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(54) Title: 1,3-THIAZOL-2-YL SUBSTITUTED BENZAMIDES FOR THE TREATMENT OF DISEASES ASSOCIATED WITH NERVE FIBER SENSITIZATION

(57) Abstract: The present invention relates to use 1,3-thiazol-2-yl substituted benzamide compounds of general formula (I) as described and defined herein, to pharmaceutical compositions and combinations comprising said compounds for the treatment or prophylaxis of diseases which are 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.

1,3-THIAZOL-2-YL SUBSTITUTED BENZAMIDES FOR THE TREATMENT OF DISEASES ASSOCIATED WITH NERVE FIBER SENSITIZATION

The present invention relates to the use of 1,3-thiazol-2-yl substituted benzamide compounds of general formula (I) as a sole agent or in combination with other active ingredients as well as to the use of pharmaceutical compositions and combinations comprising said compounds for the treatment or prophylaxis of diseases which are associated with nerve fiber sensitization and/ or autonomic imbalance, in particular cardiovascular diseases, heart failure and hypertension.

BACKGROUND OF THE INVENTION

The present invention relates to the use of chemical compounds that inhibit P2X3 receptor for the treatment of diseases associated with nerve fiber sensitization P2X purinoceptor 3 is a protein that in humans is encoded by the P2RX3 gene (Garcia-Guzman M, Stuehmer W, Soto F, 1997, 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, cardiovascular and respiratory conditions and disorders, including overactive bladder, chronic cough, heart failure and hypertension (Ford 2013, front Cell Neurosci 7:267; Burnstock 2014, Purin Signal 10(1):3-50; Pijacka et al, Nat Med. 2016. 22(10): 1151–1159). In these examples, ATP release is involved in activation of reflex pathways including contraction of bladder and lung muscles, and the peripheral chemoreflex.

P2X3 subunits do not only form homotrimers but also heterotrimers with P2X2 subunits. P2X3 subunits and P2X2 subunits are also expressed on nerve fibers innervating the tongue, therein taste buds (Kinnamon 2013, front Cell Neurosci 7:264). In a phyiosological 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, 2(3), 267-77). Clinical Phase 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, 385 (9974), 1198-1205; 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, 310 (5753), 1495-99), whereas P2X3 subunit single knock-outs exhibit a mild or no change in phenotype with respect to taste. Moreover, two distinct populations of neurons have been described in the geniculate ganglion expressing either P2X2 and P2X3 subunits or P2X3 subunit alone (Vandenbeuch et al, J Physiol, 2015, 593(Pt 5): 1113-1125). The population expressing P2X2/P2X3 heterotrimers has been described as being less sensitive to a non-selective P2X2/P2X3 antagonist compared to the population expressing P2X3 homomers, i.e. requiring a higher concentration of this antagonist to be inhibited. 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 the less sensitive P2X2 and P2X3 subunit expressing population plays a major role in taste sensation than the P2X3 subunit expressing population (Vandenbeuch et al, J Physiol, 2015, 593(Pt 5): 1113-1125). 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 PhII trials (Strand et al, 2015 ACR/ARMP Annual Meeting, Abstract 2240 and A. Ford, London 2015 Pain Therapeutics Conference, congress report).

Increased sympathetic nervous system (SNS) activity and sympathetic neural factors such as norepinephrine (NE, also known as noradrenaline) are involved in the genesis of cardiovascular disease (CVD) in general (Grassi et al, Circ Res, 2015, 116(6):976-990). Common comorbidities with heart failure (HF) and CVD are also associated with increased sympathetic tone and decreased parasympathetic tone, termed autonomic imbalance. Taken together, clinical studies indicate that patients suffering from autonomic imbalance have decreased exercise tolerance, higher incidence of central sleep apneas, higher incidence of arrhythmias, and increased mortality (Joyner, J Physiol, 2016, 549(14): 4009-4013). Autonomic imbalance is an independent predictor of mortality in HF and CVD patients regardless of the etiology of the condition and is caused by chronic pathological over-activation of afferent inputs such as peripheral chemoreceptors.

Recent preclinical and clinical studies have demonstrated that the carotid body peripheral chemoreflex should be considered as a target for cardiovascular diseases associated with autonomic imbalance (Del Rio et al, J Am Coll Cardiol, 2013, 62(25):2422-2430; McBryde et al, Nat Commun, 2013, 4:2395; Niewinsky et al, Int J Cardiol, 2013, 168(3):2506-2509; Paton et al, Hypertension, 2013, 61(1):5-13; Marcus et al, J Physiol, 2014, 592(2):391-408; Del Rio et al, Exp Physiol, 2015, 100(2):136-142). Chemoreflex hypersensitivity has been demonstrated in animal models of CVD with different etiology including: genetic modifications, chronic intermittent hypoxia, myocardial infarction, rapid ventricular pacing, genetic cardiomyopathy, and pressure overload.

