostanoid EP4 receptor (prostaglandin E2 receptor 4).

In particular, the compounds of the present invention can be administered in combination with pharmacological endometriosis agents, intended to treat inflammatory diseases, inflammatory pain or general pain conditions and/or interfering with endometriotic proliferation and endometriosis associated symptoms, namely with inhibitors of Aldo-keto-reductase1C3 (AKR1C3) and with functional blocking antibodies of the prolactin receptor.

For the treatment and/ or prophylaxis of chronic cough and symptoms related to chronic cough, the compounds of the present invention can be administered in combination or as comedication with cough suppressants like dextromethorphan, benzonatate, codeine or hydrocodone; with inhalative agents to treat eosinophilic bronchitis, COPD or asthma like budesonide, beclomethasone, fluticasone, theophylline, ipatropiumbromid, montelukast or salbutamol; with drugs like proton pump inhibitors which are used to treat acid reflux, for example omeprazole, esomeprazole, lansoprazole, ranitidine, famotidine, cimetidine; and promotility agents such as

metoclopramide; with nasal or topical glucocorticoids like fluticasone or mometasone or triamcinolone; or with oral antihistamines like loratadine, fexofenadine or cetirizine.

The compounds of the present invention can be combined with other pharmacological agents and compounds that are intended for the treatment, prevention or management of cancer.

In particular, the compounds of the present invention can be administered in combination with 131I-chTNT, abarelix, abiraterone, aclarubicin, ado-trastuzumab emtansine, afatinib, aflibercept, aldesleukin, alemtuzumab, Alendronic acid, alitretinoin, altretamine, amifostine, aminoglutethimide, Hexyl aminolevulinate,amrubicin, amsacrine, anastrozole, ancestim, anethole dithiolethione, angiotensin II, antithrombin III, aprepitant, arcitumomab, arglabin, arsenic trioxide, asparaginase, axitinib, azacitidine, basiliximab, belotecan, bendamustine, belinostat, bevacizumab, bexarotene, bicalutamide, bisantrene, bleomycin, bortezomib, buserelin, bosutinib, brentuximab vedotin, busulfan, cabazitaxel, cabozantinib, calcium folinate, calcium levofolinate, capecitabine, capromab, carboplatin, carfilzomib, carmofur, carmustine, catumaxomab, celecoxib, celmoleukin, ceritinib, cetuximab, chlorambucil, chlormadinone, chlormethine, cidofovir, cinacalcet, cisplatin, cladribine, clodronic acid, clofarabine, copanlisib, crisantaspase, cyclophosphamide, cyproterone, cytarabine, dacarbazine, dactinomycin, darbepoetin alfa, dabrafenib, dasatinib, daunorubicin, decitabine, degarelix, denileukin diftitox, denosumab, depreotide, deslorelin, dexrazoxane, dibrospidium chloride, dianhydrogalactitol, diclofenac, docetaxel, dolasetron, doxifluridine, doxorubicin, doxorubicin + estrone, dronabinol, eculizumab, edrecolomab, elliptinium acetate, eltrombopag, endostatin, enocitabine, enzalutamide, epirubicin, epitiostanol, epoetin alfa, epoetin beta, epoetin zeta, eptaplatin, eribulin, erlotinib, esomeprazole, estradiol, estramustine, etoposide, everolimus, exemestane, fadrozole, fentanyl, filgrastim, fluoxymesterone, floxuridine, fludarabine, fluorouracil, flutamide, folinic acid, formestane, fosaprepitant, fotemustine, fulvestrant, gadobutrol, gadoteridol, gadoteric acid meglumine, gadoversetamide, gadoxetic acid, gallium nitrate, ganirelix, gefitinib, gemcitabine, gemtuzumab, Glucarpidase, glutoxim, GM-CSF, goserelin, granisetron, granulocyte colony stimulating factor, histamine dihydrochloride, histrelin, hydroxycarbamide, I-125 seeds, lansoprazole, ibandronic acid, ibritumomab tiuxetan, ibrutinib, idarubicin, ifosfamide, imatinib, imiquimod, improsulfan, indisetron, incadronic acid, ingenol mebutate, interferon alfa, interferon beta, interferon gamma, iobitridol, iobenguane (123I), iomeprol, ipilimumab, irinotecan, Itraconazole, ixabepilone, lanreotide, lapatinib, lasocholine, lenalidomide, lenograstim, lentinan, letrozole, leuprorelin, levamisole, levonorgestrel, levothyroxine sodium, lisuride, lobaplatin, lomustine, lonidamine, masoprocol, medroxyprogesterone, megestrol, melarsoprol, melphalan, mepitiostane, mercaptopurine, mesna, methadone, methotrexate, methoxsalen, methylaminolevulinate, methylprednisolone, methyltestosterone, metirosine, mifamurtide, miltefosine, miriplatin, mitobronitol, mitoguazone, mitolactol, mitomycin, mitotane,

mitoxantrone, mogamulizumab, molgramostim, mopidamol, morphine hydrochloride, morphine sulfate, nabilone, nabiximols, nafarelin, naloxone + pentazocine, naltrexone, nartograstim, nedaplatin, nelarabine, neridronic acid, nivolumabpentetreotide, nilotinib, nilutamide, nimorazole, nimotuzumab, nimustine, nitracrine, nivolumab, obinutuzumab, octreotide, ofatumumab, omacetaxine mepesuccinate, omeprazole, ondansetron, oprelvekin, orgotein, orilotimod, oxaliplatin, oxycodone, oxymetholone, ozogamicine, p53 gene therapy, paclitaxel, palifermin, palladium-103 seed, palonosetron, pamidronic acid, panitumumab, pantoprazole, pazopanib, pegaspargase, PEG-epoetin beta (methoxy PEG-epoetin beta), pembrolizumab, pegfilgrastim, peginterferon alfa-2b, pemetrexed, pentazocine, pentostatin, peplomycin, Perflubutane, perfosfamide, Pertuzumab, picibanil, pilocarpine, pirarubicin, pixantrone, plerixafor, plicamycin, poliglusam, polyestradiol phosphate, polyvinylpyrrolidone + sodium hyaluronate, polysaccharide-K, pomalidomide, ponatinib, porfimer sodium, pralatrexate, prednimustine, prednisone, procarbazine, procodazole, propranolol, quinagolide, rabeprazole, racotumomab, radium-223 chloride, radotinib, raloxifene, raltitrexed, ramosetron, ramucirumab, ranimustine, rasburicase, razoxane, refametinib , regorafenib, risedronic acid, rhenium-186 etidronate, rituximab, romidepsin, romiplostim, romurtide, roniciclib , samarium (153Sm) lexidronam, sargramostim, satumomab, secretin, sipuleucel-T, sizofiran, sobuzoxane, sodium glycididazole, sorafenib, stanozolol, streptozocin, sunitinib, talaporfin, tamibarotene, tamoxifen, tapentadol, tasonermin, teceleukin, technetium (99mTc) nofetumomab merpentan, 99mTc-HYNIC-[Tyr3]-octreotide, tegafur, tegafur + gimeracil + oteracil, temoporfin, temozolomide, temsirolimus, teniposide, testosterone, tetrofosmin, thalidomide, thiotepa, thymalfasin, thyrotropin alfa, tioguanine, tocilizumab, topotecan, toremifene, tositumomab, trabectedin, tramadol, trastuzumab, trastuzumab emtansine, treosulfan, tretinoin, trifluridine + tipiracil, trilostane, triptorelin, trametinib, trofosfamide, thrombopoietin, tryptophan, ubenimex, valatinib , valrubicin, vandetanib, vapreotide, vemurafenib, vinblastine, vincristine, vindesine, vinflunine, vinorelbine, vismodegib, vorinostat, vorozole, yttrium-90 glass microspheres, zinostatin, zinostatin stimalamer, zoledronic acid, zorubicin.

Furthermore, the compounds of the present invention can be combined with active ingredients, which are well known for the treatment of cancer-related pain and chronic pain. Such combinations include, but are not limited to NSAIDS (either unselective NSAIDS like ibuprofen, diclofenac, aspirin, naproxen, ketoprofen and indomethacin; and Cox-2 selective NSAIDS like Parecoxib, Etoricoxib and Celecoxib), step II opiods like codeine phosphate, dextropropoxyphene, dihydro¬codeine,Tramadol), step III opiods like morphine, fentanyl, buprenorphine, oxymorphone, oxycodone and hydromorphone; and other medications used for the treatment of cancer pain like steroids as Dexamethasone and methylprednisolone; bisphosphonates like Etidronate, Clodronate, Alendronate, Risedronate, and Zoledronate;

tricyclic antidepressants like Amitriptyline, Clomipramine, Desipramine, Imipramine and Doxepin; class I antiarrhythmics like mexiletine and lidocaine; anticonvulsants like carbamazepine, Gabapentin, oxcarbazepine, phenytoin, pregabalin, topiramate, alprazolam, diazepam, flurazepam, pentobarbital and phenobarbital.

Based upon standard laboratory techniques known to evaluate compounds useful for the treatment of neurogenic, by standard toxicity tests and by standard pharmacological assays for the determination of treatment of the conditions identified above in mammals, and by comparison of these results with the results of known active ingredients or medicaments that are used to treat these conditions, the effective dosage of the compounds of the present invention can readily be determined for treatment of each desired indication. The amount of the active ingredient to be administered in the treatment of one of these conditions can vary widely according to such considerations as the particular compound and dosage unit employed, the mode of administration, the period of treatment, the age and sex of the patient treated, and the nature and extent of the condition treated.

The total amount of the active ingredient to be administered will generally range from about 0.001 mg/kg to about 200 mg/kg body weight per day, and preferably from about 0.01 mg/kg to about 50 mg/kg body weight per day. Clinically useful dosing schedules will range from one to three times a day dosing to once every four weeks dosing. In addition, it is possible for "drug holidays", in which a patient is not dosed with a drug for a certain period of time, to be beneficial to the overall balance between pharmacological effect and tolerability. It is possible for a unit dosage to contain from about 0.5 mg to about 400 mg of active ingredient and can be administered one or more times per day or less than once a day. The average daily dosage for administration by injection, including intravenous, intramuscular, subcutaneous and parenteral injections, and use of infusion techniques will preferably be from 0.01 to 200 mg/kg of total body weight. The average daily rectal dosage regimen will preferably be from 0.01 to 200 mg/kg of total body weight. The average daily vaginal dosage regimen will preferably be from 0.01 to 200 mg/kg of total body weight. The average daily topical dosage regimen will preferably be from 0.1 to 200 mg administered between one to four times daily. The transdermal concentration will preferably be that required to maintain a daily dose of from 0.01 to 200 mg/kg. The average daily inhalation dosage regimen will preferably be from 0.01 to 100 mg/kg of total body weight.

Of course the specific initial and continuing dosage regimen for each patient will vary according to the nature and severity of the condition as determined by the attending diagnostician, the activity of the specific compound employed, the age and general condition of the patient, time of administration, route of administration, rate of excretion of the drug, drug combinations, and the like. The desired mode of treatment and number of doses of a compound of the present invention

or a pharmaceutically acceptable salt or ester or composition thereof can be ascertained by those skilled in the art using conventional treatment tests.

Methods of testing for a particular pharmacological or pharmaceutical property are well known to persons skilled in the art.

The example testing experiments described herein serve to illustrate the present invention and the invention is not limited to the examples given.

EXPERIMENTAL SECTION

The example testing experiments described herein serve to illustrate the present invention and the invention is not limited to the examples given.

The following table lists the abbreviations used in this paragraph, and in the examples section.

Abbreviation	Meaning
2-MeTHF	2-methyltetrahydrofuran
Boc	*tert*-butoxycarbonyl
Br_2	Bromine
CAN	ceric ammonium nitrate
CDI	1,1'-carbonyldiimidazole
$(COCl)_2$	oxalyl chloride
CPME	cyclopentyl methyl ether
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulfoxide
EDC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
h	hour(s)
HATU	1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate
HCl	hydrochloric acid
HPLC	high performance liquid chromatography
LC-MS	liquid chromatography – mass spectrometry
LCMS	liquid chromatography – mass spectrometry
M	Molar

MIDA	*N*-methylimidodiacetic acid
min	minute(s)
MsCl	methanesulfonyl chloride
MTBE	methyl tert-butyl ether
N	Normal
NCS	*N*-chlorosuccinimide
NBS	*N*-bromosuccinimide
nd	not determined
NMP	*N*-methyl-2-pyrrolidone
NMR	nuclear magnetic resonance spectroscopy
Pd	Palladium
PMB	*p*-methoxybenzyl
$POCl_3$	phosphoryl chloride
ppm	parts per million
rt	room temperature
R_t	retention time
sat.	Saturated
$SOCl_2$	thionyl chloride
T_3P	propylphosphonic anhydride
TFA	trifluoroacetic acid
THF	Tetrahydrofuran
THP	tetrahydropyran-2-yl

Other abbreviations have their meanings customary per se to the skilled person.

The various aspects of the invention described in this application are illustrated by the following examples which are not meant to limit the invention in any way.

The example testing experiments described herein serve to illustrate the present invention and the invention is not limited to the examples given.

EXPERIMENTAL SECTION - GENERAL PART

All reagents, for which the synthesis is not described in the experimental part, are either commercially available, or are known compounds or may be formed from known compounds by known methods by a person skilled in the art.

The compounds and intermediates produced according to the methods of the invention may require purification. Purification of organic compounds is well known to the person skilled in the art and there may be several ways of purifying the same compound. In some cases, no purification may be necessary. In some cases, the compounds may be purified by crystallization. In some cases, impurities may be stirred out using a suitable solvent. In some cases, the compounds may be purified by chromatography, particularly flash column chromatography, using for example prepacked silica gel cartridges, e.g. Biotage SNAP cartidges KP-Sil® or KP-NH® in combination with a Biotage autopurifier system (SP4® or Isolera Four®) and eluents such as gradients of hexane/ethyl acetate or DCM/methanol. In some cases, the compounds may be purified by preparative HPLC using for example a Waters autopurifier equipped with a diode array detector and/or on-line electrospray ionization mass spectrometer in combination with a suitable prepacked reverse phase column and eluents such as gradients of water and acetonitrile which may contain additives such as trifluoroacetic acid, formic acid or aqueous ammonia.

In some cases, purification methods as described above can provide those compounds of the present invention which possess a sufficiently basic or acidic functionality in the form of a salt, such as, in the case of a compound of the present invention which is sufficiently basic, a trifluoroacetate or formate salt for example, or, in the case of a compound of the present invention which is sufficiently acidic, an ammonium salt for example. A salt of this type can either be transformed into its free base or free acid form, respectively, by various methods known to the person skilled in the art, or be used as salts in subsequent biological assays. It is to be understood that the specific form (e.g. salt, free base etc.) of a compound of the present invention as isolated and as described herein is not necessarily the only form in which said compound can be applied to a biological assay in order to quantify the specific biological activity.

Furthermore, the intermediates and examples according to the invention may be present as rotational isomers, in particular in NMR studies. In cases where the presence of rotamers are clearly visible by NMR, it is stated in the experimental section. Purity figures are generally based on corresponding peak integrations in the LC/MS chromatogram, but may additionally also have been determined with the aid of the ^{1}H NMR spectrum.

In solvent-containing or contaminated batches, the formal yield may be ">100%"; in these cases the yield is not corrected for solvent or purity.

The multiplicities of proton signals in ^{1}H NMR spectra reported in the paragraphs which follow represent the signal form observed in each case and do not take account of any higher-order signal phenomena. In general, the stated chemical shift refers to the centre of the signal in question. In the case of broad multiplets, an interval is given. Signals obscured by solvent or water were either tentatively assigned or have not been listed. Significantly broadened signals – caused, for example, by rapid rotation of molecular moieties or because of exchanging protons – were likewise assigned tentatively (often referred to as a broad multiplet or broad singlet or broad doublet) or are not listed.

The ^{1}H NMR data of selected synthesis intermediates and working examples are stated in the form of ^{1}H NMR peak lists. For each signal peak, first the δ[ppm] = value in ppm and then the signal intensity in round brackets are listed. The δ[ppm] = value/signal intensity number pairs for different signal peaks are listed with separation from one another by commas. The peak list for an example therefore takes the following form: δ[ppm] = $_1$ (intensity$_1$), δ[ppm] = $_2$ (intensity$_2$), ... , δ[ppm] = $_i$ (intensity$_i$), ... , δ[ppm] = $_n$ (intensity$_n$).

The intensity of sharp signals correlates with the height of the signals in a printed example of an NMR spectrum in cm and shows the true ratios of the signal intensities in comparison with other signals. In the case of broad signals, several peaks or the middle of the signal and the relative intensity thereof may be shown in comparison to the most intense signal in the spectrum. The lists of the ^{1}H NMR peaks are similar to the conventional ^{1}H NMR printouts and thus usually contain all peaks listed in a conventional NMR interpretation. In addition, like conventional ^{1}H NMR printouts, they may show solvent signals, signals of stereoisomers of the target compounds which are likewise provided by the invention, and/or peaks of impurities. The peaks of stereoisomers of the target compounds and/or peaks of impurities usually have a lower intensity on average than the peaks of the target compounds (for example with a purity of > 90%). Such stereoisomers and/or impurities may be typical of the particular preparation process. Their peaks can thus help in identifying reproduction of our preparation process with reference to "by-product fingerprints". An expert calculating the peaks of the target compounds by known methods (MestreC, ACD simulation, or using empirically evaluated expected values) can, if required, isolate the peaks of the target compounds, optionally using additional intensity filters. This isolation would be similar to the peak picking in question in conventional ^{1}H NMR interpretation. A detailed description of the presentation of NMR data in the form of peak lists can be found in the publication "Citation of NMR Peaklist Data within Patent Applications" (cf. Research Disclosure Database Number 605005, 2014, 1 August 2014 or http://www.researchdisclosure.com/searching-disclosures). In the peak picking routine described in Research Disclosure Database Number 605005, the parameter "MinimumHeight" can be set between 1% and 4%. Depending on the type of chemical structure and/or depending

on the concentration of the compound to be analysed, it may be advisable to set the parameters "MinimumHeight" to values of < 1%.

Analysis methods:

LC-MS, Analytical Method A :

Instrument: Waters Acquity UPLCMS SingleQuad; Column: Acquity UPLC BEH C18 1.7 µm, 50x2.1mm; eluent A: water + 0.1 vol % formic acid (99%), eluent B: acetonitrile; gradient: 0-1.6 min 1-99% B, 1.6-2.0 min 99% B; flow 0.8 ml/min; temperature: 60 °C; DAD scan: 210-400 nm.

LC-MS, Analytical Method B :

Instrument: Waters Acquity UPLCMS SingleQuad; Column: Acquity UPLC BEH C18 1.7 µm, 50x2.1mm; eluent A: water + 0.2 vol % aqueous ammonia (32%), eluent B: acetonitrile; gradient: 0-1.6 min 1-99% B, 1.6-2.0 min 99% B; flow 0.8 ml/min; temperature: 60 °C; DAD scan: 210-400 nm.

LC-MS, Analytical Method C :

Instrument: SHIMADZU LCMS-2020 SingleQuad; Column: Chromolith@Flash RP-18E 25-2 MM; eluent A: water + 0.0375 vol % trifluoroacetic acid, eluent B: acetonitrile + 0.01875 vol % trifluoroacetic acid; gradient: 0-0.8 min, 5-95% B, 0.8-1.2 min 95% B; flow 1.5 ml/min; temperature: 50 °C; PDA: 220 nm & 254 nm.

Purification Methods:

Biotage Isolera™ chromatography system (http://www.biotage.com/product-area/flash-purification) using pre-packed silica and pre-packed modified silica cartridges.