Increased chemoreflex sensitivity is observed in 40-60 % of optimally treated HF patients (Giannoni et al, J Am Coll Cardiol, 2009, 53(21):1975-1980; Niewinski et al, J Card Fail, 2013, 19(6):408-415). Chemoreflex hypersensitivity is also associated with a higher prevalence of unstable ventilatory control during wakefulness, ventilatory insufficiency during exercise, sleep related breathing disorders, Cheyne-Stokes respiration, persistent atrial fibrillation, and paroxysmal ventricular tachycardia, and impaired baroreflex control of blood pressure (Ponikowski et al, Circulation. 2001. 104(5):544-549; Corra et al, Circulation, 2006, 113(1):44-50; Giannoni et al, Clin Sci (Lond). 2008. 114(7):489-497; Despas et al, J Hypertens, 2012, 30(4):753-760; Dempsey and Smith, Adv Exp Med Biol. 2014. 758:343-349; Andrade et al, Biomed Res Int. 2015. 467597; Floras and Ponikowski, Eur Heart J, 2015, 36(30):1974-1982b; Grassi et al, Circ Res, 2015, 116(6):976-990).

In the case of CVD, neurotransmitter release, including ATP release from Type I and Type II glumus cells of the carotid body (glomus caroticum) is involved in the the physiological response to hypoxia. Recent studies (Pijacka et al, Nat Med, 2016, 22(10): 1151–1159) demonstrate that overexpression of P2X3 in the carotid body of spontaneously hypertensive rats increases tonic activation of the peripheral chemoreflex leading to increased sympathetic nervous system activity and autonomic imbalance (Pijacka et al, Nat Med, 2016, 22(10): 1151–1159). Therefore blockade of P2X3 could be considered as a treatment option for CVD associated with tonically active or hypersensitive peripheral chemoreflex.

WO2015/027212 (Afferent Pharmaceutical Inc.) discloses new diaminopyrimidine compounds having activity as antagonists of P2X purinergic receptors, and methods for treatment of diseases associated with P2X receptors comprising administering an effective amount of a diaminopyrimidine compound. More particularly, methods are provided for using P2X3 and/or P2X2/3 antagonists in the treatment of cough, chronic cough and urge to cough in respiratory conditions and disorders.

Afferent Pharmaceuticals is developing AF-219 (5-(2,4-diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-benzenesulfonamide), which is an oral, small molecule P2X3 antagonist, for the potential treatment of chronic cough and pain, including chronic bladder pain syndrome and osteoarthritis pain, and asthma. Several clinical trials are ongoing, amongst them for example an US phase II trial in patients with idiopathic pulmonary fibrosis with persistent cough and breathlessness (ClinicalTrials.gov Identifier: NCT02502097) as well as a phase IIb cough trial in patients with refractory chronic cough (NCT02349425) which are completed.

With regard to CVD and hypertension, chemoreflex hypersensitivity persists in patients that are treated under the current standard of care (Neurohumoral blockade), including beta adrenergic antagonism, aldosterone receptor antagonism, angiotensin converting enzyme inhibition, and/or angiotensin receptor block (Ponikowski et al, Circulation, 2001, 104(5):544-549; Soares Barreto-Filho et al, Circulation, 2001, 104(15):1792-1798; Giannoni et al, Clin Sci (Lond), 2008, 114(7):489-497; Niewinski et al, Exp Physiol, 2014, 99(3):552-561; Mirizzi et al,

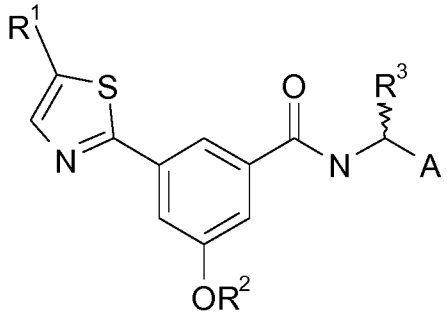
PLoS One, 2016, 11(4):e0153510). In these studies, patients that demonstrate chemoreflex hypersensitivity have worsened outcomes compared to patients with normal chemoreflex sensitivity. Current standard of care therapies do not pharmacologically inhibit the peripheral chemoreflex. Therefore, a significant residual risk exists in these patients in spite of optimal treatment with standard of care therapies. Because P2X3 overexpression in the type I glomus cell of the carotid body is associated with chemoreflex hypersensitivity and cardiovascular disease, P2X3 inhibitor compounds could be used to attenuate chemoreflex hypersensitivity as a treatment for cardiovascular disease.

Thus, there is an urgent need for medicaments which are effective in the treatment of diseases which are associated with nerve fiber sensitization, and/or other pathological conditions associated with autonomic imbalance, for example caused by increased chemoreceptor sensitivity like cardiovascular diseases, heart failure and hypertension, which do not have the disadvantages of the prior art. These disadvantages include not directly targeting chemoreflex hyper-sensitivity and dysguesia associated with dual P2X2/3 blockade.

The underlying problem of the present invention therefore lies in the provision of medication for long-term oral treatment of diseases associated with nerve fiber sensitization and/or other pathological conditions associated with autonomic imbalance caused by increased chemoreceptor sensitivity like cardiovascular diseases, heart failure and hypertension, which are related to increased activity of P2X3 receptors.

Summary of the invention

It has now been found, and this constitutes the basis of the present invention, that compounds of the general formula (I)



(I),

in which

R^1 represents a halogen atom, C_1-C_4-alkyl or C_3-C_6-cycloalkyl, wherein C_1-C_4-alkyl is optionally substituted with 1-5 halogen atoms which are the same or different;

R^2 represents -C_2-C_6-alkyl-OR^4 , -$(CH_2)_q$-(C_3-C_7-cycloalkyl), -$(CH_2)_q$-(6- to 12-membered heterobicycloalkyl), -$(CH_2)_q$-(4- to 7-membered heterocycloalkyl), -$(CH_2)_q$-(5- to 10-membered heteroaryl) or -C_2-C_6-alkynyl; and

wherein said -$(CH_2)_q$-(C_3-C_7-cycloalkyl), -$(CH_2)_q$-(6- to 12-membered heterobicycloalkyl) and -$(CH_2)_q$-(4- to 7-membered heterocycloalkyl) are optionally substituted with one or more substituents which are the same or different, at any ring carbon atom and selected from the group consisting of

C_1-C_4 alkyl, optionally substituted with 1-5 halogen atoms which are the same or different, a halogen atom, -NR^aR^b, $COOR^5$ and oxo (=O); and

wherein independently any ring nitrogen atom, if present in said -$(CH_2)_q$-(6- to 12-membered heterobicycloalkyl) and -$(CH_2)_q$-(4- to 7-membered heterocycloalkyl) is substituted with R^c; and

wherein said -$(CH_2)_q$-(5- to 10-membered heteroaryl) is optionally substituted with one or more substituents which are the same or different, and selected from the group consisting of C_1-C_4-alkyl, optionally substituted with 1-5 halogen atoms which are the same or different, a halogen atom, -NR^aR^b and -$COOR^5$;

R^3 represents hydrogen or C_1-C_4-alkyl, which is optionally substituted with 1-5 halogen atoms which are the same or different;

R^4 and R^5 represent hydrogen or C_1-C_4-alkyl;

R^a and R^b represent hydrogen or C_1-C_4-alkyl;

R^c represents hydrogen, C_1-C_4-alkyl, optionally substituted with 1-5 halogen atoms which are the same or different, -C(O)O-C_1-C_4-alkyl, or -C(O)-C_1-C_4-alkyl;

A represents 5- to 10-membered heteroaryl which is optionally substituted with one or more substituents, which are the same or different, and selected from the group consisting of a halogen atom, C_1-C_3-alkyl, and C_1-C_3-alkoxy, wherein C_1-C_3-alkyl and C_1-C_3-alkoxy are optionally substituted with 1-5 halogen atoms which are the same or different;

q represents an integer of 0, 1, or 2;

or an isomer, enantiomer, diastereomer, racemate, hydrate, solvate, or a salt thereof, or a mixture of same can be used for the treatment or prophylaxis of diseases or disorders which are 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.

By providing said treatment options, it is possible to solve the problem of significant side effects known from present SoC (standard of care) therapies for cardiovascular diseases (CVD), and hypertension.

The prevention of additional significant side effects to important physiological functions, i.e. taste, wakefulness, or heart rate, that may weaken the potential clinical effectiveness of medicaments, is an advantage of this invention.

That means, for example, the avoidance of negatively effecting important physiological functions, like taste sensation, the avoidance of physical dependency, increased heart rate, xerostomia, constipation, nausea, drowsiness or sedation, which all have severe impact to the quality of life of patients. This makes it possible to provide a for the treatment of breathing disorders, Cheyne Stokes respiration, Central and obstructive sleep apnea, cardiovascular disease, hypertension, resistant hypertension, and heart failure which is usable for a chronic treatment of the mentioned diseases. Furthermore, the oral treatment of breathing disorders, Cheyne Stokes respiration, Central and obstructive sleep apnea, cardiovascular disease, hypertension, resistant hypertension, and heart failure, is possible with the provided treatment approach.

The present invention is based on the discovery that compounds of general formula (I) are highly potent and sufficient selective at the P2X3 receptor. Therefore the subject matter of the present invention is directed to the use of compounds of general formula (I) for the treatment or prophylaxis of diseases or disorders, which are associated with nerve fiber sensitization and/or associated with autonomic imbalance. The autonomic imbalance can be caused by increased chemoreceptor sensitivity.

In accordance with a first aspect, the present invention covers the use of compounds of general formula (I) for the treatment or prophylaxis of breathing disorders, Cheyne Stokes respiration, Central and obstructive sleep apnea, cardiovascular disease, hypertension, resistant hypertension, and heart failure.

In accordance with a second aspect, the present invention relates to the use of compounds of general formula (I) for long-term treatment of breathing disorders, Cheyne Stokes respiration, Central and obstructive sleep apnea, cardiovascular disease, hypertension, resistant hypertension, and heart failure.

In accordance with a third aspect, the present invention relates to the use of compounds of general formula (I) for oral treatment of breathing disorders, Cheyne Stokes respiration, Central and obstructive sleep apnea, cardiovascular disease, hypertension, resistant hypertension, and heart failure.

In accordance with a fourth aspect, the present invention relates to the use of compounds of general formula (I) for long-term and oral treatment of breathing disorders, Cheyne Stokes respiration, Central and obstructive sleep apnea, cardiovascular disease, hypertension, resistant hypertension, and heart failure.

In accordance with a fifth aspect, the present invention relates to the use of compounds of general formula (I) for long-term and oral treatment of breathing disorders, Cheyne Stokes respiration, Central and obstructive sleep apnea, cardiovascular disease, hypertension, resistant hypertension, and heart failure.

In accordance with a seventh aspect, the present invention covers a method of treatment or prophylaxis of breathing disorders, Cheyne Stokes respiration, Central and obstructive sleep apnea, cardiovascular disease, hypertension, resistant hypertension, and heart failure in a subject in need thereof.