Preparative HPLC, Method 1: Instrument: pump: Labomatic HD-5000 or HD-3000, head HDK 280, lowpressure gradient module ND-B1000; manual injection valve: Rheodyne 3725i038; detector: Knauer Azura UVD 2.15; collector: Labomatic Labocol Vario-4000; column: Chromatorex RP C-18 10 µm, 125x30mm; eluent A: water + 0.1 vol % formic acid (99%), eluent B: acetonitrile;
gradient A: 0 - 15 min 1 – 25% B; flow: 60 mL/min;
gradient B: 0 - 15 min 10 – 50% B; flow: 60 mL/min;
gradient C: 0 - 15 min 15 – 55% B; flow: 60 mL/min;
gradient D: 0 - 15 min 30 – 70% B; flow: 60 mL/min;
gradient E: 0 - 15 min 40 – 80% B; flow: 60 mL/min;

gradient F: 0 - 15 min 65 – 100% B; flow: 60 mL/min;

temperature: 25 °C; solution: max. 250 mg / 2ml dimethyl sulfoxide; injection: 1 x 2 ml; Detection: UV 254 nm; Software: SCPA PrepCon5.

Preparative HPLC, Method 2: Instrument: pump: Labomatic HD-5000 or HD-3000, head HDK 280, lowpressure gradient module ND-B1000; manual injection valve: Rheodyne 3725i038; detector: Knauer Azura UVD 2.15; collector: Labomatic Labocol Vario-4000; column: Chromatorex RP C-18 10 µm, 125x30mm; eluent A: water + 0.2 vol-% ammonia (32%), eluent B: acetonitrile;

gradient A: 0 - 15 min 1 – 25% B; flow: 60 mL/min;

gradient B: 0 - 15 min 10 – 50% B; flow: 60 mL/min;

gradient C: 0 - 15 min 15 – 55% B; flow: 60 mL/min;

gradient D: 0 - 15 min 30 – 70% B; flow: 60 mL/min;

gradient E: 0 - 15 min 40 – 80% B; flow: 60 mL/min;

gradient F: 0 - 15 min 65 – 100% B; flow: 60 mL/min;

temperature: 25 °C; solution: max. 250 mg / 2ml dimethyl sulfoxide; injection: 1 x 2 ml; Detection: UV 254 nm; Software: SCPA PrepCon5.

Preparative HPLC, Method 3: Instrument: Waters Autopurification MS SingleQuad; Column: Waters XBrigde C18 5µ 100x30mm; eluent A: water + 0.1 vol % formic acid (99%), eluent B: acetonitrile; gradient: 0-5.5 min 5-100% B; flow 70 ml/min; temperature: 25 °C; DAD scan: 210-400 nm.

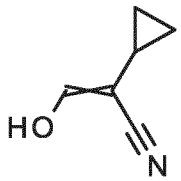
EXPERIMENTAL SECTION - INTERMEDIATES

Reaction times are either specified explicitly in the protocols of the experimental section, or reactions were run until completion. Chemical reactions were monitored and their completion was judged using methods well known to the person skilled in the art, such as thin layer chromatography, *e.g.* on plates coated with silica gel, or by LC-MS methods.

Chemical naming of the examples and intermediates was performed using ACD software by ACD/LABS (Batch version 12.01.) or Marvin software by ChemAxon (Batch version 4.1.7 or higher).

Intermediate 1

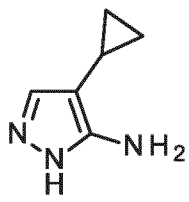
2-cyclopropyl-3-hydroxyprop-2-enenitrile



A solution of cyclopropylacetonitrile (28 ml, 310 mmol; CAS-RN:[6542-60-5]) in 200 ml dry THF was cooled to -70°C with a dry-ice/aceton bath, then a solution of lithium diisopropylamide (200 ml, 2.0 M, 400 mmol; CAS-RN:[4111-54-0]) was added drop-wise (1 h) into the cold solution. The temperature was maintained between -70 and -65°C. The brown solution was stirred for 1 h at -70°C. Keeping this temperature a prepared solution of ethyl formate (50 ml, 620 mmol; CAS-RN:[109-94-4]) in 100 ml THF was added drop-wise over a period of 1 h. The reaction mixture was stirred at -70°C for 1 h. Then the solution was warmed to room temperature and stirred for further 2 h. The mixture was acidified to pH 5 with approximately 400 ml hydrochloric acid (2M) and extracted with ethyl acetate. The combined organics were washed with brine, dried with a water-repellant filter and concentrated to afford 42.1 g (crude) of the title compound.

Intermediate 2

4-cyclopropyl-1H-pyrazol-5-amine



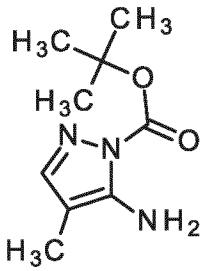
To a stirred solution of 2-cyclopropyl-3-hydroxyprop-2-enenitrile (40.5 g, 80 % purity, 297 mmol; intermediate 1) in dry ethanol (350 ml) was added hydrazine monohydrate (29 ml, 590 mmol; CAS-RN:[7803-57-8]) and acetic acid (25 ml). The solution was heated at 80°C for 4 h. After this time the solution was allowed to cool to rt, then the mixture was basified with an aqueous sodium hydroxide solution (1M; 200 ml) to pH 9-10. The mixture was diluted with water (150 ml) and extracted three times with ethyl acetate (150 ml). The combined organic layers were washed twice with brine (75 ml), dried with a water-repellant filter and concentrated. The obtained amorphous residue was taken up in methyl tert-butyl ether (50 ml) and added to hexane (600 ml). The mixture was intensively stirred for 30 min and the precipitate was collected by filtration. The filter cake was washed twice with hexane (30 ml) and the solid was dried to afford 22.5 g (60% yield, 97% purity) of the title compound.

^{1}H NMR (400 MHz, CHLOROFORM-d) δ [ppm]: 0.63-0.70 (m, 2H), 0.96-1.04 (m, 2H), 1.66 (ttd, 1H), 7.26 (d, 1H).

LC-MS (Method B): R_t = 0.55 min; MS (ESIpos): m/z = 124 $[M+H]^+$

Intermediate 3

tert-butyl 5-amino-4-methyl-1H-pyrazole-1-carboxylate

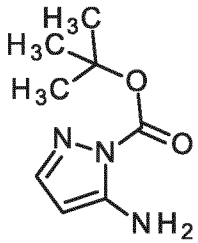
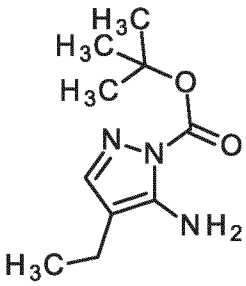
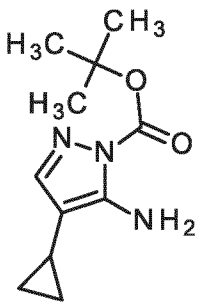


4-methyl-1H-pyrazol-5-amine (15.0 g, 154 mmol; CAS-RN:[64781-79-9]) was dissolved in dichloromethane (450 ml) and N,N-diisopropylethylamine (40 ml, 230 mmol; CAS-RN:[7087-68-5]) was added. The mixture was cooled with an ice-bath (4°C) and a solution of di-tert-butyl dicarbonate (43 ml, 190 mmol; CAS-RN:[24424-99-5]) in dichloromethane (100 ml) was added dropwise into the cold solution over a period of 30 minutes. The reaction mixture was stirred for 30 minutes under cooling and further 16 h at rt. The solution was quenched with water (100 ml) and extracted twice with dichloromethane (100 ml). The organic phase was once washed with brine (100 ml), dried with a water repellant filter and concentrated. The residue was suspended with ethyl acetate (25 ml) and added to hexane (250 ml). The suspension was virgorously stirred for 1 h and cooled down to 4°C with an ice-bath. The solid was collected by vacuum filtration, washed twice with hexane (50 ml) and dried in vacuum to afford 21.8 g (72% yield, 95% purity) of the title compound as a white solid.

^{1}H NMR (400 MHz, CHLOROFORM-d) δ [ppm]: 1.64 (s, 9H), 1.85 (s, 3H), 5.03 (br s, 2H), 7.27 (s, 1H).

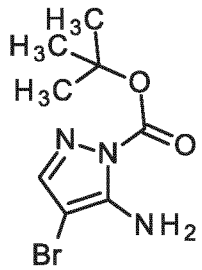
LC-MS (Method B): R_t = 0.81 min; MS (ESIpos): m/z = 198 $[M+H]^+$

In analogy to the procedure described for Intermediate 3, the following aminopyrazoles were protected with di-tert-butyl dicarbonate.

Inter-mediate	Structure IUPAC-Name	Analytical Data	Starting Materials Yield
3 1	 **tert-butyl 5-amino-1H-pyrazole-1-carboxylate**	^{1}H NMR (400 MHz, CHLOROFORM-d) δ [ppm]: 1.54 (s, 9H), 5.21 (br s, 2H), 5.28 (d, 1H), 7.26 (d, 1H) LC-MS (Method B): R_t = 0.75 min; MS (ESIpos): m/z = 184 $[M+H]^+$	CAS-RN:[916420-28-5] 27.5 g (83% yield)
3 2	 **tert-butyl 5-amino-4-ethyl-1H-pyrazole-1-carboxylate**	^{1}H NMR (400 MHz, DMSO-d6) δ [ppm]: 1.03 (t, 3H), 1.54 (s, 9H), 2.23 (q, 3H), 5.99 (s, 2H), 7.23 (s, 1H). LC-MS (Method A): R_t = 0.92 min; MS (ESIpos): m/z = 212 $[M+H]^+$	CAS-RN:[203062-02-6] 1.19 g (86% yield, 90% purity)
3 3	 **tert-butyl 5-amino-4-cyclopropyl-1H-pyrazole-1-carboxylate**	^{1}H NMR (400 MHz, CHLOROFORM-d) δ [ppm]: 0.44-0.50 (m, 2H), 0.75-0.83 (m, 2H), 1.33-1.42 (m, 1H), 1.68 (s, 9H), 5.27 (br s, 1H), 7.26 (s, 1H), 7.24-7.27 (m, 1H), 7.30 (s, 1H), 7.52 (s, 1H) LC-MS (Method B): R_t = 1.00 min; MS (ESIpos): m/z = 224 $[M+H]^+$	Intermediate 2 17.5 g (80% yield, 75% purity)

Intermediate 4

tert-butyl 5-amino-4-bromo-1H-pyrazole-1-carboxylate



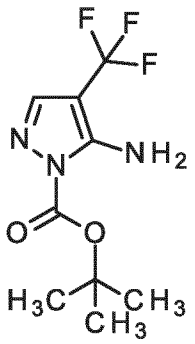
4-bromo-1H-pyrazol-3-amine (1.00 g, 6.17 mmol; CAS-RN:[16461-94-2]) was dissolved in tetrahydrofuran (20 ml). At 0°C triethylamine (860 µl, 6.2 mmol; CAS-RN:[121-44-8]), 4-dimethylaminopyridine (75.4 mg, 617 µmol; CAS-RN:[584-08-7]) and di-tert-butyl dicarbonate (1.35 g, 6.17 mmol) were added and the reaction stirred for 16 h at room temperature. The mixture was quenched with water and extracted with ethyl acetate. The organic layerwas concentrated and dried in vacuo to afford 1.58 mg (crude) of the title compound that was used without further purification in the next step.

^{1}H NMR (400 MHz, DMSO-d6) δ [ppm]: 1.52 (s, 9H), 5.65 (s, 2H), 8.16 (s, 1H).

LC-MS (Method 1): Rt = 0.96 min; MS (ESIpos): m/z = 264 $[M+H]^+$.

Intermediate 5

tert-butyl 5-amino-4-(trifluoromethyl)-1H-pyrazole-1-carboxylate



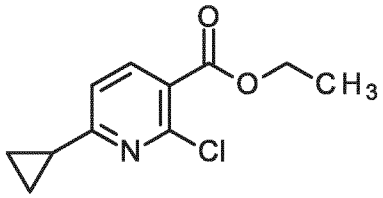
4-(trifluoromethyl)-1H-pyrazol-5-amine hydrogen chloride (1/1) (500 mg, 2.67 mmol; CAS-RN:[1956365-83-5]) was suspended in tetrahydrofuran (20 ml) and cooled to 0°C. Triethylamine (370 µl, 2.7 mmol) and di-tert-butyl dicarbonate (698 mg, 3.20 mmol) were added. The mixture was stirred at 0°C for 16 h. 4-dimethylaminopyridine (32.6 mg, 267 µmol) was added and the mixture was stirred at room temperature for 24 h. The mixture was quenched with water and extracted with ethyl acetate. The organic phases was concentrated in vacuo, and then mixed with diethylether. After filtration, the precipitate was dried in vacuo to afford 198 mg (30% yield) of the title compound that was used without further purification in the next step.

^{1}H NMR (400 MHz, DMSO-d6) δ [ppm]: 1.56 (s, 9H), 7.01 (br s, 2H), 7.66 (s, 1H)

LC-MS (Method A): Rt = 1.04 min; MS (ESIpos): m/z = 252 $[M+H]^+$

Intermediate 6

ethyl 2-chloro-6-cyclopropylpyridine-3-carboxylate



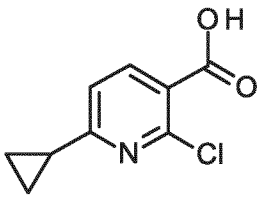
Ethyl 2,6-dichloropyridine-3-carboxylate (3.60 g, 16.4 mmol), potassium phosphate (10.4 g, 49.1 mmol; CAS-RN:[7778-53-2]), palladium acetate (184 mg, 818 µmol; CAS-RN:[3375-31-3]) and tricyclohexylphosphine (688 mg, 2.45 mmol; CAS-RN:[2622-14-2]) were suspended in toluene (50 ml) / water (5.0 ml). The mixture was degassed with nitrogen for 10 minutes. Then cyclopropylboronic acid (1.55 g, 18.0 mmol; CAS-RN:[411235-57-9]) was added. The reaction mixture was heated at 115°C for 18 h. The mixture was allowed to cool to ambient temperature, then it was filtered through celite rinsed with ethyl acetate. The filtrate was washed with water, brine and concentrated. The crude material was purified by Biotage Isolera™ chromatography (SNAP KP-Sil – 50 g, eluting with hexane-ethyl acetate, 1:0 to 17:5) to afford 2.31 g (38% yield, 60% purity) of the title compound.

^{1}H NMR (400 MHz, CHLOROFORM-d) δ [ppm]: 1.18-1.29 (m, 4H), 1.54 (t, 3H), 2.12-2.27 (m, 1H), 4.53 (q, 2H), 7.25 (d, 1H), 8.16 (d, 1H).

LC-MS (Method A): R_t = 1.27 min; MS (ESIpos): m/z = 226 $[M+H]^+$

Intermediate 7

2-chloro-6-cyclopropylpyridine-3-carboxylic acid



To a solution of ethyl 2-chloro-6-cyclopropylpyridine-3-carboxylate (2.30 g, 70 % purity, 7.13 mmol, intermediate 6) in ethanol (30 ml) was added an aqueous solution of sodium hydroxide (2M) (14 ml, 2.0 M, 29 mmol; CAS-RN:[1310-73-2]). The reaction mixture was stirred for 1 h at rt. The solvent was removed under reduced pressure and the aqueous residue was acidified with concentrated hydrochloric acid to pH 3. The obtained precipitate was collected by vacuum filtration, washed with water and dried. The residue was diluted with 15 ml acetonitrile / water

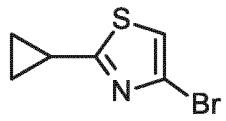
(1:1) and purified by preparative HPLC (Method A, gradient C). The product fractions were pooled and concentrated *in vacuo* to afford 1.07 g (35% yield, 67% purity) of the title compound.

^{1}H NMR (400 MHz, DMSO-d6) δ [ppm]: 0.91 - 0.98 (m, 2 H) 1.03 - 1.10 (m, 2 H) 2.18 (tt, 1 H) 7.41 (d, 1 H) 8.08 (d, 1 H) 13.23 - 13.52 (m, 1 H).

LC-MS (Method A): R_t = 1.27 min; MS (ESIpos): m/z = 226 $[M+H]^+$.

Intermediate 8

4-bromo-2-cyclopropyl-1,3-thiazole



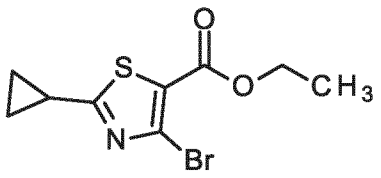
To a solution of 2,4-dibromo-1,3-thiazole (100.0 g, 0.411 mol, CAS-RN:[4175-77-3]) and cyclopropylboronic acid (38.9 g, 0.452 mmol, CAS-RN:[411235-57-9]) in tetrahydrofuran (1.5 l) were added palladium(II) acetate (9.24 g, 41.2 mmol) and 4,5-bis-(diphenylphosphino)-9,9-dimethyl xanthene (35.7 g, 61.7 mmol, CAS-RN:[161265-03-8]), potassium phosphate (262 g, 1.23 mol) in one portion at room temperature. The reaction mixture was stirred at 60°C for 16 h under nitrogen atmosphere. The reaction mixture was filtered and the filtrate was concentrated to give a residue. The residue was purified by flash column chromatography (petroleum ether: ethyl acetate = 10: 1) to give 4-bromo-2-cyclopropyl-1,3-thiazole (150 g, crude) as yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm]: 6.98 (s, 1H), 2.35-2.29 (m, 1H), 1.45-1.11 (s, 4H).

LC-MS (Method C): R_t = 0.739 min; MS (ESIpos): m/z = 204.0/206.0 $[M+H]^+$.

Intermediate 9

ethyl 4-bromo-2-cyclopropyl-1,3-thiazole-5-carboxylate



To a solution of 4-bromo-2-cyclopropyl-1,3-thiazole (110 g, 539 mmol, intermediate 8) in tetrahydrofuran (800 ml) was added lithium bis(trimethylsilyl)amide (490 ml, 490 mmol, 1 M in tetrahydrofuran) dropwise at -70 °C. After stirring for 0.5 h, a solution of diethyl dicarbonate (87.4 g, 539 mmol) in tetrahydrofuran (300 ml) was added dropwise at -70 °C. The reaction mixture was stirred at room temperature for 16 h. The mixture was poured into saturated ammonium chloride solution and extracted with ethyl acetate. The organic phase was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by

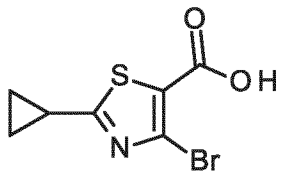
column chromatography (200-300 mesh, petroleum ether: ethyl acetate = 50: 1) to give 37.5 g of ethyl 4-bromo-2-cyclopropyl-1,3-thiazole-5-carboxylate (98% purity, 25% yield) as a light yellow solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ [ppm]: 4.28 (q, 2H), 2.54-2.51 (m, 1H), 1.28 (t, 3H), 1.25-1.23 (m, 2H), 1.07-1.06 (m, 2H).

LC-MS (Method C): R_t = 0.90 min; MS (ESIpos): m/z = 277.9 $[M+H]^+$.