In accordance with an eighth aspect, the present invention covers a method of long-term treatment of breathing disorders, Cheyne Stokes respiration, Central and obstructive sleep apnea, cardiovascular disease, hypertension, resistant hypertension, and heart failure in a subject in need thereof.

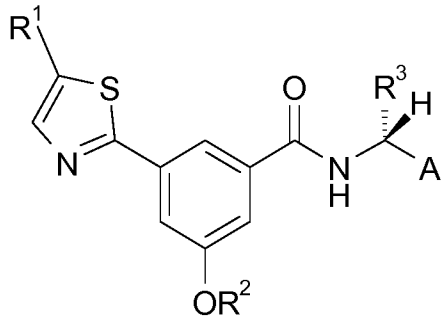
In accordance with a ninth aspect, the present invention covers a method of oral treatment of breathing disorders, Cheyne Stokes respiration, Central and obstructive sleep apnea, cardiovascular disease, hypertension, resistant hypertension, and heart failure in a subject in need thereof.

In accordance with a tenth aspect, the present invention covers a method of long-term and oral treatment of breathing disorders, Cheyne Stokes respiration, Central and obstructive sleep apnea, cardiovascular disease, hypertension, resistant hypertension, and heart failure in a subject in need thereof.

In accordance with an eleventh aspect, the present invention covers a method of long-term and oral treatment of breathing disorders, Cheyne Stokes respiration, Central and obstructive sleep apnea, cardiovascular disease, hypertension, resistant hypertension, and heart failure in a subject in need thereof.

A method in accordance with the invention comprises administering to the subject in need thereof an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof. The method comprises administering an effective amount of a compound of Formula (I).

The present invention further relates to the use of compounds of general formula (Ia),



(Ia)

in which A, R^1, R^2 and R^3 have the meanings as defined in formula (I), preferably R^3 represents C_1-C_4-alkyl, more preferably methyl;

or an isomer, enantiomer, diastereomer, racemate, hydrate, solvate, or a salt thereof, or a mixture of same for the treatment or prophylaxis of diseases or disorders which are 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.

The present invention further relates to the use of pharmaceutical compositions and combinations comprising the compounds of general formula (I) for the treatment or prophylaxis of diseases or disorders which are 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.

The present invention further relates to the use of pharmaceutical compositions and combinations comprising the compounds of general formula (I) for the treatment or prophylaxis of diseases or disorders which are 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.

Description of figures

Figure 1 shows the breathing rate response of anesthetized adult male Sprague Dawley rats to acute hypocapnic hypoxia by compounds of general formula (I), i.e. patent example 348 as described in WO2016/091776 in comparison with Afferent's AF-219. Pictured here is the breathing rate of anesthetized male Sprague Dawley rats as measured by esophageal catheter under normoxia (21% Oxygen) and during hypoxic (12% Oxygen) challenge. Compound causes a lowering of baseline breathing rate and a blunted response to hypoxia are observed in rats treated with P2X3 inhibitor, i.e. compounds of general formula (I), i.e. patent example 348 as described in WO2016/091776 in comparison with Afferent's AF-219.

Figure 2 shows the baseline ventilation in conscious animals by whole-body plethysmography (respiration measured by whole body plethysmography in SHR). Animals were treated with compounds of general formula (I), i.e. patent example 11 as described in WO2016/091776 p.o. before being placed into plethysmography chambers. The data shown are the average of 30 minutes of continuous minute ventilation measurements from 1.5 to 2 hours after the start of the measurement. Data shown mean ± SE. **, $p<0.01$.

Figure 3 shows the ventilatory response in conscious animals by whole-body plethysmography in Sprague dawley rats. Animals were treated with compounds of general formula (I), i.e. patent example 348 as described in WO2016/091776 p.o. before being placed into plethysmography chambers. Compound was administered 3 hours before initiation of a 10 minute hypoxic challenge (10% O_2 balanced with N_2). The data shown are the area under the curve during the last 5 minutes of hypoxic challenge 95-100 minutes after the start of the measurement. Data shown are mean ± SE. *, $p<0.05$; **, $p<0.01$

Figure 4 shows the blood pressure monitoring in conscious animals by radiotelemetry (percent deviation of mean arterial pressure (MAP) in SHR). Compound or vehicle was given p.o. at time zero. Data shown are 30 minute averages over a 24 hour period. Lower MAP is observed in SHR treated with P2X3 inhibitors i.e. compounds of general formula (I), i.e. patent example 348 as described in WO2016/091776.

Detailed description of the invention

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

The term “halogen atom”, “halo-” or “Hal-” is to be understood as meaning a fluorine, chlorine, bromine or iodine atom, preferably a fluorine or a chlorine atom.

The term “alkyl” is to be understood as meaning a linear or branched, saturated, monovalent hydrocarbon group with the number of carbon atoms as specified and having as a rule, 2 to 6 in case of R^2, and 1 to 4 for all other alkyl substituents, preferably 1 to 3, carbon atoms, by way of example and by preference a methyl, ethyl, propyl, butyl, pentyl, hexyl, *iso*-propyl, *iso*-butyl, *sec*-butyl, *tert*-butyl, *iso*-pentyl, 2-methylbutyl, 1-methylbutyl, 1-ethylpropyl, 1,2-dimethylpropyl, *neo*-pentyl, 1,1-dimethylpropyl, 4-methylpentyl, 3-methylpentyl, 2-methylpentyl, 1-methylpentyl, 2-ethylbutyl, 1-ethylbutyl, 3,3-dimethylbutyl, 2,2-dimethylbutyl, 1,1-dimethylbutyl, 2,3-dimethylbutyl, 1,3-dimethylbutyl, or 1,2-dimethylbutyl group, or an isomer thereof. Particularly, said group has 1, 2, 3 or 4 carbon atoms (“C_1-C_4-alkyl”), *e.g.* a methyl, ethyl, n-propyl, n-butyl, iso-propyl, iso-butyl, sec-butyl, tert-butyl group, more particularly 1, 2 or 3 carbon atoms (“C_1-C_3-alkyl”), *e.g.* a methyl, ethyl, n-propyl- or iso-propyl group, and even more particularly 1 or 2 carbon atoms (“C_1-C_2-alkyl”), *e.g.* a methyl or ethyl group.

The term “C_1-C_4-alkyl, optionally substituted with 1-5 halogen atoms”, or in analogy “C_1-C_3-alkyl, optionally substituted with 1-5 halogen atoms” or “C_1-C_2-alkyl which are optionally substituted with 1-5 halogen atoms”, is to be understood as meaning a linear or branched, saturated, monovalent hydrocarbon group in which the term “C_1-C_4-alkyl”, “C_1-C_3-alkyl” or “C_1-C_2-alkyl” is defined *supra*, and in which one or more hydrogen atoms is replaced by a halogen atom, which are the same or different, *i.e.* one halogen atom being independent from another. In particular, halogen is fluorine or chlorine.

The term "C_1-C_4-alkyl, optionally substituted with 1-5 fluorine atoms", or in analogy "C_1-C_3-alkyl, optionally substituted with 1-5 fluorine atoms" or "C_1-C_2-alkyl, optionally substituted with 1-5 fluorine atoms", is to be understood as meaning a linear or branched, saturated, monovalent hydrocarbon group in which the term "C_1-C_4-alkyl", "C_1-C_3-alkyl" or "C_1-C_2-alkyl" is defined *supra*, and in which one or more hydrogen atoms is replaced by a fluorine atom.

Said "C_1-C_4-alkyl, optionally substituted with 1-5 fluorine atoms" or "C_1-C_4-alkyl group, optionally substituted with 1-5 halogen atoms" is, for example,

$-CH_2CH_2CH_2CF_3$.

Similarly, the above-mentioned applies to "C_1-C_3-alkyl, optionally substituted with 1-5 halogen atoms", or "C_1-C_2-alkyl, optionally substituted with 1-5 halogen atoms", or "C_1-C_3-alkyl, optionally substituted with 1-5 fluorine atoms", or "C_1-C_2-alkyl, optionally substituted with 1-5 fluorine atoms". Thus said "C_1-C_3-alkyl optionally substituted with 1-5 halogen atoms" or "C_1-C_3-alkyl optionally substituted with 1-5 fluorine atoms" is, for example,
$-CH_2CH_2CF_3$.

Said "C_1-C_2-alkyl optionally substituted with 1-5 halogen atoms" or "C_1-C_2-alkyl optionally substituted with 1-5 fluorine atoms" is, for example,
$-CF_3$, $-CHF_2$, $-CH_2F$, $-CF_2CF_3$, $-CH_2CHF_2$, or $-CH_2CF_3$.

Under the proviso, that R^2 in formula (I) or (Ia) is $-C_2$-C_6-alkyl-OR^4, "C_2-C_6-alkyl" is to be understood as C_1-C_5-alkylene which is bound to the phenolic oxygen via $-CH_2$-group. For example C_1-C_5-alkylene is methylene, ethylene, propylene, butylene, pentylene, *iso-p*ropylene, *iso-b*utylene, *sec*-butylene, *tert*-butylene, *iso*-pentylene, 2-methylbutylene, 1-methylbutylene, 1-ethylpropylene, 1,2-dimethyl-propylene, *neo-p*entylene, 1,1-dimethylpropylene.
Under the proviso, that R^2 in formula (I) or (Ia) is $-C_2$-C_6-alkyl-OR^4, "C_2-C_6-alkyl" is also to be understood as C_1-C_4-alkylene which is bound to the phenolic oxygen via -CH-CH_3 group.
Under the proviso, that R^2 in formula (I) or (Ia) is $-C_2$-C_4-alkyl-OR^4, "C_2-C_4-alkyl" is to be understood as C_1-C_3-alkylene which is bound to the phenolic oxygen via $-CH_2$-group. Under the proviso that R^2 in formula (I) or (Ia) is $-C_2$-C_4-alkyl-OR^4, "C_2-C_4-

alkyl" is also to be understood as C_1-C_2-alkylene which is bound to the phenolic oxygen via -CH-CH_3 group.

Under the proviso, that R^2 in formula (I) or (Ia) is -C_2-C_4-alkyl-OH, "C_2-C_4-alkyl" is to be understood as C_1-C_3-alkylene which is bound to the phenolic oxygen via -CH_2-group. Under the proviso that R^2 in formula (I) or (Ia) is -C_2-C_4-alkyl-OH, "C_2-C_4-alkyl" is also to be understood as C_1-C_2-alkylene which is bound to the phenolic oxygen via -CH-CH_3 group.

Under the proviso, that R^2 in formula (I) or (Ia) is -C_2-C_6-alkyl-OR^4, "-OR^4" is either at a tertiary, secondary or primary carbon atom of the -C_2-C_6-alkyl chain.