Intermediate 10

4-bromo-2-cyclopropyl-1,3-thiazole-5-carboxylic acid



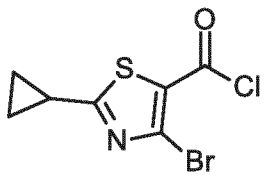
To a solution of ethyl 4-bromo-2-cyclopropyl-1,3-thiazole-5-carboxylate (32.0 g, 80 % purity, 92.7 mmol, intermediate 9) in methanol (300 ml) and water (100 ml) was added potassium hydroxide (10.4 g, 185 mmol; CAS-RN:[1310-58-3]). The mixture was stirred at 25 °C for 2 h. The reaction mixture was removed methanol. The mixture was diluted with water, washed with petroleum ether. The aqueous phase pH~5 with hydrochloric acid (2 M), extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, filtered, concentrated to afford 24.3 g (97% yield, 92% purity) of the title compound.

^{1}H NMR (400 MHz, DMSO-d6) δ [ppm]: 1.00-1.09 (m, 2H), 1.18-1.25 (m, 2H), 2.44-2.49 (m, 1H), 13.55 (br s, 1H).

LC-MS (Method C): R_t = 0.75 min; MS (ESIpos): m/z = 250.0 $[M+H]^+$.

Intermediate 11

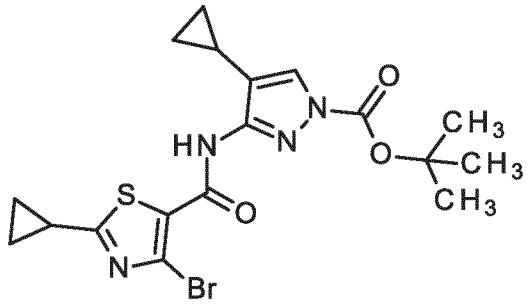
4-bromo-2-cyclopropyl-1,3-thiazole-5-carbonyl chloride



To a solution of 4-bromo-2-cyclopropyl-1,3-thiazole-5-carboxylic acid (1.00 g, 4.03 mmol; intermediate 10) in dichloromethane were added oxalyl chloride (1.1 ml, 12 mmol; CAS-RN:[79-37-8]) and three drops N,N-dimethylformamide at room temperature. The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated in vacuo and directly used next step.

Intermediate 12

tert-butyl 3-[(4-bromo-2-cyclopropyl-1,3-thiazole-5-carbonyl)amino]-4-cyclopropyl-1H-pyrazole-1-carboxylate

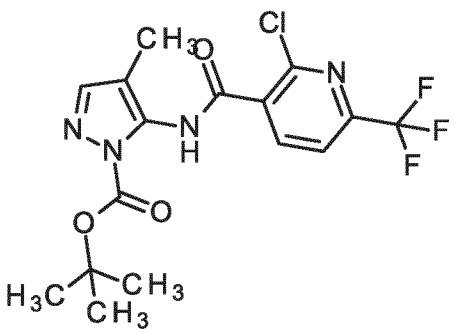


To a solution of tert-butyl 3-amino-4-cyclopropyl-1H-pyrazole-1-carboxylate (896 mg, 4.01 mmol; intermediate 3-3) in dichloromethane (15 ml) were added *N,N*-diisopropylethylamine (2.1 ml, 12 mmol; CAS-RN:[7087-68-5]) and a solution of 4-bromo-2-cyclopropyl-1,3-thiazole-5-carbonyl chloride (1.07 g, 4.01 mmol; intermediate 11) in dichloromethane (10 ml) at room temperature. The reaction mixture was stirred for 2 h at room temperature. The mixture was diluted with dichloromethane and washed with saturated ammonium chloride. The organic phase was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to give a residue. The residue was purified by flash column chromatography (petroleum ether: ethyl acetate = 10: 1 to 4: 1, then 4:1) to afford 800 mg (44% yield) of the title compound as a yellow solid.

^{1}H-NMR (400 MHz, DMSO-d_6) δ [ppm]: 10.6 (s, 1H), 7.92 (s, 1H), 1.61-1.49 (m, 11H), 1.25-1.19 (m, 2H), 1.08-1.13 (m, 2H), 0.80-0.74 (m, 2H), 0.59-0.52 (m, 2H).
LC-MS (Method C): R_t = 0.88 min; MS (ESIpos): m/z = 399 $[M+H]^+$

Intermediate 13

tert-butyl 5-{[2-chloro-6-(trifluoromethyl)pyridine-3-carbonyl]amino}-4-methyl-1H-pyrazole-1-carboxylate



To a solution of 2-chloro-6-(trifluoromethyl)pyridine-3-carboxylic acid (11.5 g, 51.0 mmol; CAS-RN:[280566-45-2]) in *N,N*-dimethylformamide (200 ml) was added tert-butyl 5-amino-4-methyl-

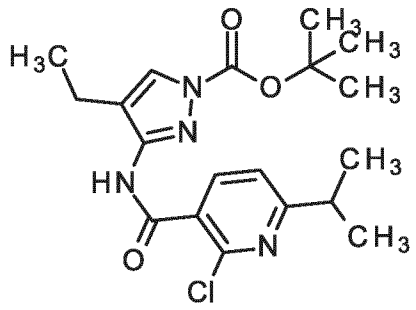
1H-pyrazole-1-carboxylate (10.1 g, 51.0 mmol; intermediate 3), pyridine (16 ml, 200 mmol; CAS-RN:[110-86-1]) and under ice-cooling methanesulfonyl chloride (5.9 ml, 77 mmol; CAS-RN:[124-63-0]). The mixture was stirred at room temperature for 16 h. The reaction mixture was quenched with water and extracted with ethyl acetate. The combined organic phases were filtered over a water-repellent filter and concentrated and dried *in vacuo*. After redissolving in ethyl acetate the organic layer was washed with diluted aqueous HCl sotuion and concentrated and dried *in vacuo* again to afford 16.8 g (49% yield, 60% purity) of the title compound.

^{1}H NMR (400 MHz, DMSO-d6) δ [ppm]:1.54 (s, 9H), 1.98 (s, 3H), 7.68 (s, 1H), 8.17 (d, 1H), 8.34 (d, 1H), 10.76 (s, 1H).

LC-MS (Method A): R_t = 1.17 min; MS (ESIpos): m/z = 405 $[M+H]^+$

Intermediate 14

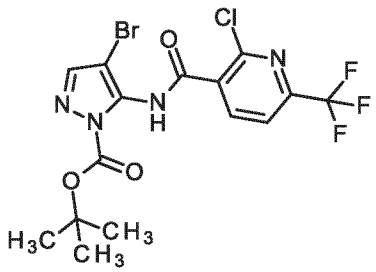
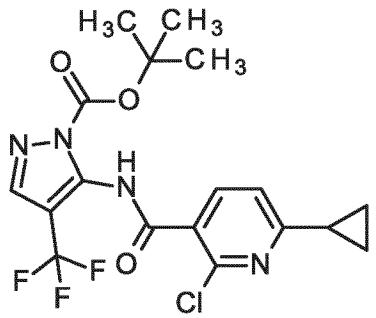
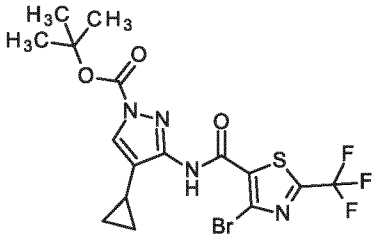
tert-butyl 3-{[2-chloro-6-(propan-2-yl)pyridine-3-carbonyl]amino}-4-ethyl-1H-pyrazole-1-carboxylate



2-chloro-6-(propan-2-yl)pyridine-3-carboxylic acid (160 mg, 800 µmol; CAS-RN:[166331-65-3]) was dissolved in *N,N*-dimethylacetamide (3.0 ml) and pyridine (260 µl) and methanesulfonyl chloride (93 µl, 1.2 mmol; CAS-RN:[124-63-0]) were added. After stirring für 5 minutes, tert-butyl 5-amino-4-ethyl-1H-pyrazole-1-carboxylate (203 mg, 960 µmol; intermediate 3-2) was added and stirring was continued for 16 h at room temperature. After quenching with water, the reaction mixture was extracted with ethyl acetate. The organic layer was filtered over an water-repellant filter and concentrated *in vacuo* to afford 381 mg (99% yield, 82% purity) of the title compound.

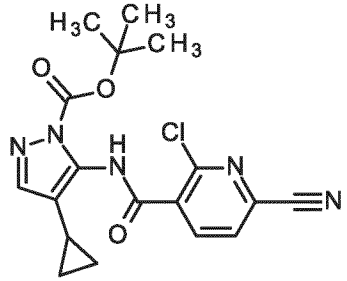
LC-MS (Method A): R_t = 1.29 min; MS (ESIpos): m/z = 393 $[M+H]^+$

In analogy to the procedure described for Intermediate 14, the following Intermediates were prepared from the the appropriate carboxylic acid and aminopyrazole as starting materials.

Inter-mediate	Structure IUPAC-Name	Analytical Data	Starting Materials Yield
14 1	 **tert-butyl 4-bromo-5-{[2-chloro-6-(trifluoromethyl)pyridine-3-carbonyl]amino}-1H-pyrazole-1-carboxylate**	LC-MS (Method A): R_t = 1.27 min; MS (ESIpos): m/z = 470 $[M+H]^+$	CAS-RN:[280566-45-2] and Intermediate 4 829 mg (98% yield, 80% purity)
14 2	 **tert-butyl 5-[(2-chloro-6-cyclopropylpyridine-3-carbonyl)amino]-4-(trifluoromethyl)-1H-pyrazole-1-carboxylate**	^{1}H NMR (400 MHz, CHLOROFORM-d) δ [ppm]: 1.09-1.15 (m, 4H), 1.66 (s, 9H), 2.05-2.11 (m, 1H), 7.21 (d, 1H), 8.18 (br d, 1H), 8.39 (d, 1H), 8.63 (br d, 1H). LC-MS (Method A): R_t = 1.32 min; MS (ESIpos): m/z = 431 $[M+H]^+$	Intermediate 7 and Intermediate 5 68.0 mg (26% yield, 96% purity)
14 3	 **tert-butyl 3-{[4-bromo-2-(trifluoromethyl)-1,3-thiazole-5-carbonyl]amino}-4-cyclopropyl-1H-pyrazole-1-carboxylate**	^{1}H NMR (400 MHz, DMSO-d6) δ [ppm]: 0.55-0.61 (m, 2H), 0.77-0.84 (m, 2H), 1.56 (s, 9H), 1.57-1.65 (m, 1H), 7.96 (d, 1H), 11.11 (s, 1H). LC-MS (Method A): R_t = 1.37 min; MS (ESIpos): m/z = 482 $[M+H]^+$	CAS-RN:[1445906-51-3] and Intermediate 3-3 560 mg (99% yield, 85% purity)

Intermediate 15

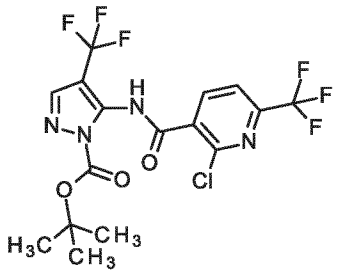
tert-butyl 5-[(2-chloro-6-cyanopyridine-3-carbonyl)amino]-4-cyclopropyl-1H-pyrazole-1-carboxylate



2-Chloro-6-cyanopyridine-3-carboxylic acid (183 mg, 1.00 mmol; CAS-RN:[1356850-56-0]) was dissolved in toluene (8.0 ml) together with 1-chloro-*N*,*N*,2-trimethylpropenylamine (160 µl, 1.2 mmol; CAS-RN:[26189-59-3]) and stirred for 2 h at 60°C. Afterwards *N*-cyclohexyl-*N*-methylcyclohexanamine (320 µl, 1.5 mmol; CAS-RN:[7560-83-0]) and tert-butyl 5-amino-4-cyclopropyl-1H-pyrazole-1-carboxylate (268 mg, 1.20 mmol; intermediate 3-3) were added and stirring was continued for 16 h at room temperature. The reaction mixture was acidified with 5% aqueous acetic acid solution (5 ml) and layers were separated. The organic layer was concentrated and dried *in vacuo* to afford 2.00 mg (1% yield, 20% purity) of the title compound.

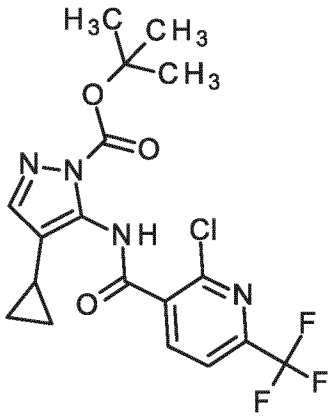
LC-MS (Method A): R_t = 1.16 min; MS (ESIpos): m/z = 388 $[M+H]^+$

In analogy to the procedure described for Intermediate 15, the following Intermediate was prepared from the the appropriate carboxylic acid and aminopyrazole as starting material.

Inter-mediate	Structure IUPAC-Name	Analytical Data	Starting Materials Yield
15 1	 **tert-butyl 5-{[2-chloro-6-(trifluoromethyl)pyridine-3-carbonyl]amino}-4-(trifluoromethyl)-1H-pyrazole-1-carboxylate**	LC-MS (Method A): Rt = 1.29 min; MS (ESIpos): m/z = 459 $[M+H]^+$	CAS-RN:[280566-45-2] and Intermediate 5 422 mg (63% yield)

Intermediate 16

tert-butyl 5-{[2-chloro-6-(trifluoromethyl)pyridine-3-carbonyl]amino}-4-cyclopropyl-1H-pyrazole-1-carboxylate

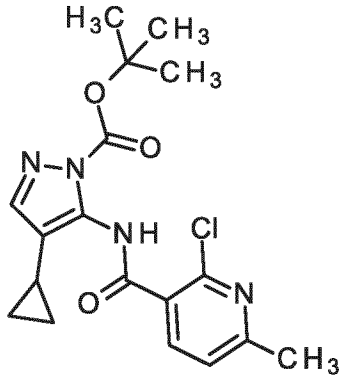
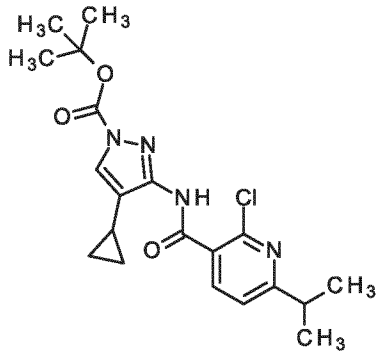


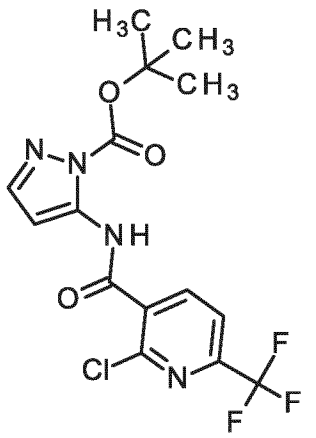
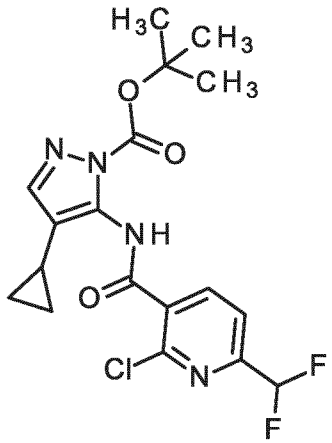
To a solution of 2-chloro-6-(trifluoromethyl)pyridine-3-carboxylic acid (7.50 g, 33.3 mmol; CAS-RN:[280566-45-2]) in toluene (200 ml) was added 1-chloro-*N*,*N*,2-trimethylpropenylamine (6.6 ml, 50 mmol; CAS-RN:[26189-59-3]). The mixture was heated at 60°C for 2 h. After cooling to ambient temperature tert-butyl 5-amino-4-cyclopropyl-1H-pyrazole-1-carboxylate (7.42 g, 33.3 mmol; intermediate 3-3) and *N*-cyclohexyl-*N*-methylcyclohexanamine (11 ml, 50 mmol; CAS-RN:[7560-83-0]) were added. The reaction mixture was stirred for further 2 h at 40°C. After cooling to room temperature, aqueous acetic acid (20 ml) was added and the phases were separated. The organic phase was washed with water, dried with a water-repellant filter and concentrated *in vacuo*. The residue was taken up in ethyl acetate (5 ml) and hexane (75 ml) was added. The precipitate was collected by filtration, washed with hexane and dried. The crude material was purified by Biotage Isolera™ chromatography (SNAP KP-Sil – 25 g, eluting with hexane-ethyl acetate, 1:0 to 11:9) to afford 2.64 g (13% yield, 70% purity) of the title compound as a yellow foam.

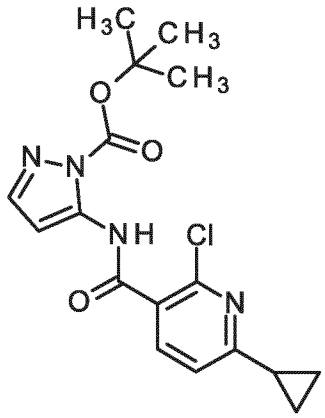
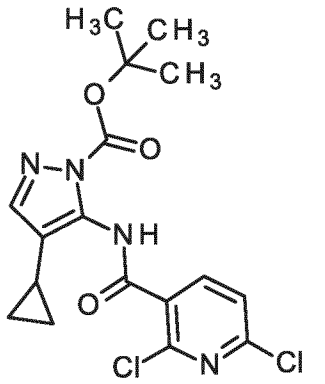
^{1}H NMR (400 MHz, CHLOROFORM-d) δ [ppm]: 0.56 (br d, 2H), 0.83-0.97 (m, 2H), 1.58 (br s, 3H), 1.78 (br s, 1H), 7.67 (br s, 1H), 7.74 (br d, 1H), 8.32 (br d, 1H), 8.87 (br s, 1H).

LC-MS (Method A): R_t = 1.22 min; MS (ESIneg): m/z = 429 $[M-H]^-$

In analogy to the procedure described for Intermediate 16, the following Intermediates were prepared from the the appropriate carboxylic acid and aminopyrazole as starting materials.