Under the proviso, that R^2 in formula (I) or (Ia) is -C_2-C_4-alkyl-OR^4, "-OR^4" is either at a tertiary, secondary or primary carbon atom of the -C_2-C_4-alkyl chain.

Under the proviso, that R^2 in formula (I) or (Ia) is -C_2-C_4-alkyl-OH, "-OH" is either at a tertiary, secondary or primary carbon atom of the -C_2-C_4-alkyl chain.

For example, said -C_2-C_6-alkyl-OR^4 is 3-hydroxybutan-2-yl, (2R,3R)-3-hydroxybutan-2-yl, (2S,3S)-3-hydroxybutan-2-yl, (2R,3S)-3-hydroxybutan-2-yl, (2S,3R)-3-hydroxybutan-2-yl, (2R,3R)-3-methoxybutan-2-yl, (2S,3S)-3-methoxybutan-2-yl, (2R,3S)-3-methoxybutan-2-yl, (2S,3R)-3-methoxybutan-2-yl, 3-methoxybutan-2-yl, 2-hydroxy-2-methylpropan-1-yl, 2-methoxy-2-methylpropan-1-yl, 3-hydroxypropan1-yl, 3-hydroxybutan-1-yl, 3-hydroxy-3-methylbutan-1-yl, 3-hydroxy-2-methylbutan-1-yl, 3-hydroxy-2,2-dimethylpropan-1-yl, 4-hydroxy-3-methylbutan-2-yl, 4-hydroxy-3-methylpent-1-yl, 4-hydroxy-4-methylpent-1-yl, 2-hydroxy-2-methylpropan-1-yl, 2-methoxy-2-methyl-propan-1-yl, 2-methoxyethan-1-yl, 3-methoxypropan-1-yl, 4-methoxybutan-1-yl, 2-ethoxyethan-1-yl, 3-ethoxypropan-1-yl, 4-ethoxybutan-1-yl, 2-iso-propoxyethan-1-yl, 3-iso-propoxypropan-1-yl, 4-iso-propoxybutan-1-yl, 2-hydroxyethan-1-yl, 3-hydroxy-propan-1-yl, 4-hydroxybutan-1-yl, preferably 3-hydroxybutan-2-yl, (2R,3R)-3-hydroxybutan-2-yl, (2S,3S)-3-hydroxybutan-2-yl, (2R,3S)-3-hydroxybutan-2-yl, (2S,3R)-3-hydroxybutan-2-yl, more preferably (2R,3R)-3-hydroxybutan-2-yl, (2S,3S)-3-hydroxybutan-2-yl.

For example, said -C_2-C_4-alkyl-OR^4 or -C_2-C_4-alkyl-OH is preferably 3-hydroxybutan-2-yl, (2R,3R)-3-hydroxybutan-2-yl, (2S,3S)-3-hydroxybutan-2-yl, (2R,3S)-3-hydroxybutan-2-yl, (2S,3R)-3-hydroxybutan-2-yl, more preferably (2R,3R)-3-hydroxybutan-2-yl, (2S,3S)-3-hydroxybutan-2-yl.

The term “alkoxy” is to be understood as meaning a linear or branched, saturated, monovalent, hydrocarbon group of formula –O-alkyl, in which the term “alkyl” is defined as meaning a linear or branched, saturated, monovalent hydrocarbon group with the number of carbon atoms atoms as specified and having as a rule, 1 to 3, preferably 1 to 2 alkyl substituents, especially preferably 1, carbon atoms. Particularly, said group has 1, 2 or 3 carbon atoms (“C_1-C_3-alkoxy”), *e.g.* a methoxy, ethoxy, n-propoxy or iso-propoxy group, and even more particularly 1 or 2 carbon atoms (“C_1-C_2-alkoxy”), *e.g.* a methoxy or ethoxy group.

The term “C_1-C_3-alkoxy optionally substituted with 1-5 halogen atoms” is to be understood as meaning a linear or branched, saturated, monovalent hydrocarbon group in which the term “C_1-C_3-alkoxy” is defined *supra*, and in which one or more hydrogen atoms is replaced by a halogen atom, which are the same or different, i.e. one halogen atom being independent from another. In particular, halogen is fluorine or chlorine.

Said “C_1-C_3-alkoxy” group is optionally substituted with 1 to 5 fluorine atoms, for example, –OCF_3, -$OCHF_2$, -OCH_2F, -OCF_2CF_3, -OCH_2CHF_2, -OCH_2CF_3, -$OCH_2CH_2CF_3$, or -$OCH_2CF_2CF_3$. In particular, said “C_1-C_3-alkoxy” group optionally substituted with fluorine is -OCF_3.