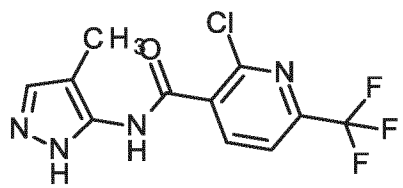
Inter-mediate	Structure IUPAC-Name	Analytical Data	Starting Materials Yield
16 1	 **tert-butyl 5-[(2-chloro-6-methylpyridine-3-carbonyl)amino]-4-cyclopropyl-1H-pyrazole-1-carboxylate**	^{1}H NMR (400 MHz, CHLOROFORM-d) δ [ppm]: 0.55 (m, 2H), 0.83-0.92 (m, 2H), 1.62 (s, 9H), 1.76 (br d, 1H), 2.60 (s, 3H), 7.23 (d, 1H), 7.70 (s, 1H), 8.14 (br d, 1H), 8.51 (br s, 1H). LC-MS (Method B): R_t = 1.15 min; MS (ESIpos): m/z = 377 $[M+H]^+$	CAS-RN:[30529-70-5] and Intermediate 3-3 287 mg (50% yield, 95% purity)
16 2	 **tert-butyl 3-{[2-chloro-6-(propan-2-yl)pyridine-3-carbonyl]amino}-4-cyclopropyl-1H-pyrazole-1-carboxylate**	^{1}H NMR (400 MHz, CHLOROFORM-d) δ [ppm]: 0.54 (br d, 2H), 0.84-0.92 (m, 2H), 1.31 (d, 6H), 1.61 (s, 9H), 1.76 (br d, 1H), 3.09 (spt, 1H), 7.24 (d, 1H), 7.69 (s, 1H), 8.16 (br d, 1H), 8.59 (br s, 1H). LC-MS (Method B): R_t = 1.32 min; MS (ESIpos): m/z = 405 $[M+H]^+$	CAS-RN:[166331-65-3] and Intermediate 3-3 671 mg (60% yield, 91% purity)

16 3	 **tert-butyl 5-{[2-chloro-6-(trifluoromethyl)pyridine-3-carbonyl]amino}-1H-pyrazole-1-carboxylate**	^{1}H NMR (400 MHz, CHLOROFORM-d) δ [ppm]: 1.68 (s, 9H), 7.05 (d, 1H), 7.67 (d, 1H), 7.79 (d, 1H), 8.33 (dd, 1H), 11.18 (s, 1H). LC-MS (Method B): R_t = 1.23 min; MS (ESIneg): m/z = 389 $[M-H]^-$	CAS-RN:[280566-45-2] and Intermediate 3-1 505 mg (26% yield, 88% purity)
16 4	 **tert-butyl 5-{[2-chloro-6-(difluoromethyl)pyridine-3-carbonyl]amino}-4-cyclopropyl-1H-pyrazole-1-carboxylate**	^{1}H NMR (400 MHz, CHLOROFORM-d) δ [ppm]: 0.55 (br d, 2H), 0.85-0.93 (m, 2H), 1.59 (s, 9H), 1.74-1.82 (m, 1H), 6.61(t, 1H), 7.61-7.74 (m, 2H), 8.29 (br d, 1H), 8.87 (br s, 1H). LC-MS (Method A): R_t = 1.24 min; MS (ESIneg): m/z = 411 $[M-H]^-$	CAS-RN:[1105985-15-6] and Intermediate 3-3 171 mg (34% yield, 99% purity)

16 5	 **tert-butyl 5-[(2-chloro-6-cyclopropylpyridine-3-carbonyl)amino]-1H-pyrazole-1-carboxylate**	^{1}H NMR (CHLOROFORM-d) δ [ppm]: 9.13 (s, 1H), 8.06 (d, 1H), 8.01 (d, 1H), 7.19 (d, 1H), 7.08 (d, 1H), 2.06 (m, 1H), 1.64 (s, 9H), 1.08-1.15 (m, 4H). LC-MS (Method A): R_t = 1.31 min; MS (ESIneg): m/z = 361 $[M-H]^-$	Intermediate 7 and Intermediate 3-1 11.3 g (30% yield, 98% purity)
16 6	 **tert-butyl 4-cyclopropyl-5-[(2,6-dichloropyridine-3-carbonyl)amino]-1H-pyrazole-1-carboxylate**	^{1}H NMR (400 MHz, CHLOROFORM-d) δ [ppm]: 0.50-0.58 (m, 2H), 0.84-0.94 (m, 2H), 1.60 (s, 9H), 1.75 (br t, 1H), 7.39 (br d, 1H), 7.67 (br s, 1H), 8.15 (br d, 1H), 8.78 (br s, 1H). LC-MS (Method B): R_t = 1.19 min; MS (ESIneg): m/z = 395 $[M-H]^-$	CAS-RN:[38496-18-3] and Intermediate 3-3 592 mg (57% yield, 97% purity)

Intermediate 17

2-chloro-N-(4-methyl-1H-pyrazol-5-yl)-6-(trifluoromethyl)nicotinamide



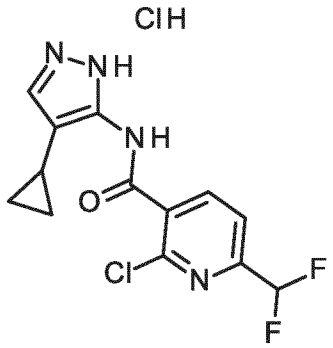
To a suspension of tert-butyl 3-[[2-chloro-6-(trifluoromethyl)pyridine-3-carbonyl]amino]-4-methyl-pyrazole-1-carboxylate (301.3 g, 719.81 mmol; intermediate 13) in ethyl acetate (400 mL) was added HCl/dioxane (2.2 L, 4 M). The mixture was stirred at room temperature (25 °C) for 2 hrs. The reaction mixture was concentrated under reduced pressure. The residue was

triturated with ethyl acetate (200 mL) to give 2-chloro-N-(4-methyl-1H-pyrazol-5-yl)-6-(trifluoromethyl)pyridine-3-carboxamide (269 g, HCl salt, crude) as a white solid.

^{1}H NMR (400 MHz, DMSO-d6) δ [ppm]: 10.71 (s, 1H), 9.53 (brs, 3H), 8.37 (d, 1H), 8.09 (d, 1H), 7.60 (s, 1H), 2.00 (s, 3H).

Intermediate 18

2-chloro-N-(4-cyclopropyl-1H-pyrazol-5-yl)-6-(difluoromethyl)pyridine-3-carboxamide hydrogen chloride (1/1)

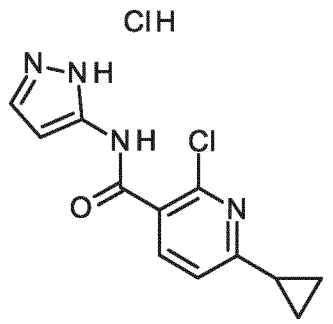


To a stirred solution of tert-butyl 5-{[2-chloro-6-(difluoromethyl)pyridine-3-carbonyl]amino}-4-cyclopropyl-1H-pyrazole-1-carboxylate (170 mg, 412 µmol; intermediate 16-4) in dichloromethane (2.0 ml) was added hydrochloric acid in dioxane (620 µl, 4.0 M, 2.5 mmol; CAS-RN:[7647-01-0]). The reaction mixture was stirred for 16 h at room temperature. The obtained precipitate was collected by vacuum filtration, washed with methyl tert-butyl ether and dried to afford 123 mg (1% yield, 100% purity) of the title compound as a white solid.

LC-MS (Method A): R_t = 0.89 min; MS (ESIpos): m/z = 313 $[M+H]^+$

Intermediate 19

2-chloro-6-cyclopropyl-N-(1H-pyrazol-5-yl)pyridine-3-carboxamide hydrogen chloride (1/1)



To a solution of tert-butyl 5-[(2-chloro-6-cyclopropylpyridine-3-carbonyl)amino]-1H-pyrazole-1-carboxylate (16.5 g, 45.5 mmol; intermediate 16-5) in dichloromethane (300 ml) was added hydrochloric acid in dioxane (68 ml, 4.0 M, 270 mmol; CAS-RN:[7647-01-0]). The reaction

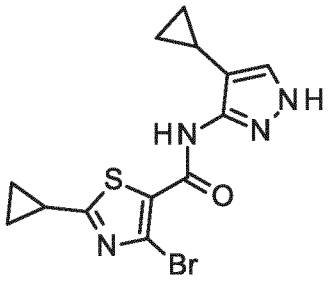
mixture was stirred at room temperature for 16 h. The solvents were evaporated, and the precipitate was suspended in methyl tert-butyl ether (250 ml). The solid was collected by vacuum filtration, washed with hexane and dried to afford 13.4 g (96% yield, 97% purity) of the title compound as a white solid.

^{1}H NMR (400 MHz, DMSO-d6) [ppm]: δ 0.89-0.96 (m, 2H), 1.01-1.07 (m, 2H), 2.13-2.22 (m, 1H), 6.58 (d, 1H), 7.40 (d, 1H), 7.69 (d, 1H), 7.83 (d, 1H), 11.06 (s, 1H).

LC-MS (Method A): R_t = 0.81 min; MS (ESIneg): m/z = 261 $[M-H]^-$

Intermediate 20

4-bromo-2-cyclopropyl-N-(4-cyclopropyl-1H-pyrazol-3-yl)-1,3-thiazole-5-carboxamide

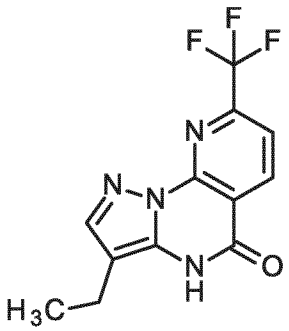


To a solution of tert-butyl 5-[(4-bromo-2-cyclopropyl-1,3-thiazole-5-carbonyl)amino]-4-cyclopropyl-1H-pyrazole-1-carboxylate (3.50 g, 7.72 mmol; intermediate 12) in dichloromethane (80 ml) was added trifluoroacetic acid (20 ml) at room temperature. The mixture was stirred at room temperature for 2 hours. The mixture was concentrated to give a residue. The residue was diluted with ethyl acetate and washed with saturated sodium bicarbonate solution. The organic phase was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to give a residue. The residue was purified by column chromatography (100-200 mesh, petroleum ether: ethyl acetate = 3: 1, then 0: 1) to afford 2.70 g (99% yield) of the title compound.

LC-MS (Method C): R_t = 0.853 min; MS (ESIpos): m/z = 353.1, 353.2 $[M+H]^+$.

Intermediate 21

3-ethyl-8-(trifluoromethyl)pyrazolo[1,5-a]pyrido[3,2-e]pyrimidin-5(4H)-one

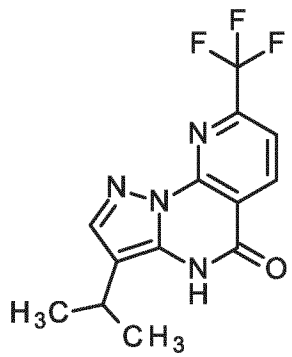


4-ethyl-1H-pyrazol-5-amine (225 mg, 2.02 mmol; CAS-RN:[203062-02-6]) and methyl 2-chloro-6-(trifluoromethyl)pyridine-3-carboxylate (485 mg, 2.02 mmol; CAS-RN:[1073129-57-3]) were dissolved in polyphosphoric acid (10 ml). The reaction mixture was heated to 180°C overnight. After cooling to room temperature, the reaction mixture was quenched with 10% sodium bicarbonate solution and extracted with a mixture of dichloromethane / isopropanol (4:1). The organic layer was concentrated in vacuo and the residue triturated with ethyl acetate.The precipitate obtained was collected by filtration, washed with ethyl acetate and dried to afford 87.0 mg (15% yield) of the title compound.

^{1}H NMR (400 MHz, DMSO-d6) δ [ppm]: 1.15 (t, 3H), 2.54 (q, 2H), 7.83 (s, 1H), 7.97 (d, 1H), 8.73 (d, 1H), 12.45 (s, 1H).

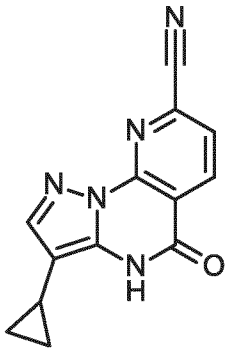
LC-MS (Method A): R_t = 0.90 min; MS (ESIpos): m/z = 283 $[M+H]^+$

In analogy to the procedure described for Intermediate 21, the following Intermediate was prepared from the the appropriate acylated aminopyrazole as starting material.

Inter-mediate	Structure IUPAC-Name	Analytical Data	Starting Materials Yield
21 1	 **3-(propan-2-yl)-8-(trifluoromethyl)pyrazolo[1,5-a]pyrido[3,2-e]pyrimidin-5(4H)-one**	^{1}H NMR (400 MHz, DMSO-d6) δ [ppm]: 1.20 (d, 6H), 3.11 (spt, 1H), 7.87 (s, 1H), 7.96 (d, 1H), 8.73 (d, 1H), 12.43 (br s, 1H). LC-MS (Method A): R_t = 0.98 min; MS (ESIpos): m/z = 297 $[M+H]^+$	Intermediate 261 mg (35% yield, 95% purity)

Intermediate 22

3-cyclopropyl-5-oxo-4,5-dihydropyrazolo[1,5-a]pyrido[3,2-e]pyrimidine-8-carbonitrile

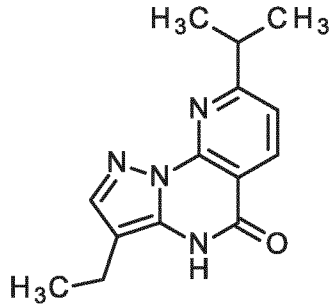


tert-butyl 5-[(2-chloro-6-cyanopyridine-3-carbonyl)amino]-4-cyclopropyl-1H-pyrazole-1-carboxylate (497 mg, 1.28 mmol; intermediate 15) was dissolved in dry *N*-methyl-2-pyrrolidone (10 mL) and stirred at 120°C over night. The reaction mixture was partitioned between water and ethyl acetate. The organic layer was dried and concentrated *in vacuo*. The residue was purified by preparative HPLC (Method 3). The product fractions were pooled and concentrated *in vacuo* to afford 3.0 mg (1% yield, 95% purity) of the title compound.

^{1}H NMR (400 MHz, DMSO-d6) δ [ppm]: 0.57-0.64 (m, 2H), 0.84-0.90 (m, 2H), 1.89 (tt, 1H), 7.63 (s, 1H), 8.08 (d, 1H), 8.66 (d, 1H), 12.61 (br s, 1H).

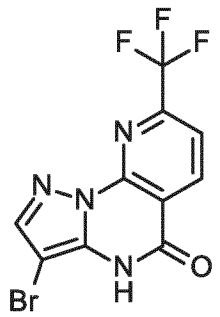
LC-MS (Method A): R_t = 0.75 min; MS (ESIpos): m/z = 252 $[M+H]^+$

In analogy to the procedure described for Intermediate 22, the following Intermediate was prepared from the the appropriate acylated aminopyrazole as starting material.

Intermediate	Structure IUPAC-Name	Analytical Data	Starting Materials Yield
22 1	 **3-ethyl-8-(propan-2-yl)pyrazolo[1,5-a]pyrido[3,2-e]pyrimidin-5(4H)-one**	^{1}H NMR (400 MHz, DMSO-d6) δ [ppm]: 1.14 (t, 3H), 1.30 (d, 6H), 2.52 (q, 2H), 3.16 (spt, 1H), 7.74 (s, 1H), 8.15 (d, 1H), 8.41 (d, 1H), 12.18 (s, 1H). LC-MS (Method A): R_t = 0.92 min; MS (ESIpos): m/z = 257 $[M+H]^+$	Intermediate 14 3.00 mg (2% yield)

Intermediate 23

3-bromo-8-(trifluoromethyl)pyrazolo[1,5-a]pyrido[3,2-e]pyrimidin-5(4H)-one



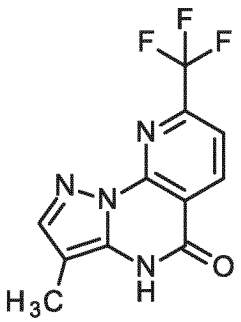
tert-butyl 4-bromo-5-{[2-chloro-6-(trifluoromethyl)pyridine-3-carbonyl]amino}-1H-pyrazole-1-carboxylate (400 mg, 80 % purity, 681 µmol; intermediate 14-1) was dissolved in dry *N*-methyl-2-pyrrolidone (4.0 ml). After addition of potassium carbonate (188 mg, 1.36 mmol) the reaction mixture was stirred at 130°C for 72 h and cooled to room temperature. The reaction mixture was quenched with water and extracted with ethyl acetate and 1-butanol. The combined organic layers were concentrated and dried in vacuo. The residue was purified by preparative HPLC (Method 3). The product fractions were pooled and concentrated *in vacuo* to afford 4.00 mg (2% yield, 99% purity) of the title compound.

^{1}H NMR (400 MHz, DMSO-d6) δ [ppm]: 8.03 (s, 1H), 8.03 (d, 1H), 8.76 (d, 1H), 12.81 (br s, 1H).

LC-MS (Method A): R_t = 0.90 min; MS (ESIpos): m/z = 333 $[M+H]^+$

Intermediate 24

3-methyl-8-(trifluoromethyl)pyrazolo[1,5-a]pyrido[3,2-e]pyrimidin-5(4H)-one



This reaction was performed as two parallel batches: To a mixture of potassium carbonate (90 g, 651.20 mmol) in dimethyl sulfoxide (2 L) was added 2-chloro-N-(4-methyl-1H-pyrazol-5-yl)-6-(trifluoromethyl)pyridine-3-carboxamide (100 g, HCl salt, crude from 17) in portions at 110°C (oil bath temperature: 130°C) with nitrogen flow. The resulting mixture was stirred at 110°C for 1 h. The reaction mixture was cooled to rt and poured into 10 L water (containing 40 mL conc. HCl) respectively. The combined mixture (2 batches) was filtered. The residue was purified with other batches together (108 g rare material was charged). The combined crude product was

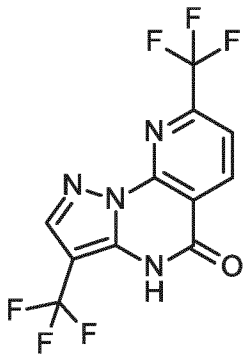
triturated with a mixed solvent (*N,N*-dimethylformamide : acetonitrile = 1: 4, 2 L) to give 3-methyl-8-(trifluoromethyl)pyrazolo[1,5-a]pyrido[3,2-e]pyrimidin-5(4H)-one (197 g) as a light yellow solid and a mother liquid. The mother liquid was concentrated under reduced pressure and triturated with acetonitrile (500 mL) to give 3-methyl-8-(trifluoromethyl)pyrazolo[1,5-a]pyrido[3,2-e]pyrimidin-5(4H)-one (20 g) as a light yellow solid.

^{1}HNMR: (400 MHz, CDCl3-d) δ [ppm]: 10.71 (s, 1H), 8.71 (d, 1H), 7.95 (d, 1H), 7.74 (s, 1H), 2.07 (s, 3H).

LC-MS (Method A): R_t = 0.81 min; MS (ESIpos): m/z = 269 $[M+H]^+$

Intermediate 25

3,8-bis(trifluoromethyl)pyrazolo[1,5-a]pyrido[3,2-e]pyrimidin-5(4H)-one



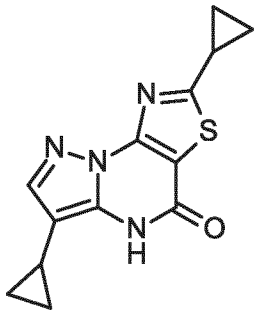
tert-butyl 5-{bis[2-chloro-6-(trifluoromethyl)pyridine-3-carbonyl]amino}-4-(trifluoromethyl)-1H-pyrazole-1-carboxylate (365 mg, 548 µmol; intermediate 15-1) was dissolved in 4 N HCl in dioxane (10 ml) and stirred for 16 h at room temperature. After concentration in vacuo, the residue was dissolved in trifluoroacetic acid (7.0 ml) and heated at 130°C for 3 h. The reaction mixture was evaporated and the crude material was purified by Biotage Isolera™ chromatography (SNAP KP-Sil – 10 g, eluting with hexane-ethyl acetate, 11:3 to 0:1) to afford 54 mg (26% yield, 87% purity) of the title compound.

^{1}H NMR (400 MHz, DMSO-d6) δ [ppm]: 8.10 (d, 1H), 8.29 (s, 1H), 8.81 (d, 1H), 13.08 (br s, 1H).

LC-MS (Method A): Rt = 0.96 min; MS (ESIpos): m/z = 323 $[M+H]^+$

Intermediate 26

2,6-dicyclopropylpyrazolo[1,5-a][1,3]thiazolo[5,4-e]pyrimidin-4(5H)-one

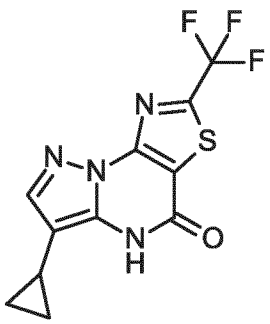


A mixutre of 4-bromo-2-cyclopropyl-N-(4-cyclopropyl-1H-pyrazol-5-yl)-1,3-thiazole-5-carboxamide (600 mg, 1.70 mmol; intermediate 20), 1,1'-bis(diphenylphosphino)ferrocenepalladium(II) chloride (124 mg, 0.17 mmol), (9,9-dimethyl-9H-xanthene-4,5-diyl)bis(diphenylphosphine) (197 mg, 0.34 mmol) and cesium carbonate (1.11 g, 3.40 mmol) in bis(2-methoxy ethyl)ether (2.0 ml) was stirred at 130 °C for 16 hours under nitrogen protection. The reaction was concentrated to give a residue. The residue was purified by reversed phase column chromatography (Instrument: Agela HP1000; Column: Welch Ultimate XB_C18 57*235mm 20-40 µm; eluent A: water (0.1% trifluoroacetic acid), eluent B: acetonitrile; gradient B%: 5%-35%, 9 min; 35%,6 min; flow 60 ml/min; temperature: room temperature; Detector: UV 220/254 nm) to give 2,6-dicyclopropylpyrazolo[1,5-a][1,3]thiazolo[5,4-e]pyrimidin-4(5H)-one (20.0 mg, 4% yield) as a yellow solid.

LC-MS (Method C): Rt = 0.774 min; MS (ESIpos): m/z = 273.0 [M+H]+.

Intermediate 27

6-cyclopropyl-2-(trifluoromethyl)pyrazolo[1,5-a][1,3]thiazolo[5,4-e]pyrimidin-4(5H)-one



tert-butyl 3-{[4-bromo-2-(trifluoromethyl)-1,3-thiazole-5-carbonyl]amino}-4-cyclopropyl-1H-pyrazole-1-carboxylate (560 mg, 85 % purity, 989 µmol; intermediate 14-3), potassium carbonate (273 mg, 1.98 mmol; CAS-RN:[584-08-7]), tris(dibenzylideneaceonte)dipalladium (0) (272 mg, 297 µmol), and 4,5-Bis-(diphenylphosphino)-9,9-dimethyl xanthene (258 mg, 445 µmol; CAS-RN:[161265-03-8]) were dissolved in toluene (6.0 ml) and heated for 3 h at 140°C and 16 h at 120°C. The reaction mixture was acidified to pH 4 with 5% aqueous acetic acid solution and the phases were separated. The organic layer was washed with water and concentrated in vacuo. The residue was dissolved in ethyl acetate and precipitated by the

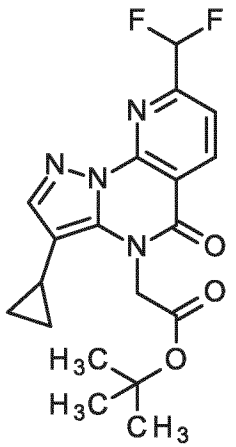
addition of hexane. The precipitate obtained was collected by filtration, and dried to afford 438 mg (99% yield, 67% purity) of the title compound.

^{1}H NMR (400 MHz, DMSO-d6) δ [ppm]: 0.58-0.64 (m, 2H), 0.84-0.91 (m, 2H), 1.91 (tt, 1H), 7.66 (s, 1H), 12.89 (br s, 1H).

LC-MS (Method A): R_t = 0.99 min; MS (ESIpos): m/z = 301 $[M+H]^+$

Intermediate 28

tert-butyl [3-cyclopropyl-8-(difluoromethyl)-5-oxopyrazolo[1,5-a]pyrido[3,2-e]pyrimidin-4(5H)-yl]acetate

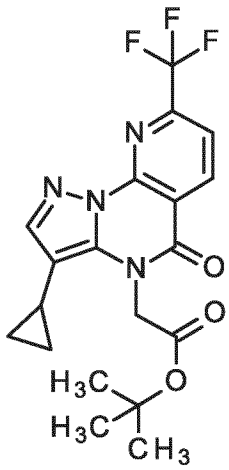
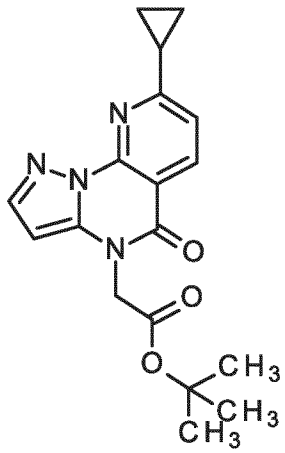


To a solution of 2-chloro-N-(4-cyclopropyl-1H-pyrazol-5-yl)-6-(difluoromethyl)pyridine-3-carboxamide hydrogen chloride (1/1) (120 mg, 344 µmol; intermediate 18) in dimethyl sulfoxide (1.8 ml) was added potassium carbonate (190 mg, 1.37 mmol; CAS-RN:[584-08-7]). The suspension was heated at 110°C for 1,5 h. After this time, the reaction mixture was cooled to room temperature and tert-butyl bromoacetate (66 µl, 450 µmol; CAS-RN:[5292-43-3]) was added. The mixture was stirred for further 1,5 h at room temperature. Then the mixture was diluted with ethyl acetate (30 ml) and the organic phase was washed with water (2 x 15 ml). The organic phase was dried with a water repellant filter and concentrated. The crude material was purified by Biotage Isolera™ chromatography (SNAP KP-Sil – 10 g, eluting with hexane-ethyl acetate, 1:0 to 3:2) to afford 69.0 mg (51% yield, 99% purity) of the title compound as an off white solid.

^{1}H NMR (400 MHz, CHLOROFORM-d) δ [ppm]: 0.71-0.77 (m, 2H), 0.94-1.01 (m, 2H), 1.49 (s, 9H), 1.62-1.77 (m, 1H), 5.21 (s, 2H), 6.81 (t, 1H), 7.67 (s, 1H), 7.76 (d, 1H), 8.78 (d, 1H)

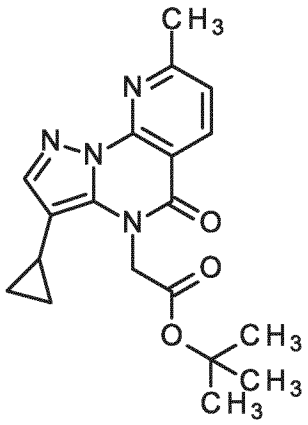
LC-MS (Method A): R_t = 1.24 min; MS (ESIpos): m/z = 392 $[M+H]^+$

In analogy to the procedure described for Intermediate 28, the following Intermediates were prepared from the the appropriate acylated aminopyrazole as starting materials.

Inter-mediate	Structure IUPAC-Name	Analytical Data	Starting Materials Yield
28 1	 **tert-butyl [3-cyclopropyl-5-oxo-8-(trifluoromethyl)pyrazolo[1,5-a]pyrido[3,2-e]pyrimidin-4(5H)-yl]acetate**	^{1}H NMR (400 MHz, CHLOROFORM-d) δ [ppm]: 0.71-0.76 (m, 2H), 0.94-1.00 (m, 2H), 1.49 (s, 9H), 1.64-1.74 (m, 1H), 5.21 (s, 2H), 7.69 (s, 1H), 7.76 (d, 1H), 8.79-8.82 (m, 1H). LC-MS (Method A): R_t = 1.28 min; MS (ESIneg): m/z = 407 $[M-H]^-$	Intermediate 16 201 mg (57% yield, 98% purity)
28 2	 **tert-butyl (8-cyclopropyl-5-oxopyrazolo[1,5-a]pyrido[3,2-e]pyrimidin-4(5H)-yl)acetate**	^{1}H NMR (400 MHz, CHLOROFORM-d) δ [ppm]: 1.18-1.28 (m, 2H), 1.32-1.39 (m, 2H), 1.50 (s, 9H), 2.32 (tt, 1H), 4.74 (s, 2H), 5.91 (d, 1H), 7.25 (d, 1H), 7.89 (d, 1H), 8.49 (d, 1H). LC-MS (Method A): R_t = 1.10 min; MS (ESIpos): m/z = 341 $[M+H]^+$	Intermediate 19 12.4 g (77% yield, 95% purity)

Intermediate 29

tert-butyl (3-cyclopropyl-8-methyl-5-oxopyrazolo[1,5-a]pyrido[3,2-e]pyrimidin-4(5H)-yl)acetate

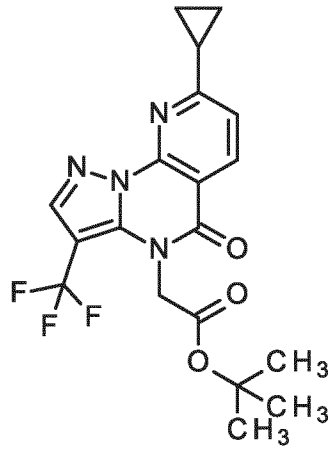
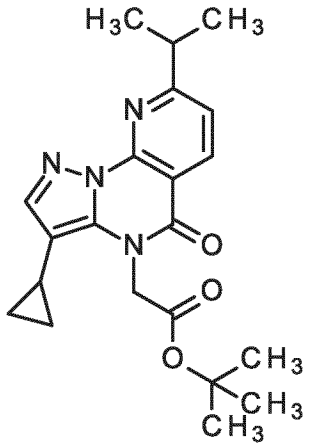


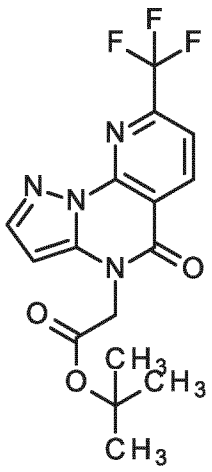
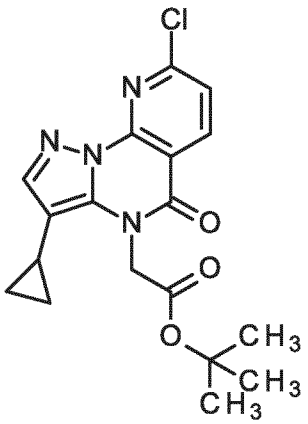
tert-Butyl 5-[(2-chloro-6-methylpyridine-3-carbonyl)amino]-4-cyclopropyl-1H-pyrazole-1-carboxylate (150 mg, 398 µmol; intermediate 16-1) was dissolved in dry *N*-methyl-2-pyrrolidone (1.6 ml). To the stirred solution was added potassium carbonate (220 mg, 1.59 mmol; CAS-RN:[584-08-7]) and the reaction mixture was heated at 130°C for 1 h. After this time the mixture was allowed to cool to room temperature then tert-butyl bromoacetate (88 µl, 600 µmol; CAS-RN:[5292-43-3]) was added and stirred for further 1 h at room temperature. The reaction mixture was quenched with water, and extracted with ethyl acetate. The combined organic layers were washed twice with brine, dried with a water-repellant filter and concentrated to dryness. The residue was taken up in dichloromethane, adsorbed on isolute and purified by Biotage Isolera™ chromatography (SNAP KP-Sil – 10 g, eluting with hexane-ethyl acetate, 1:0 to 1:1) to afford 59.0 mg (41% yield, 98% purity) of the title compound as a white foam.

^{1}H NMR (400 MHz, CHLOROFORM-d) δ [ppm]: 0.68-0.75 (m, 2H), 0.91-0.98 (m, 2H), 1.48 (s, 9H), 1.69 (tt, 1H), 2.76 (s, 3H), 5.20 (s, 2H), 7.26 (d, 1H), 7.62 (s, 1H), 8.48 (d, 1H)

LC-MS (Method B): R_t = 1.19 min; MS (ESIpos): m/z = 356 $[M+H]^+$

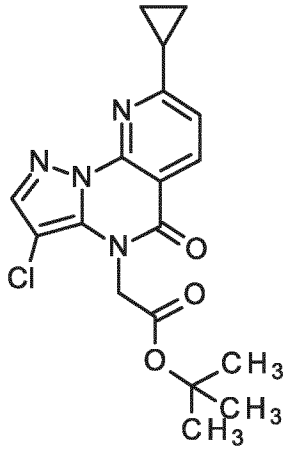
In analogy to the procedure described for Intermediate 29, the following Intermediates were prepared from the the appropriate acylated aminopyrazoles as starting materials.

Inter-mediate	Structure IUPAC-Name	Analytical Data	Starting Materials Yield
29 1	 **tert-butyl [8-cyclopropyl-5-oxo-3-(trifluoromethyl)pyrazolo[1,5-a]pyrido[3,2-e]pyrimidin-4(5H)-yl]acetate**	^{1}H NMR (400 MHz, CHLOROFORM-d) δ [ppm]: 1.23-1.25 (m, 2H), 1.31-1.34 (m, 2H), 1.47 (s, 9H), 2.27-2.32 (m, 1H), 4.89 (s, 2H), 7.28 (d, 1H), 8.05 (s, 1H), 8.47 (d, 1H). LC-MS (Method A): R_t = 1.40 min; MS (ESIpos): m/z = 410 $[M+H]^+$	Intermediate 14-2 58.0 mg (17% yield)
29 2	 **tert-butyl [3-cyclopropyl-5-oxo-8-(propan-2-yl)pyrazolo[1,5-a]pyrido[3,2-e]pyrimidin-4(5H)-yl]acetate**	^{1}H NMR (400 MHz, CHLOROFORM-d) δ [ppm]: 0.69-0.75 (m, 2H), 0.91-0.97 (m, 2H), 1.38 (d, 6H), 1.48 (s, 9H), 1.66-1.74 (m, 1H), 3.33 (spt, 1H), 5.20 (s, 2H), 7.31 (d, 1H), 7.64 (s, 1H), 8.53 (d, 1H). LC-MS (Method B): R_t = 1.34 min; MS (ESIpos): m/z = 384 $[M+H]^+$	Intermediate 16-2 71.0 mg (38% yield, 98% purity)

29 3	 **tert-butyl [5-oxo-8-(trifluoromethyl)pyrazolo[1,5-a]pyrido[3,2-e]pyrimidin-4(5H)-yl]acetate**	^{1}H NMR (400 MHz, CHLOROFORM-d) δ [ppm]: 1.48 (s, 9H), 4.73 (s, 2H), 5.94 (d, 1H), 7.81 (d, 1H), 7.91 (d, 1H), 8.85 (d, 1H). LC-MS (Method B): R_t = 1.03 min; MS (ESIpos): m/z = 370 $[M+H]^+$	Intermediate 16-3 412 mg (86% yield, 98% purity)
29 4	 **tert-butyl (8-chloro-3-cyclopropyl-5-oxopyrazolo[1,5-a]pyrido[3,2-e]pyrimidin-4(5H)-yl)acetate**	^{1}H NMR (500 MHz, CHLOROFORM-d) δ [ppm]: 0.70-0.76 (m, 2H), 0.94-0.99 (m, 2H), 1.49 (s, 9H), 1.68 (tt, 1H), 5.19 (s, 2H), 7.40 (d, 1H), 7.65 (s, 1H), 8.53 (d, 1H). LC-MS (Method B): Rt = 1.25 min; MS (ESIpos): m/z = 375 $[M+H]^+$	Intermediate 16-6 428 mg (52% yield, 96% purity)

Intermediate 30

tert-butyl (3-chloro-8-cyclopropyl-5-oxopyrazolo[1,5-a]pyrido[3,2-e]pyrimidin-4(5H)-yl)acetate

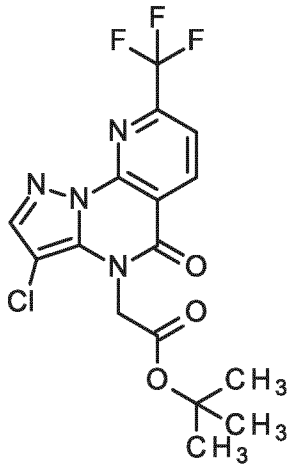


To a solution of tert-butyl (8-cyclopropyl-5-oxopyrazolo[1,5-a]pyrido[3,2-e]pyrimidin-4(5H)-yl)acetate (12.5 g, 36.7 mmol; intermediate 28-2) in ethyl acetate (400 ml) was added 1-chloropyrrolidine-2,5-dione (5.39 g, 40.4 mmol; CAS-RN:[128-09-6]) and sulfuric acid (590 µl, 11 mmol; CAS-RN:[7664-93-9]). The reaction mixture was stirred at room temperature for 2 h. The reaction was neutralized with saturated sodium bicarbonate solution (100 ml) and extracted with ethyl acetate. The combined organic phases were washed with brine, dried with a water repellant filter and concentrated. The crude product was suspended in methyl tert-butyl ether (200 ml) and stirred intensively at 0°C for 1 h. The solid was collected by vacuum filtration washed with hexane (2x 30 ml) and dried in vacuo to afford 12.4 g (86% yield, 95% purity) of the title compound as a pale yellow solid.

^{1}H NMR (400 MHz, CHLOROFORM-d) δ [ppm]: 1.18-1.24 (m, 2H), 1.26-1.32 (m, 2H), 1.48 (s, 9H), 2.27 (tt, 1H), 5.11 (s, 2H), 7.21 (d, 1H), 7.78 (s, 1H), 8.43 (d, 1H)

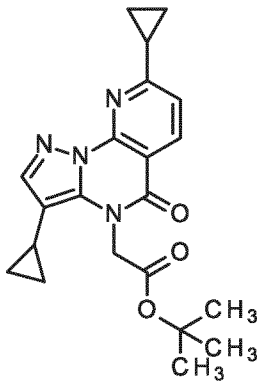
LC-MS (Method A): R_t = 1.26 min; MS (ESIpos): m/z = 375 $[M+H]^+$

In analogy to the procedure described for Intermediate 30, the following Intermediate was prepared from the the appropriate tricyclic core as starting material.

Inter-mediate	Structure IUPAC-Name	Analytical Data	Starting Materials Yield
30 1	 **tert-butyl [3-chloro-5-oxo-8-(trifluoromethyl)pyrazolo[1,5-a]pyrido[3,2-e]pyrimidin-4(5H)-yl]acetate**	^{1}H NMR (400 MHz, CHLOROFORM-d) δ [ppm]: 1.50 (s, 9H), 5.14 (s, 2H), 7.82 (d, 1H), 7.85 (s, 1H), 8.84 (d, 1H). LC-MS (Method B): R_t = 1.32 min; MS (ESIpos): m/z = 403 $[M+H]^+$	Intermediate 29-3 357 mg (52% yield, 96% purity)

Intermediate 31

tert-butyl (3,8-dicyclopropyl-5-oxopyrazolo[1,5-a]pyrido[3,2-e]pyrimidin-4(5H)-yl)acetate



tert-Butyl (8-chloro-3-cyclopropyl-5-oxopyrazolo[1,5-a]pyrido[3,2-e]pyrimidin-4(5H)-yl)acetate (420 mg, 1.12 mmol; intermediate 29-4), potassium phosphate (832 mg, 3.92 mmol; CAS-RN:[7778-53-2]), palladium acetate (12.6 mg, 56.0 µmol; CAS-RN:[3375-31-3]) and tricyclohexylphosphine (47.1 mg, 168 µmol; CAS-RN:[2622-14-2]) were suspended in toluene (9.0 ml) / water (900 µl). The mixture was degassed with nitrogen for 10 minutes. Then cyclopropylboronic acid (116 mg, 1.34 mmol; CAS-RN:[411235-57-9]) was added. The reaction mixture was heated at 115°C for 16 h. The mixture was allowed to cool to room temperature then it was filtered through celite. The filtrate was partitioned between water and ethyl acetate

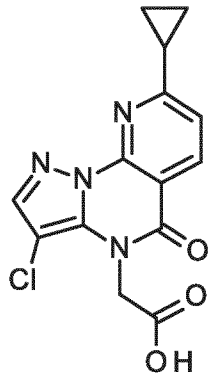
and the aqueous layer was extracted two times with ethyl acetate. The combined organics were washed with brine, dried with a water-repellant filter and concentrated. The obtained residue was adsorbed on isolute and purified by Biotage Isolera™ chromatography (SNAP KP-Sil – 25 g, eluting with hexane-ethyl acetate, 19:1 to 3:17) to afford 225 mg (42% yield, 79% purity) of the title compound as a white solid.