The term “C_2-C_6-alkynyl” is to be understood as meaning a linear or branched, monovalent hydrocarbon group which contains one or more triple bonds, preferably one triple bond, and which contains 2, 3, 4, 5 or 6 carbon atoms, particularly 3 or 4 carbon atoms (“C_3-C_4-alkynyl”). Said C_2-C_6-alkynyl group is, for example, ethynyl, prop-1-ynyl, prop-2-ynyl, but-1-ynyl, but-2-ynyl, but-3-ynyl, pent-1-ynyl, pent-2-ynyl, pent-3-ynyl, pent-4-ynyl, hex-1-ynyl, hex-2-ynyl, hex-3-ynyl, hex-4-ynyl, hex-5-ynyl, 1-methylprop-2-ynyl, 2-methylbut-3-ynyl, 1-methylbut-3-ynyl, 1-methylbut-2-ynyl, 3-methylbut-1-ynyl, 1-ethylprop-2-ynyl, 3-methylpent-4-ynyl, 2-methylpent-4-ynyl, 1-methylpent-4-ynyl, 2-methylpent-3-ynyl, 1-methylpent-3-ynyl, 4-methylpent2-ynyl, 1-methyl-

pent-2-ynyl, 4-methylpent-1-ynyl, 3-methylpent-1-ynyl, 2-ethylbut-3-ynyl, 1-ethylbut-3-ynyl, 1-ethylbut-2-ynyl, 1-propylprop-2-ynyl, 1-isopropylprop-2-ynyl, 2,2-dimethylbut-3-ynyl, 1,1-dimethylbut-3-ynyl, 1,1-dimethylbut-2-ynyl, or 3,3-dimethylbut-1-ynyl group. Particularly, said alkynyl group is prop-1-ynyl or prop-2-ynyl.

The term "cycloalkyl" is to be understood as meaning a saturated, monovalent, monocyclic hydrocarbon ring with the number of carbon atoms as specified and having as a rule, 3 to 7 or 3 to 6 ring carbon atoms, preferably 3 to 4 ring carbon atoms.

"C_3-C_7-cycloalkyl" is to be understood as meaning a saturated, monovalent, monocyclic hydrocarbon ring which contains 3, 4, 5, 6 or 7 carbon atoms. Said C_3-C_7-cycloalkyl group is for example a cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl ring. Each hydrogen of a cycloalkyl carbon may be replaced by a substituent as further specified. Particularly, said ring contains 3, 4, 5 or 6 carbon atoms ("C_3-C_6-cycloalkyl"), preferably 3 or 4 carbon atoms ("C_3-C_4-cycloalkyl").

In case of R^2 in formula (I) or (Ia), said "C_3-C_7-cycloalkyl" in "$(CH_2)_q$-(C_3-C_7-cycloalkyl)" is, unless indicated otherwise, optionally substituted with one or more substituents which are the same or different, at any ring carbon atom and selected from the group consisting of C_1-C_4 alkyl, optionally substituted with 1-5 halogen atoms which are the same or different, a halogen atom, -NR^aR^b, $COOR^5$ and oxo (=O). In case of R^2 in formula (I) or (Ia), said "C_3-C_4-cycloalkyl" as such or "C_3-C_4-cycloalkyl" in "CH_2-(C_3-C_4-cycloalkyl)" is, unless indicated otherwise, optionally substituted with one or more substituents which are the same or different, at any ring carbon atom and selected from a group consisting of C_1-C_4-alkyl, optionally substituted with 1-5 halogen atoms which are the same or different, a halogen atom, -NR^aR^b, -$COOR^5$ and oxo (=O).

The term "heterocycloalkyl" is to be understood as meaning a saturated, monovalent, monocyclic hydrocarbon ring with the number of ring atoms as specified in which one, two or three ring atoms of the hydrocarbon ring is/ are

replaced by one, two or three heteroatoms or heteroatom-containing groups independently selected from O, S, S(=O), $S(=O)_2$, or N.

"4- to 7-membered heterocycloalkyl" is to be understood as meaning a saturated, monovalent, monocyclic "heterocycloalkyl" ring as defined *supra* which contains 4, 5, 6 or 7 ring atoms.

Similarly, "4- to 6-membered heterocycloalkyl" is to be understood as meaning a saturated, monovalent, monocyclic "heterocycloalkyl" ring as defined *supra* which contains 4, 5 or 6 ring atoms.

In case of R^2 in formula (I) or (Ia), said 4- to 7-membered heterocycloalkyl or 4- to 6-membered heterocycloalkyl is, unless indicated otherwise, optionally substituted with one or more substituents which are the same or different, at any ring carbon atom and selected from the group consisting of C_1-C_4 alkyl, optionally substituted with 1-5 halogen atoms which are the same or different, a halogen atom, $-NR^aR^b$, $COOR^5$ and oxo (=O); and wherein independently any ring nitrogen atom, if present in said 4- to 7-membered or 4- to 6-membered heterocycloalkyl is substituted with R^c; it being possible for said 4- to 7-membered or 4- to 6-membered heterocycloalkyl group to be attached to the rest of the molecule via any one of the carbon atoms or, if present, a nitrogen atom. Accordingly, any ring nitrogen atom if present in said 4- to 7-membered or 4- to 6-membered heterocycloalkyl group is only substituted with R^c, if the designated atom's normal valency under the existing circumstances is not exceeded.

Particularly, said 4- to 7-membered heterocycloalkyl can contain 3, 4, 5 or 6 carbon atoms, and one or two of the above-mentioned heteroatoms or heteroatom-containing groups provided that the total number of ring atoms is not greater than 7, more particularly said heterocycloalkyl can contain 3, 4 or 5 carbon atoms, and one or two of the above-mentioned heteroatoms or heteroatom-containing groups provided that the total number of ring atoms is not greater than 6 (a "4- to 6-membered heterocycloalkyl").

Particularly, without being limited thereto, said heterocycloalkyl can be a 4-membered ring, such as an azetidinyl, oxetanyl, or a 5-membered ring, such as tetrahydrofuranyl, dioxolinyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, or a

6-membered ring, such as tetrahydropyranyl, piperidinyl, morpholinyl, dithianyl, thiomorpholinyl, piperazinyl, or a 7-membered ring, such as a diazepanyl ring, for example.