^{1}H NMR (400 MHz, CHLOROFORM-d) δ [ppm]: 0.67-0.74 (m, 2H), 0.90-0.97 (m, 2H), 1.14-1.22 (m, 2H), 1.25-1.31 (m, 2H), 1.47-1.49 (m, 9H), 1.69 (tt, 1H), 2.27 (tt, 1H), 5.16-5.21 (m, 2H), 7.15 (d, 1H), 7.62 (s, 1H), 8.42 (d, 1H)

LC-MS (Method B): R_t = 1.29 min; MS (ESIpos): m/z = 392 $[M+H]^+$

Intermediate 32

(3-chloro-8-cyclopropyl-5-oxopyrazolo[1,5-a]pyrido[3,2-e]pyrimidin-4(5H)-yl)acetic acid

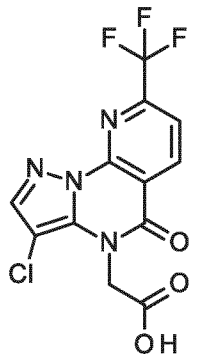
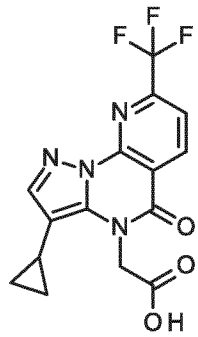


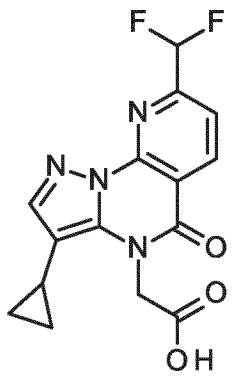
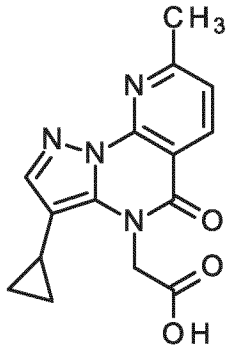
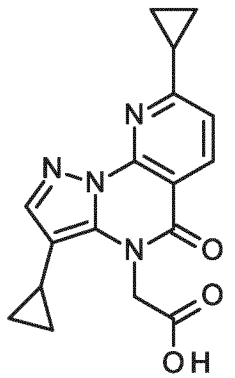
To a solution of tert-butyl (3-chloro-8-cyclopropyl-5-oxopyrazolo[1,5-a]pyrido[3,2-e]pyrimidin-4(5H)-yl)acetate (200 mg, 534 µmol, intermediate 30) in dichloromethane (2.0 ml) was added trifluoroacetic acid (750 µl, 9.7 mmol; CAS-RN:[76-05-1]). The reaction mixture was stirred for 16 h at room temperature. The mixture was acidified with concentrated hydrochloric acid to pH 3 and the solvent was evaporated under reduced pressure. The obtained solid was triturated with water, collected by filtration and dried to afford 166 mg (96% yield, 98% purity) of the title compound.

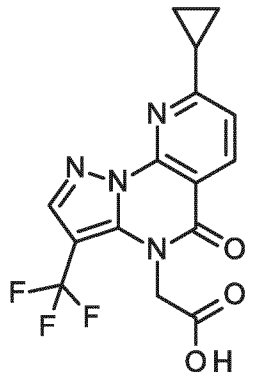
^{1}H NMR (400 MHz, DMSO-d6) δ [ppm]: 1.12-1.20 (m, 4H), 2.29-2.41 (m, 1H), 5.04 (s, 2H), 7.56 (d, 1H), 8.04 (s, 1H), 8.40 (d, 1H), 13.46 (br s, 1H).

LC-MS (Method A): Rt = 0.86 min; MS (ESIpos): m/z = 319 $[M+H]^+$.

In analogy to the procedure described for Intermediate 32, the following Intermediates were prepared from the the appropriate esters as starting materials.

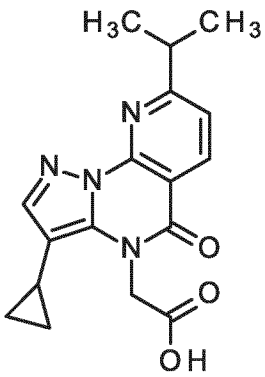
Inter-mediate	Structure IUPAC-Name	Analytical Data	Starting Materials Yield
32 1	 **[3-chloro-5-oxo-8-(trifluoromethyl)pyrazolo[1,5-a]pyrido[3,2-e]pyrimidin-4(5H)-yl]acetic acid**	^{1}H NMR (400 MHz, DMSO-d6) δ [ppm]: 5.08 (s, 2H), 8.10 (d, 1H), 8.17 (s, 1H), 8.83-8.89 (m, 1H), 13.57 (br s, 1H). LC-MS (Method A): R_t = 0.89 min; MS (ESIpos): m/z = 347 $[M+H]^+$	Intermediate 30-1 298 mg (94% yield, 95% purity)
32 2	 **[3-cyclopropyl-5-oxo-8-(trifluoromethyl)pyrazolo[1,5-a]pyrido[3,2-e]pyrimidin-4(5H)-yl]acetic acid**	^{1}H NMR (400 MHz, DMSO-d6) δ [ppm]: 0.64-0.74 (m, 2H), 0.85-0.93 (m, 2H), 1.72-1.86 (m, 1H), 5.17 (s, 2H), 7.82 (s, 1H), 8.03 (d, 1H), 8.82 (d, 1H), 13.49 (br s, 1H). LC-MS (Method A): R_t = 0.91 min; MS (ESIpos): m/z = 353 $[M+H]^+$	Intermediate 28-1 9.00 mg (80% yield, 99% purity)

32 3	 **[3-cyclopropyl-8-(difluoromethyl)-5-oxopyrazolo[1,5-a]pyrido[3,2-e]pyrimidin-4(5H)-yl]acetic acid**	^{1}H NMR (400 MHz, DMSO-d6) δ [ppm]: 0.66-0.71 (m, 2H), 0.85-0.91 (m, 2H), 1.80 (tt, 1H), 3.38 (br s, 1H), 5.17 (s, 2H), 7.16 (t, 1H), 7.79 (s, 1H), 7.84 (d, 1H), 8.75 (d, 1H), 13.46 (br s, 1H). LC-MS (Method A): R_t = 0.82 min; MS (ESIpos): m/z = 335 $[M+H]^+$	Intermediate 28 53.0 mg (91% yield, 99% purity)
32 4	 **(3-cyclopropyl-8-methyl-5-oxopyrazolo[1,5-a]pyrido[3,2-e]pyrimidin-4(5H)-yl)acetic acid**	^{1}H NMR (400 MHz, DMSO-d6) δ [ppm]: 0.64-0.69 (m, 2H), 0.82-0.89 (m, 2H), 1.78 (tt, 1H), 2.65 (s, 3H), 5.15 (s, 2H), 7.46 (d, 1H), 7.72 (s, 1H), 8.43 (d, 1H), 13.39 (br d, 1H). LC-MS (Method A): R_t = 0.74 min; MS (ESIpos): m/z = 299 $[M+H]^+$	Intermediate 29 44.0 mg (91% yield, 98% purity)
32 5	 **(3,8-dicyclopropyl-5-oxopyrazolo[1,5-a]pyrido[3,2-e]pyrimidin-4(5H)-yl)acetic acid**	^{1}H NMR (400 MHz, DMSO-d6) δ [ppm]: 0.62-0.68 (m, 2H), 0.84-0.90 (m, 2H), 1.11-1.18 (m, 4H), 1.73-1.81 (m, 1H), 2.30-2.36 (m, 1H), 5.14 (s, 2H), 7.49 (d, 1H), 7.69 (s, 1H), 8.37 (d, 1H), 13.37 (br s, 1H). LC-MS (Method A): R_t = 1.00 min; MS (ESIpos): m/z = 326 $[M+H]^+$	Intermediate 31 15.0 mg (60% yield, 79% purity)

32 6	 **[8-cyclopropyl-5-oxo-3-(trifluoromethyl)pyrazolo[1,5-a]pyrido[3,2-e]pyrimidin-4(5H)-yl]acetic acid**	^{1}H NMR (400 MHz, DMSO-d6) δ [ppm]: 1.20-1.27 (m, 4H), 2.42-2.47 (m, 1H), 5.12 (s, 2H), 7.73 (d, 1H), 8.44 (s, 1H), 8.50 (d, 1H), 13.24 (br s, 1H). LC-MS (Method A): R_t = 1.06 min; MS (ESIpos): m/z = 353 $[M+H]^+$	Intermediate 29-1 41.0 mg (95% yield, 95% purity)

Intermediate 33

[3-cyclopropyl-5-oxo-8-(propan-2-yl)pyrazolo[1,5-a]pyrido[3,2-e]pyrimidin-4(5H)-yl]acetic acid



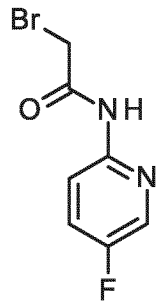
To a solution of tert-butyl [3-cyclopropyl-5-oxo-8-(propan-2-yl)pyrazolo[1,5-a]pyrido[3,2-e]pyrimidin-4(5H)-yl]acetate (65.0 mg, 170 µmol; intermediate 29-2) in dichloromethane (700 µl) was added trifluoroacetic acid (420 µl, 4.0 M, 1.7 mmol; CAS-RN:[7647-01-0]). The reaction mixture was stirred at room temperature for 16 h. The mixture was concentrated to dryness and the residue was triturated with ethyl acetate. The solid thus obtained was collected by vacuum filtration, washed with hexane and dried to afford 52.0 mg (91% yield, 97% purity) of the title compound as a white solid.

^{1}H NMR (400 MHz, DMSO-d6) δ [ppm]: 0.60-0.69 (m, 2H), 0.83-0.91 (m, 2H), 1.69-1.83 (m, 1H), 4.05 (s, 3H), 5.14 (s, 2H), 6.96 (d, 1H), 7.73 (s, 1H), 8.39 (d, 1H), 13.24 (br s, 1H)

LC-MS (Method A): R_t = 0.93 min; MS (ESIpos): m/z = 327 $[M+H]^+$

Intermediate 34

2-bromo-N-(5-fluoropyridin-2-yl)acetamide



To an ice-cooled solution of 5-fluoropyridin-2-amine (10.0 g, 89.2 mmol) and *N*,*N*-diisopropylethylamine (16 ml, 89 mmol; CAS-RN:[7087-68-5]) in dichloromethane (150 ml, 2.3 mol; CAS-RN:[75-09-2]) was added bromoacetyl bromide (7.8 ml, 89 mmol). The reaction mixture was stirred at room temperature for 16 h. The solution was cooled with an ice-bath and *N*,*N*-diisopropylethylamine (4 ml, 22 mmol; CAS-RN:[7087-68-5]) and bromoacetyl bromide (1.95 ml, 22 mmol) were added. After further 2 h at room temperature aqueous saturated sodium bicarbonate solution was added. The aqueous phase was extracted with dichloromethane. The combined organic phases were washed with brine, filtered over a water repellant filter and concentrated. The formed solid was triturated with hexane (150 ml) and the brown solid was collected by filtration. The crude product was re-dissolved in dichloromethane and purified by Biotage Isolera™ chromatography (SNAP KP-Sil – 340 g, eluting with dichloromethane-ethanol, 1:0 to 19:1). The product fractions were pooled and the residue was dissolved in ethyl acetate (30 ml) and hexane (250 ml) was added. The formed precipitate was collected by vacuum filtration, washed with hexane and dried in vacuum to afford 15.36 g (74% yield, 98% purity) of the title compound as a light brown solid.

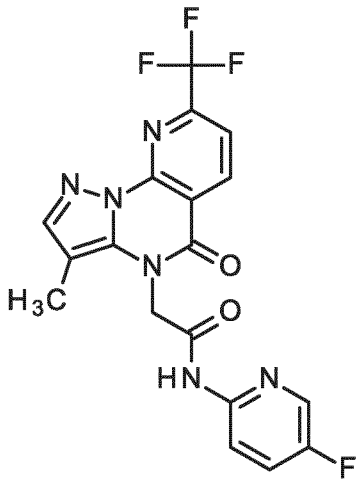
^{1}H NMR (400 MHz, CHLOROFORM-d) δ [ppm]: 4.02 (s, 2H), 7.47 (ddd, J=9.06, 7.67, 3.04 Hz, 1H), 8.14-8.24 (m, 2H), 8.74 (br s, 1H)

LC-MS (Method B): R_t = 0.79 min; MS (ESIneg): m/z = 231 $[M-H]^-$

EXPERIMENTAL SECTION - EXAMPLES

Example 1

N-(5-fluoropyridin-2-yl)-2-[3-methyl-5-oxo-8-(trifluoromethyl)pyrazolo[1,5-a]pyrido[3,2-e]pyrimidin-4(5H)-yl]acetamide



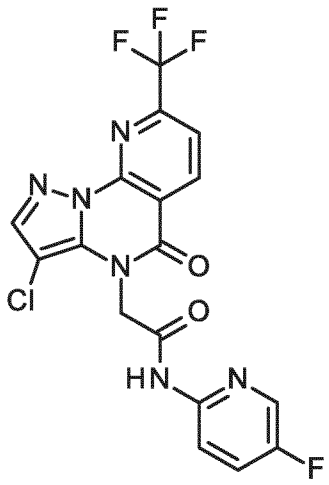
This reaction was performed as two parallel batches: To a mixture of 3-methyl-8-(trifluoromethyl)pyrazolo[1,5-a]pyrido[3,2-e]pyrimidin-5(4H)-one (90 g, 335.58 mmol; intermediate 24) and caesium carbonate (216.00 g, 662.94 mmol) in *N*-methyl-2-pyrrolidone (1350 mL) was added 2-bromo-N-(5-fluoro-2-pyridyl)acetamide (89.9 g, 385.77 mmol; intermediate 34) in portions at 0°C. The mixture was stirred at 0 - 5°C for 6 h. The reaction mixture was poured into water (each batch 12 L) respectively. 300 g crude product was collected by filtration. This crude product was purified with other batches together (30 g rare material). The combined crude product was triturated with ethanol (1.5 L) at rt, dichloromethane (1.5 L) at rt, ethanol (1.5 L) at reflux, dichloromethane (1 L) at rt and dichloromethane (2.5 L) at rt to give 197 g off-white solid (89% purity). This product was suspended in dimethyl sulfoxide (1 L) at 60 °C. Most of the solid was dissolved. The mixture was filtered while hot. The filtrate was diluted with ethanol (3.8 L). The resulting solution was placed at 0°C for 48 h. A white solid was formed. The mixture was filtered, washed with ethanol (200 mL x 2) and dried in high vacuum to give 125 g white solid. The white solid was suspended in ethanol (500 mL) and stirred at reflux (oil bath temparture: 80°C) for 16 h, then cooled to 25 °C (rt). The mixture was filtered. The filter cake was washed with ethanol (100 mL x 2) and dried in high vacuum to give N-(5-fluoropyridin-2-yl)-2-(3-methyl-5-oxo-8-(trifluoromethyl)pyrazolo[1,5-a]pyrido[3,2-e]pyrimidin-4(5H)-yl)acetamide (123 g) as a white solid.

^{1}H NMR (400 MHz, DMSO-d6) δ [ppm]: 2.19 (s, 3H), 5.11 (s, 2H), 7.73-7.80 (m, 1H), 7.83 (s, 1H), 8.02 (d, 1H), 8.04-8.07 (m, 1H), 8.37 (d, 1H), 8.77-8.85 (m, 1H), 11.13 (s, 1H).

LC-MS (Method A): R_t = 1.01 min; MS (ESIpos): m/z = 421 $[M+H]^+$

Example 2

2-[3-chloro-5-oxo-8-(trifluoromethyl)pyrazolo[1,5-a]pyrido[3,2-e]pyrimidin-4(5H)-yl]-N-(5-fluoropyridin-2-yl)acetamide

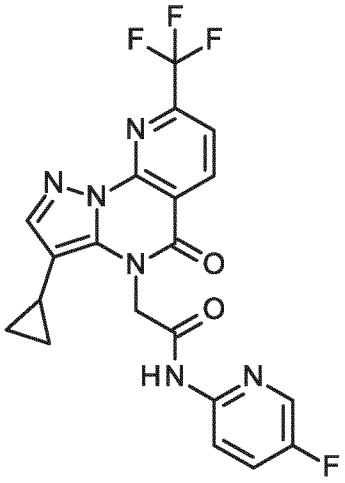
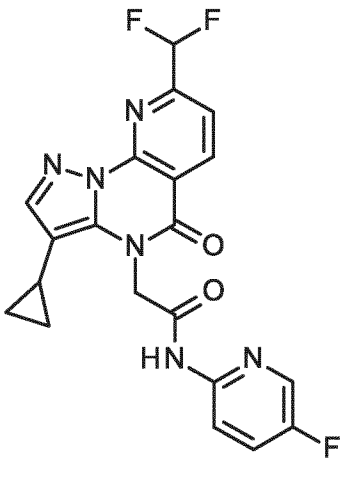


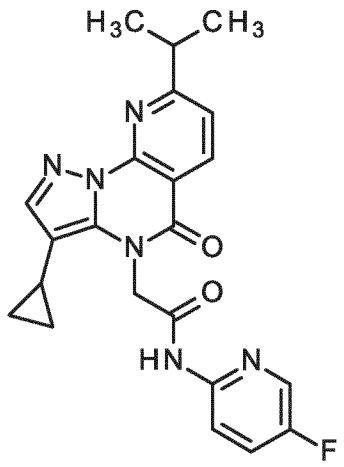
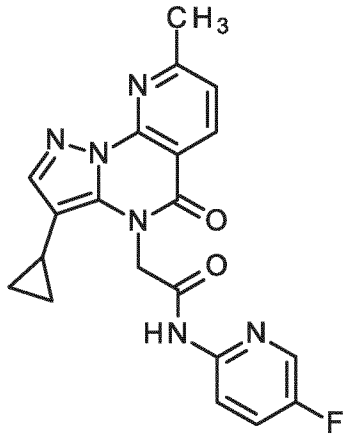
To a solution of [3-chloro-5-oxo-8-(trifluoromethyl)pyrazolo[1,5-a]pyrido[3,2-e]pyrimidin-4(5H)-yl]acetic acid (300 mg, 865 µmol; intermediate 32-1) and *N*,*N*-diisopropylethylamine (450 µl, 2.6 mmol; CAS-RN:[7087-68-5]) in dichloromethane (7.5 ml) was added T3P (50% in ethyl acetate) (1.0 ml, 50 % purity, 1.7 mmol; CAS-RN:[68957-94-8]). The mixture was stirred for 10 minutes at room temperature, then 5-fluoropyridin-2-amine (146 mg, 1.30 mmol; CAS-RN:[21717-96-4]) was added. The reaction mixture was stirred for 2 hours at room temperature. The solvent was removed under reduced pressure and the residue was taken up in 2 ml acetonitrile and added to 10 ml water. The obtained precipitate was collected by vacuum filtration. The solid was dried and suspended in 15 ml methyl tert-butyl ether. The suspension was stirred vigorously for 30 minutes and the solid was collected by vacuum filtration, washed with hexane and dried. The obtained solid was purified by Biotage Isolera™ chromatography (SNAP KP-Sil – 10 g, eluting with hexane-ethyl acetate, 19:1 to 13:9) to afford 110 mg (29% yield, 99% purity) of the title compound as a white solid.

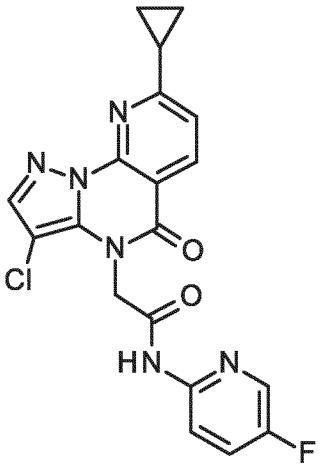
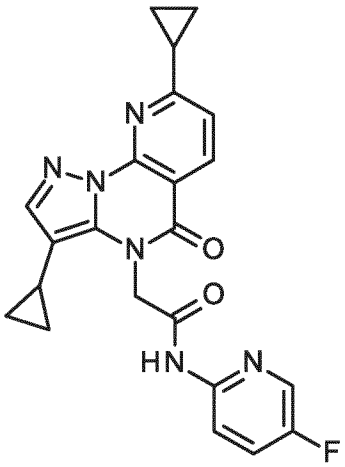
1H NMR (400 MHz, DMSO-d6) δ [ppm]: 5.23 (s, 2H), 7.72-7.81 (m, 1H), 8.05 (br dd, 1H), 8.11 (d, 1H), 8.16 (s, 1H), 8.36 (d, 1H), 8.86 (d, 1H), 11.13 (s, 1H).

LC-MS (Method B): R_t = 1.09 min; MS (ESIpos): m/z = 441 $[M+H]^+$

In analogy to the procedure described for Example 2 the following Examples were prepared from the corresponding tricyclic core Intermediates and 5-fluoropyridin-2-amine.

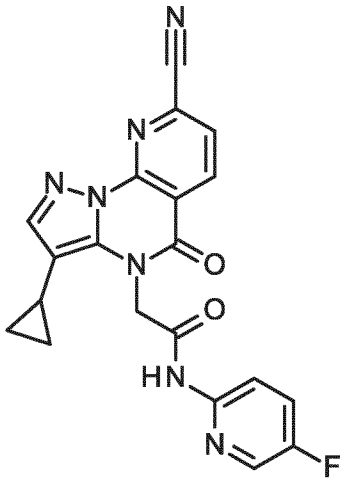
Example	Structure IUPAC-Name	Analytical Data	Starting Materials Yield
3	 **2-[3-cyclopropyl-5-oxo-8-(trifluoromethyl)pyrazolo[1,5-a]pyrido[3,2-e]pyrimidin-4(5H)-yl]-N-(5-fluoropyridin-2-yl)acetamide**	^{1}H NMR (400 MHz, DMSO-d6) δ 0.62-0.68 (m, 2H), 0.79-0.86 (m, 2H), 1.72-1.80 (m, 1H), 5.33 (s, 2H), 7.76 (td, 1H), 7.81 (s, 1H), 7.98-8.11 (m, 2H), 8.36 (d, 1H), 8.81 (d, 1H), 11.13 (s, 1H). LC-MS (Method B): R_t = 1.13 min; MS (ESIpos): m/z = 447 $[M+H]^+$	Intermediate 32-2 34.3 mg (33% yield, 97% purity)
4	 **2-[3-cyclopropyl-8-(difluoromethyl)-5-oxopyrazolo[1,5-a]pyrido[3,2-e]pyrimidin-4(5H)-yl]-N-(5-fluoropyridin-2-yl)acetamide**	^{1}H NMR (400 MHz, DMSO-d6) δ [ppm]: 0.61-0.69 (m, 2H), 0.78-0.87 (m, 2H), 1.68-1.80 (m, 1H), 5.34 (s, 2H), 6.94-7.38 (m, 1H), 7.73-7.78 (m, 1H), 7.78 (s, 1H), 7.84 (d, 1H), 8.05 (br dd, 1H), 8.36 (d, 1H), 8.75 (d, 1H), 11.14 (s, 1H). LC-MS (Method A): R_t = 1.04 min; MS (ESIneg): m/z = 427 $[M-H]^-$	Intermediate 32-3 48.9 mg (69% yield, 91% purity)

5	 **2-[3-cyclopropyl-5-oxo-8-(propan-2-yl)pyrazolo[1,5-a]pyrido[3,2-e]pyrimidin-4(5H)-yl]-N-(5-fluoropyridin-2-yl)acetamide**	^{1}H NMR (400 MHz, DMSO-d6) δ [ppm]: 0.59-0.65 (m, 2H), 0.78-0.84 (m, 2H), 1.32 (d, 6H), 1.68-1.77 (m, 1H), 3.20 (quin, 1H), 5.33 (s, 2H), 7.50 (d, 1H), 7.71 (s, 1H), 7.72-7.80 (m, 1H), 8.04 (br dd, 1H), 8.36 (d, 1H), 8.47 (d, 1H), 11.13 (s, 1H) LC-MS (Method B): R_t = 1.13 min; MS (ESIpos): m/z = 421 $[M+H]^+$	Intermediate 33 201 mg (58% yield, 99% purity)
6	 **2-(3-cyclopropyl-8-methyl-5-oxopyrazolo[1,5-a]pyrido[3,2-e]pyrimidin-4(5H)-yl)-N-(5-fluoropyridin-2-yl)acetamide**	^{1}H NMR (400 MHz, DMSO-d6) δ [ppm]: 0.61-0.66 (m, 2H), 0.77-0.84 (m, 2H), 1.73 (tt, 1H), 2.66 (s, 3H), 5.33 (s, 2H), 7.46 (d, 1H), 7.71 (s, 1H), 7.75 (td, 1H), 8.03 (br dd, 1H), 8.36 (d, 1H), 8.43 (d, 1H), 11.14 (s, 1H). LC-MS (Method B): R_t = 0.96 min; MS (ESIpos): m/z = 393 $[M+H]^+$	Intermediate 32-4 12.3 mg (23% yield, 99% purity)

7	 **2-(3-chloro-8-cyclopropyl-5-oxopyrazolo[1,5-a]pyrido[3,2-e]pyrimidin-4(5H)-yl)-N-(5-fluoropyridin-2-yl)acetamide**	^{1}H NMR (400 MHz, DMSO-d6) δ [ppm]: 1.13-1.22 (m, 4H), 2.33-2.41 (m, 1H), 5.21 (br s, 2H), 7.56 (d, 1H), 7.75 (td, 1H), 7.97-8.07 (m, 2H), 8.36 (d, 1H), 8.40 (d, 1H), 11.14 (s, 1H). LC-MS (Method B): Rt = 0.83 min; MS (ESIpos): m/z = 353 [M+H]$^+$	Intermediate 32 221 mg (80% yield, 94% purity)
8	 **2-(3,8-dicyclopropyl-5-oxopyrazolo[1,5-a]pyrido[3,2-e]pyrimidin-4(5H)-yl)-N-(5-fluoropyridin-2-yl)acetamide**	^{1}H NMR (400 MHz, DMSO-d6) δ [ppm]: 0.57-0.65 (m, 2H), 0.77-0.84 (m, 2H), 1.10-1.20 (m, 4H), 1.68-1.76 (m, 1H), 2.30-2.37 (m, 1H), 5.32 (s, 2H), 7.49 (d, 1H), 7.68 (s, 1H), 7.75 (td, 1H), 8.03 (br d, 1H), 8.34-8.38 (m, 2H), 11.12 (s, 1H). LC-MS (Method B): R_t = 1.09 min; MS (ESIpos): m/z = 419 [M+H]$^+$	Intermediate 32-5 33.0 mg (15% yield, 97% purity)

Example 9

2-(8-cyano-3-cyclopropyl-5-oxopyrazolo[1,5-a]pyrido[3,2-e]pyrimidin-4(5H)-yl)-N-(5-fluoropyridin-2-yl)acetamide

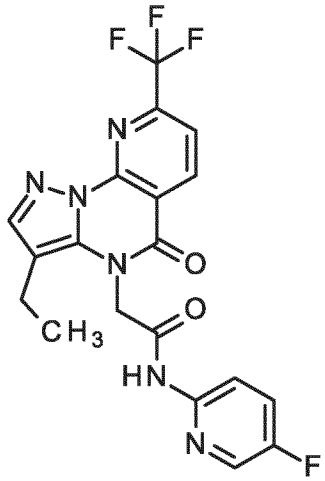
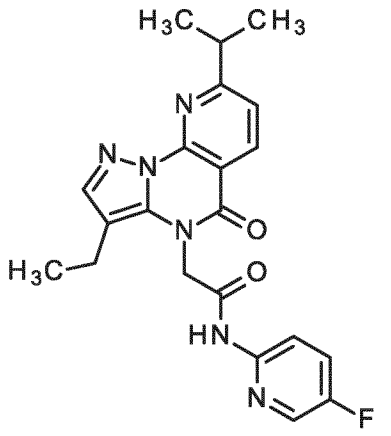


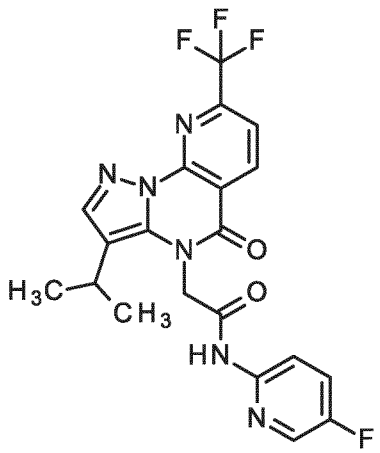
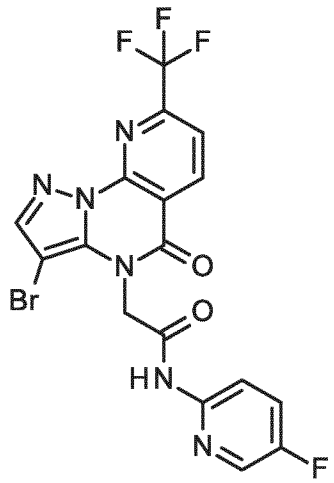
3-cyclopropyl-5-oxo-4,5-dihydropyrazolo[1,5-a]pyrido[3,2-e]pyrimidine-8-carbonitrile (50.0 mg, 199 µmol; intermediate 22) was dissolved in *N,N*-dimethylformamide (1.3 mL) and sodium carbonate (63.3 mg, 597 µmol) was added. After stirring for 10 minutes 2-bromo-N-(5-fluoropyridin-2-yl)acetamide (92.8 mg, 398 µmol; intermediate 34) was added and stirring was continued over night at room temperature. The reaction mixture was purified by preparative HPLC (Method 3). The product fractions were pooled and concentrated *in vacuo* to afford 35.2 mg (38% yield, 87% purity) of the title compound as a white solid and 3.3 mg (3% yield, 85% purity) of the O-alkylated byproduct.

^{1}H NMR (400 MHz, DMSO-d6) δ [ppm]: 0.62-0.68 (m, 2H), 0.79-0.86 (m, 2H), 1.71-1.79 (m, 1H), 5.32 (s, 2H), 7.76 (td, 1H), 7.83 (s, 1H), 8.04 (br dd, 1H), 8.16 (d, 1H), 8.36 (d, 1H), 8.75 (d, 1H), 11.13 (s, 1H).

LC-MS (Method A): R_t = 0.96 min; MS (ESIpos): m/z = 404 $[M+H]^+$

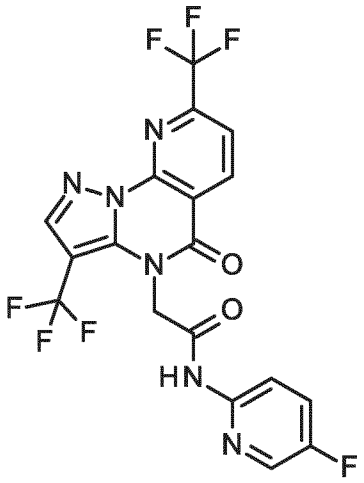
In analogy to the procedure described for Example 9 the following Examples were prepared from the corresponding tricyclic core Intermediates and 2-bromo-N-(5-fluoropyridin-2-yl)acetamide (intermediate 34).

Example	Structure IUPAC-Name	Analytical Data	Starting Materials Yield
10	 **2-[3-ethyl-5-oxo-8-(trifluoromethyl)pyrazolo[1,5-a]pyrido[3,2-e]pyrimidin-4(5H)-yl]-N-(5-fluoropyridin-2-yl)acetamide**	^{1}H NMR (400 MHz, DMSO-d6) δ [ppm]: 1.18 (t, 3H), 2.61 (q, 2H), 5.08 (s, 2H), 7.76 (td, 1H), 7.91 (s, 1H), 8.03 (d, 1H), 8.05-8.07 (m, 1H), 8.37 (d, 1H), 8.79-8.82 (m, 1H), 11.15 (s, 1H). LC-MS (Method A): R_t = 1.11 min; MS (ESIpos): m/z = 435 $[M+H]^+$	Intermediate 21 21.4 mg (14% yield, 90% purity)
11	 **2-[3-ethyl-5-oxo-8-(propan-2-yl)pyrazolo[1,5-a]pyrido[3,2-e]pyrimidin-4(5H)-yl]-N-(5-fluoropyridin-2-yl)acetamide**	^{1}H NMR (400 MHz, DMSO-d6) δ [ppm]: 1.17 (t, 3H), 1.32 (d, 6H), 2.59 (q, 2H), 3.20 (spt, 1H), 5.07 (s, 2H), 7.49 (d, 1H), 7.75 (td, 1H), 7.80 (s, 1H), 7.98-8.07 (m, 1H), 8.36 (d, 1H), 8.46 (d, 1H), 11.16 (s, 1H). LC-MS (Method A): R_t = 1.10 min; MS (ESIneg): m/z = 407 $[M-H]^-$	Intermediate 22-1 72.6 mg (54% yield, 98% purity)

12	 **N-(5-fluoropyridin-2-yl)-2-[5-oxo-3-(propan-2-yl)-8-(trifluoromethyl)pyrazolo[1,5-a]pyrido[3,2-e]pyrimidin-4(5H)-yl]acetamide**	^{1}H NMR (400 MHz, DMSO-d6) δ [ppm]: 1.21 (d, 6H), 3.03 (spt, 1H), 5.10 (s, 2H), 7.76 (td, 1H), 8.00 – 8.06 (m, 1 H), 8.02 (d, 1H), 8.05 (s, 1H), 8.37 (d, 1H), 8.80 (d, 1H), 11.13 (s, 1 H). LC-MS (Method A): R_t = 1.13 min; MS (ESIpos): m/z = 449 $[M+H]^+$	Intermediate 6.50 mg (16% yield, 91% purity)
13	 **2-[3-bromo-5-oxo-8-(trifluoromethyl)pyrazolo[1,5-a]pyrido[3,2-e]pyrimidin-4(5H)-yl]-N-(5-fluoropyridin-2-yl)acetamide**	^{1}H NMR (400 MHz, DMSO-d6) δ [ppm]: 5.27 (s, 2H), 7.77 (td, 1H), 8.06 (dd, 1H), 8.10 (d, 1H), 8.12 (s, 1H), 8.36 (d, 1H), 8.85 (d, 1H), 11.13 (s, 1H). LC-MS (Method A): R_t = 1.08 min; MS (ESIpos): m/z = 485 $[M+H]^+$	Intermediate 23 11.7 mg (18% yield, 91% purity)

Example 14

N-(5-fluoropyridin-2-yl)-2-[5-oxo-3,8-bis(trifluoromethyl)pyrazolo[1,5-a]pyrido[3,2-e]pyrimidin-4(5H)-yl]acetamide



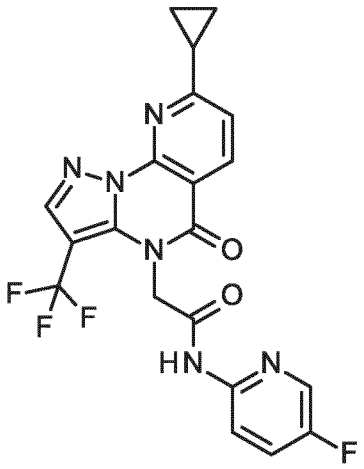
3,8-bis(trifluoromethyl)pyrazolo[1,5-a]pyrido[3,2-e]pyrimidin-5(4H)-one (52.0 mg, 161 µmol; intermediate 25) was dissolved in *N*-methyl-2-pyrrolidone (1.5 mL) and stirred for 10 minutes. Afterwards 2-bromo-N-(5-fluoropyridin-2-yl)acetamide (75.2 mg, 323 µmol) was added and stirring was continued for 16 h at room temperature. The reaction mixture was purified by preparative HPLC (Method 3). The product fractions were pooled and concentrated *in vacuo* to afford 19.7 mg (24% yield, 95% purity) of the title compound as a white solid.

1H NMR (400 MHz, DMSO-d6) δ [ppm]: 5.08 (s, 2H), 7.77 (td, 1H), 7.97-8.04 (m, 1H), 8.09 (br d, 1H), 8.16 (d, 1H), 8.37 (d, 1H), 8.64 (d, 1H), 10.99 (s, 1H).

LC-MS (Method A): R_t = 1.15 min; MS (ESIpos): m/z = 475 $[M+H]^+$

Example 15

2-[8-cyclopropyl-5-oxo-3-(trifluoromethyl)pyrazolo[1,5-a]pyrido[3,2-e]pyrimidin-4(5H)-yl]-N-(5-fluoropyridin-2-yl)acetamide



[8-cyclopropyl-5-oxo-3-(trifluoromethyl)pyrazolo[1,5-a]pyrido[3,2-e]pyrimidin-4(5H)-yl]acetic acid (50.0 mg, 142 µmol; intermediate 32-6) was dissolved in pyridine (670 µl), then 5-

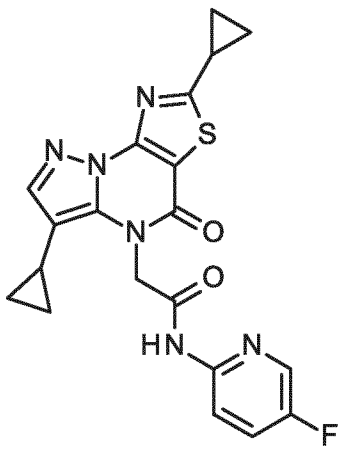
fluoropyridin-2-amine (23.9 mg, 213 µmol; CAS-RN:[21717-96-4]) and 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (109 mg, 568 µmol; CAS-RN:[25952-53-8]) were added. The reaction mixture was stirred for 1 hours at room temperature. The reaction was quenched with 10 ml hydrochloric acid (1M) and extracted with ethyl acetate. The combined organic phases were washed with brine and concentrated. The residue was diluted with 2 ml acetonitrile/water (7:3), and purified by preparative HPLC (Method 1, gradient D). The product fractions were pooled and concentrated *in vacuo* to afford 3.00 mg (4% yield, 93% purity) of the title compound as a white fluffy solid

^{1}H NMR (400 MHz, DMSO-d6) δ [ppm]: 1.15-1.24 (m, 4H), 2.37-2.45 (m, 1H), 4.96 (s, 2H), 7.65 (d, 1H), 7.74 (td, 1H), 7.98 (dd, 1H), 8.30 (s, 1H), 8.35 (d, 1H), 8.46 (d, 1H), 11.14 (s, 1H).

LC-MS (Method A): R_t = 1.16 min; MS (ESIpos): m/z = 447 $[M+H]^+$

Example 16

2-(2,6-dicyclopropyl-4-oxopyrazolo[1,5-a][1,3]thiazolo[5,4-e]pyrimidin-5(4H)-yl)-N-(5-fluoropyridin-2-yl)acetamide



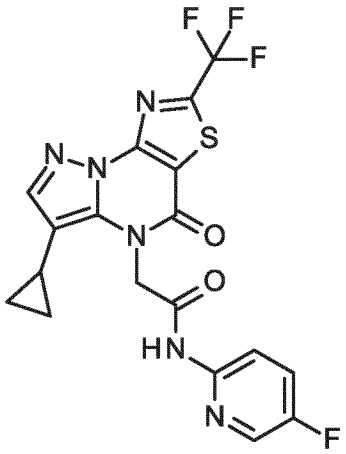
To a solution of 2,6-dicyclopropylpyrazolo[1,5-a][1,3]thiazolo[5,4-e]pyrimidin-4(5H)-one (100 mg, 0.293 mmol; intermediate 26) in N,N-dimethylformamide (3 ml) was added 2-bromo-N-(5-fluoropyridin-2-yl)acetamide (102 mg, 0.440 mmol, intermediate 34) and potassium carbonate (122 mg, 0.881 mmol). The reaction mixture was stirred at room temperature for 4 h. The mixture was filtered and the filtrate was concentrated to give a residue. The residue was purified by preparative-HPLC (Instrument: Gilson-281; Column: Phenomenex Synergi Max-RP 75*30mm*3 µm; eluent A: water (0.225% formic acid), eluent B: acetonitrile; gradient: 0-7 min 32-62% B; flow 25 ml/min; temperature: room temperature; Detector: UV 220/254 nm) to give 2-(2,6-dicyclopropyl-4-oxopyrazolo[1,5-a][1,3]thiazolo[5,4-e]pyrimidin-5(4H)-yl)-N-(5-fluoropyridin-2-yl)acetamide (150 mg, 97% purity) as a yellow solid.

LC-MS (Method C): R_t = 0.787 min; MS (ESIpos): m/z = 425.2 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-d_6) δ [ppm]: 11.10 (s, 1H), 8.35 (d, 1H), 8.10-7.93 (m, 1H), 7.78-7.71 (m, 1H), 7.69 (s, 1H), 5.33 (s, 2H), 2.77-2.64 (m, 1H), 1.81-1.66 (m, 1H), 1.42-1.31 (m, 2H), 1.28-1.19 (m, 2H), 0.85-0.73 (m, 2H), 0.66-0.57 (m, 2H).

Example 17

2-[6-cyclopropyl-4-oxo-2-(trifluoromethyl)pyrazolo[1,5-a][1,3]thiazolo[5,4-e]pyrimidin-5(4H)-yl]-N-(5-fluoropyridin-2-yl)acetamide



6-cyclopropyl-2-(trifluoromethyl)pyrazolo[1,5-a][1,3]thiazolo[5,4-e]pyrimidin-4(5H)-one (210 mg, 67 % purity, 469 µmol; intermediate 27) was dissolved in *N*-methyl-2-pyrrolidone (2.0 mL), sodium carbonate (149 mg, 1.41 mmol) was added and the suspension stirred for 10 minutes at room temperature. Afterwards 2-bromo-N-(5-fluoropyridin-2-yl)acetamide (218 mg, 937 µmol; intermediate 34) was added and stirring continued for 16 h at room temperature. The reaction mixture was purified by preparative HPLC (Method 3). The product fractions were pooled and concentrated *in vacuo*. The residue was purified again by preparative HPLC (Method 3) to afford 36.0 mg (15% yield, 90% purity) of the title compound as a white solid.

^{1}H NMR (400 MHz, DMSO-d6) δ [ppm]: 0.62-0.68 (m, 2H), 0.79-0.88 (m, 2H), 1.77 (tt, 1H), 5.37 (s, 2H), 7.76 (td, 1H), 7.84 (s, 1H), 8.00-8.07 (m, 1H), 8.36 (d, 1H), 11.16 (s, 1H)

LC-MS (Method A): R_t = 1.16 min; MS (ESIpos): m/z = 453 $[M+H]^+$

BIOLOGICAL AND PHYSICOCHEMICAL ASSAYS

1) Intracellular calcium measurement to assess antagonist activity at human P2X3 receptors (hP2X3 CHO)

The determination of antagonistic activity at the P2X3 receptor of the compounds of the invention was performed by use of a recombinant cell line. These cell line derives originally from the Chinese hamster ovary (CHO) cell line (Tjio J. H.; Puck T. T., 1958, J. Exp. Med. 108: 259–271). The cell line is stably transfected with the human P2X3 receptor and a calcium-sensitive photoprotein, mitochondrial photina, which, after reconstitution with the cofactor coelenterazine, emits light in dependence of calcium binding [Bovolenta S, Foti M, Lohmer S, Corazza S., J Biomol Screen. 2007 Aug;12(5):694-704]. The strength of the photina luminescence signal corresponds to the level of receptor activation upon agonist binding. An inhibitor would decrease the signal depending on its potency and concentration. Bioluminescence was detected using a suitable luminometer [Milligan G, Marshall F, Rees S, Trends in Pharmacological Sciences 17, 235-237 (1996)].

Test procedure:

On the day before the assay, the cells are plated out in culture medium (DMEM/F12 (PAN, P04-41451), 10% FCS) in 384-well microtiter plates and kept in a cell incubator (96% humidity, 5% v/v CO_2, 30°C). On the day of the assay medium is replaced by 2mM Ca-tyrode buffer containing 5 µg/ml coelenterazine. Plates are incubated for 3 hours at 37°C (96% humidity, 5% v/v CO_2). After incubation the test substances in various concentrations are placed for 10 minutes in the wells of the microtiter plate before the agonist α,β-methylene-ATP at EC_{50} concentration is added. The resulting light signal is measured immediately in the luminometer.

2) and 3) Intracellular calcium measurement to compare antagonist activity at human P2X3 receptors (hP2X3 1321N1) and at human P2X2/3 receptors (hP2X23 1321N1)

The comparison of antagonistic activity at the P2X3 versus the P2X23 receptor of the compounds of the invention was performed by use of recombinant cell lines. These cell lines derive originally from the human astrocytoma cell line 1312N1 (Macintyre EH, Pontén J, Vatter AE. Acta Pathol Microbiol Scand A. 1972;80(2):267-83). The cell lines are stably transfected with the human P2X3 receptor forming homotrimeric P2X3 receptors or are co-transfected with P2X2 and P2X3 forming heterotrimeric P2X23 receptors. Stimulation of the receptors with the agonist ATP leads to a conformational change of the receptors and influx of extracellular calcium ions through the open ion channel. The cytoplasmatic calcium transient is detected via the calcium sensitive dye Fluo8. The strength of Fluo8 fluorescence signal corresponds to the level of receptor activation. An inhibitor would decrease the signal depending on its potency and concentration. Fluorescence was measured by use of a suitable fluorescence reader.

Test procedure:

On the day before the assay, the cells are plated in culture medium (DMEM high glucose, 10% FCS, 1% MEM non-essential amino acids , 4mM Glutamax) in 384-well poly-D-lysine coated microtiter plates and kept in a cell incubator (96% humidity, 5% v/v CO_2, 37°C). On the day of the assay medium is exchanged by Fluo8 containing buffer and incubated for 60 minutes. Test compounds are added at various concentrations and plates are incubated for 10 minutes. In the fluorescence reader a 3 seconds baseline measurement is performed and the agonist ATP is applied at EC_{50} concentration of the respective receptor during constant fluorescence measurement for 120 seconds.

4) Kinetic solubility measurement from DMSO stock solutions (10 mM) in aqueous PBS buffer at pH 6.5

Solubility of compounds is investigated from precipitation. The dilution of each compound is prepared from DMSO stock solution (10 mM). Equilibration time in aqueous PBS medium at pH 6.5 is 24 h. The concentration of the compound in supernatant after ultracentrifugation or filtrate after filtration is determined. Analysis is done by LC-MSMS or HPLC. Solubility data are reported in µM.

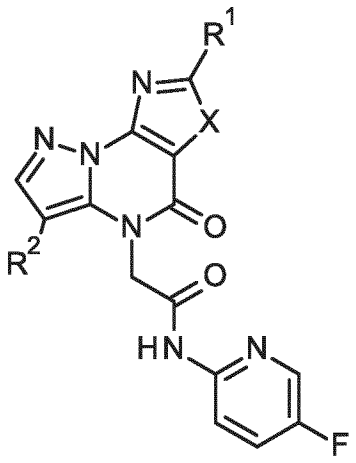
Results

Example / *CAS* No.	1) hP2X3 IC_{50} [nM] (CHO)	2) hP2X3 IC_{50} [nM] (1321N1)	3) hP2X23 IC_{50} [nM] (1321N1)	hP2X23/hP2X3 Selectivity (1321N1)	4) Solublity [µM]
1	12	17	729	43	53.4
Example 33 of WO2021115225	*113*	*68*	*nd*	*nd*	*6.4*
2	16	11	724	68	15.4
Example 79 of WO2021115225	*155*	*119*	*nd*	*nd*	*5.0*
3	7	5	232	47	31.8
Example 35 of WO2021115225	*22*	*12*	*1800*	*154*	*2.5*
4	4	nd	317	nd	4.2
5	6	6	162	27	2.1
6	10	8	450	56	35.2
7	15	19	266	14	172.2
8	7	10	175	18	42.5
9	8	6	805	127	127.4
10	8	12	375	32	37.5
Example 34 of WO2021115225	*113*	*51*	*nd*	*nd*	*5.8*
11	8	12	148	13	37.2
12	7	6	537	92	100.5
Example 36 of WO2021115225	*94*	*195*	*nd*	*nd*	*0.9*
13	11	10	556	53	108.0
Example 61 of WO2021115225	*59*	*120*	*1800*	*15*	*11.7*
14	56	41	9300	229	276.0
Example 66 of WO2021115225	*90*	*135*	*1400*	*10*	*39.6*
15	12	15	417	28	17.0
16	7	6	250	45	4.5
17	16	10	999	101	521.7

5

CLAIMS

1. A compound of formula (I):



(I)

in which:

R^1 represents C_1-C_3 alkyl, optionally substituted with one ore more halogen, cyclopropyl, or cyano

R^2 represents C_1-C_3 alkyl, optionally substituted with one ore more halogen, cyclopropyl, or halogen

X represents -CH=CH- or -S-;

or an N-oxide thereof.

2. The compound of formula (I) according to claim 1, wherein:

R^1 represents methyl, isopropyl, cyclopropyl, difluoromethyl, trifluoromethyl, or cyano;

R^2 represents methyl, ethyl, isopropyl, cyclopropyl, trifluoromethyl, chloro, or bromo;

X represents -CH=CH- or -S- ;

or an N-oxide thereof.

3. The compound of formula (I) according to claim 2, wherein:

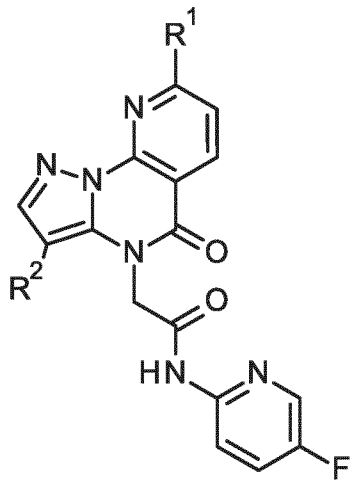
R^1 represents methyl, difluoromethyl, or trifluoromethyl;

R^2 represents methyl, ethyl, or cyclopropyl;

X represents -CH=CH- or -S- ;

or an N-oxide thereof.

4. A compound according to claim 1 having general formula (II):



(II)

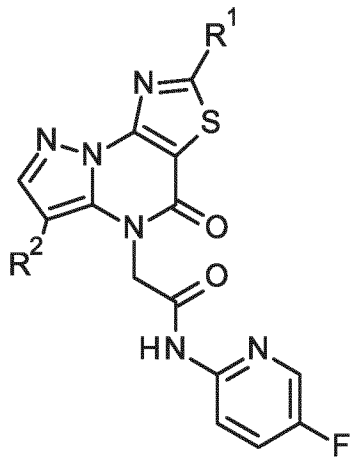
in which:

R^1 represents methyl, difluoromethyl, or trifluoromethyl;

R^2 represents methyl, ethyl, or cyclopropyl;

or an N-oxide thereof.

5. A compound according to claim 1 having general formula (III):



(III)

in which:

R^1 represents methyl, difluoromethyl, or trifluoromethyl;

R^2 represents methyl, ethyl, or cyclopropyl;

or an N-oxide thereof.

6. The compound according to any one of claims 1, 2, 3, or 4 which is:

N-(5-fluoropyridin-2-yl)-2-[3-methyl-5-oxo-8-(trifluoromethyl)pyrazolo[1,5-a]pyrido[3,2-e]pyrimidin-4(5H)-yl]acetamide,

2-[3-chloro-5-oxo-8-(trifluoromethyl)pyrazolo[1,5-a]pyrido[3,2-e]pyrimidin-4(5H)-yl]-N-(5-fluoropyridin-2-yl)acetamide,

2-[3-cyclopropyl-5-oxo-8-(trifluoromethyl)pyrazolo[1,5-a]pyrido[3,2-e]pyrimidin-4(5H)-yl]-N-(5-fluoropyridin-2-yl)acetamide,

2-[3-cyclopropyl-8-(difluoromethyl)-5-oxopyrazolo[1,5-a]pyrido[3,2-e]pyrimidin-4(5H)-yl]-N-(5-fluoropyridin-2-yl)acetamide,

2-[3-cyclopropyl-5-oxo-8-(propan-2-yl)pyrazolo[1,5-a]pyrido[3,2-e]pyrimidin-4(5H)-yl]-N-(5-fluoropyridin-2-yl)acetamide,

2-(3-cyclopropyl-8-methyl-5-oxopyrazolo[1,5-a]pyrido[3,2-e]pyrimidin-4(5H)-yl)-N-(5-fluoropyridin-2-yl)acetamide,

2-(3-chloro-8-cyclopropyl-5-oxopyrazolo[1,5-a]pyrido[3,2-e]pyrimidin-4(5H)-yl)-N-(5-fluoropyridin-2-yl)acetamide,

2-(3,8-dicyclopropyl-5-oxopyrazolo[1,5-a]pyrido[3,2-e]pyrimidin-4(5H)-yl)-N-(5-fluoropyridin-2-yl)acetamide,

2-(8-cyano-3-cyclopropyl-5-oxopyrazolo[1,5-a]pyrido[3,2-e]pyrimidin-4(5H)-yl)-N-(5-fluoropyridin-2-yl)acetamide,

2-[3-ethyl-5-oxo-8-(trifluoromethyl)pyrazolo[1,5-a]pyrido[3,2-e]pyrimidin-4(5H)-yl]-N-(5-fluoropyridin-2-yl)acetamide,

2-[3-ethyl-5-oxo-8-(propan-2-yl)pyrazolo[1,5-a]pyrido[3,2-e]pyrimidin-4(5H)-yl]-N-(5-fluoropyridin-2-yl)acetamide,

N-(5-fluoropyridin-2-yl)-2-[5-oxo-3-(propan-2-yl)-8-(trifluoromethyl)pyrazolo[1,5-a]pyrido[3,2-e]pyrimidin-4(5H)-yl]acetamide,

2-[3-bromo-5-oxo-8-(trifluoromethyl)pyrazolo[1,5-a]pyrido[3,2-e]pyrimidin-4(5H)-yl]-N-(5-fluoropyridin-2-yl)acetamide,

N-(5-fluoropyridin-2-yl)-2-[5-oxo-3,8-bis(trifluoromethyl)pyrazolo[1,5-a]pyrido[3,2-e]pyrimidin-4(5H)-yl]acetamide, and

2-[8-cyclopropyl-5-oxo-3-(trifluoromethyl)pyrazolo[1,5-a]pyrido[3,2-e]pyrimidin-4(5H)-yl]-N-(5-fluoropyridin-2-yl)acetamide.

7. The compound according to any one of claims 1, 2, 3, or 5 which is:

2-(2,6-dicyclopropyl-4-oxopyrazolo[1,5-a][1,3]thiazolo[5,4-e]pyrimidin-5(4H)-yl)-N-(5-fluoropyridin-2-yl)acetamide, and

2-[6-cyclopropyl-4-oxo-2-(trifluoromethyl)pyrazolo[1,5-a][1,3]thiazolo[5,4-e]pyrimidin-5(4H)-yl]-N-(5-fluoropyridin-2-yl)acetamide.

8. The compound according to any one of claims 1, 2, 3, 4 or 6 which is:

N-(5-fluoropyridin-2-yl)-2-[3-methyl-5-oxo-8-(trifluoromethyl)pyrazolo[1,5-a]pyrido[3,2-e]pyrimidin-4(5H)-yl]acetamide,

2-[3-chloro-5-oxo-8-(trifluoromethyl)pyrazolo[1,5-a]pyrido[3,2-e]pyrimidin-4(5H)-yl]-N-(5-fluoropyridin-2-yl)acetamide, and

2-[3-cyclopropyl-5-oxo-8-(trifluoromethyl)pyrazolo[1,5-a]pyrido[3,2-e]pyrimidin-4(5H)-yl]-N-(5-fluoropyridin-2-yl)acetamide

N-(5-fluoropyridin-2-yl)-2-[5-oxo-3-(propan-2-yl)-8-(trifluoromethyl)pyrazolo[1,5-a]pyrido[3,2-e]pyrimidin-4(5H)-yl]acetamide.

9. A compound of formula (I) according to any one of claims 1 to 8 for use in the treatment or prophylaxis of a disease.

10. A pharmaceutical composition comprising a compound of formula (I) according to any one of claims 1 to 8 and one or more pharmaceutically acceptable excipients.

11. Use of a compound of formula (I) according to any one of claims 1 to 8 for the treatment or prophylaxis of a disease.

12. Use of a compound of formula (I) according to any one of claims 1 to 8 for the preparation of a medicament for the treatment or prophylaxis of a disease.

13. Use according to any one of claims 11 or 12, wherein the disease is a neurogenic disorder, such as a gynecological disorder, urinary tract disease state, respiratory disorder or a pain-associated disease or disorder.

14. Use according to claim 13, wherein the disease is endometriosis, moderate to severe pain associated with endometriosis in women of reproductive age; overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency, urinary frequency and nocturia; interstitial cystitis and/ or bladder pain syndrome; refractory and/ or unexplained chronic cough; neuropathic pain associated with diabetic peripheral neuropathy (NP-DPN); cancer and/ or chemotherapy related neuropathic pain; postherpetic neuralgia and postsurgical and/ or posttraumatic neuropathic pain; irritable bowel syndrome with diarrhea (IBS D); Prurigo nodularis; chronic pruritus of unknown origin; itch; heart failure and/ or central and obstructive sleep apnea.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2022/086922

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D471/14 C07D513/14 A61K31/519 A61P25/00 A61P25/02
A61P25/04 A61P13/02 A61P13/10 A61P15/00 A61P11/00
A61P11/14 A61P1/00 A61P1/12 A61P17/00 A61P17/04

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D A61K A61P

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

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

EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2021/115225 A1 (SHANGHAI HANSOH BIOMEDICAL CO LTD [CN] ET AL.) 17 June 2021 (2021-06-17) cited in the application page 78; example 80 page 81, line 8 to page 96, biological assays: test examples 1 to 10, tables 1 to 10 claims 1, 14, 17, 19 (page 116, compound 80) and 20 to 25 -----	1-14

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

☒ See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 March 2023	27/03/2023

Name and mailing address of the ISA/	Authorized officer
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2022/086922

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2021115225 A1	17-06-2021	AU 2020401668 A1	21-07-2022
		CA 3160875 A1	17-06-2021
		CN 114222746 A	22-03-2022
		EP 4074714 A1	19-10-2022
		JP 2023506436 A	16-02-2023
		KR 20220113385 A	12-08-2022
		TW 202128693 A	01-08-2021
		WO 2021115225 A1	17-06-2021