Particularly, without being limited thereto, said heterocycloalkyl can be in a more preferred embodiment (3R)-tetrahydrofuran-3-yl, (3S)-tetrahydrofuran-3-yl, 4-methylmorpholin-2-yl, (2R)-4-methylmorpholin-2-yl, (2S)-4-methylmorpholin-2-yl, 4-methylmorpholin-3-yl, (3R)-4-methylmorpholin-3-yl, or (3S)-4-methylmorpholin-3-yl, most preferred (2R)-4-methylmorpholin-2-yl.

The term "6- to 12-membered heterobicycloalkyl" is to be understood as meaning a saturated, monovalent bicyclic hydrocarbon radical in which the two rings share one or two common ring atoms, and wherein said bicyclic hydrocarbon radical contains 5, 6, 7, 8, 9 or 10 carbon atoms and one, two or three heteroatoms or heteroatom-containing groups independently selected from O, S, S(=O), $S(=O)_2$, or N, provided that the total number of ring atoms is not greater than 12. Said 6- to 12-membered heterobicycloalkyl is, unless indicated otherwise, optionally substituted with one or more substituents, which are the same or different, at any ring carbon atom and selected from the group consisting of C_1-C_4 alkyl, optionally substituted with 1-5 halogen atoms which are the same or different, a halogen atom, $-NR^aR^b$, $COOR^5$ and oxo (=O); and wherein independently any ring nitrogen atom, if present in said 6- to 12-membered heterobicycloalkyl is substituted with R^c; it being possible for said 6- to 12-membered heterobicycloalkyl to be attached to the rest of the molecule via any one of the carbon atoms or, if present, a nitrogen atom. Accordingly, any ring nitrogen atom if present in said 6- to 12-membered heterobicycloalkyl is only substituted with Rc, if the designated atom's normal valency under the existing circumstances is not exceeded. Said 6- to 12-membered heterobicycoalkyl is, for example, azabicyclo[3.3.0]octyl, azabicyclo-[4.3.0]nonyl, diazabicyclo[4.3.0]nonyl, oxazabicyclo[4.3.0]nonyl, thiazabicyclo-[4.3.0]nonyl or azabicyclo[4.4.0]decyl.

Heterospirocycloalkyl and bridged heterocycloalkyl, as defined below, are also included within the scope of this definition.

The term "heterospirocycloalkyl" is to be understood as meaning a saturated, monovalent bicyclic hydrocarbon radical in which the two rings share one common ring atom, and wherein said bicyclic hydrocarbon radical contains 5, 6, 7, 8, 9 or 10 carbon atoms, and one, two or three heteroatoms or heteroatom-containing groups independently selected from O, S, S(=O), $S(=O)_2$, or N, provided that the total number of ring atoms is not greater than 12. It is possible for said heterospirocycloalkyl to be attached to the rest of the molecule via any one of the carbon atoms or, if present, a nitrogen atom. Said heterospirocycloalkyl is, for example, azaspiro[2.3]hexyl, azaspiro[3.3]heptyl, oxaazaspiro[3.3]heptyl, thiaazaspiro[3.3]heptyl, oxaspiro[3.3]heptyl, oxazaspiro[5.3]nonyl, oxazaspiro[4.3]octyl, oxazaspiro[5.5]undecyl, diazaspiro[3.3]heptyl, thiazaspiro[3.3]heptyl, thiazaspiro[4.3]octyl, or azaspiro[5.5]decyl.

The term "bridged heterocycloalkyl" is to be understood as meaning a saturated, monovalent bicyclic hydrocarbon radical in which the two rings share two common ring atoms which are not immediately adjacent, and wherein said bicyclic hydrocarbon radical contains 5, 6, 7, 8, 9 or 10 carbon atoms, and one, two or three heteroatoms or heteroatom-containing groups independently selected from O, S, S(=O), $S(=O)_2$, or N, provided that the total number of ring atoms is not greater than 12. It is possible for said bridged heterocycloalkyl to be attached to the rest of the molecule via any one of the carbon atoms or, if present, a nitrogen atom. Said bridged heterocycloalkyl is, for example, azabicyclo[2.2.1]heptyl, oxazabicyclo[2.2.1]heptyl, thiazabicyclo[2.2.1]heptyl, diazabicyclo[2.2.1]heptyl, azabicyclo[2.2.2]octyl, diazabicyclo[2.2.2]octyl, oxazabicyclo[2.2.2]octyl, thiazabicyclo[2.2.2]octyl, azabicyclo[3.2.1]octyl, diazabicyclo[3.2.1]octyl, oxazabicyclo[3.2.1]octyl, thiazabicyclo[3.2.1]octyl, azabicyclo[3.3.1]nonyl, diazabicyclo[3.3.1]nonyl, oxazabicyclo[3.3.1]nonyl, thiazabicyclo[3.3.1]nonyl, azabicyclo[4.2.1]nonyl, diazabicyclo[4.2.1]nonyl, oxazabicyclo[4.2.1]nonyl, thiazabicyclo[4.2.1]nonyl, azabicyclo[3.3.2]decyl, diazabicyclo[3.3.2]decyl, oxazabicyclo[3.3.2]decyl, thiazabicyclo[3.3.2]decyl, or azabicyclo[4.2.2]decyl.

The term "heteroaryl" is understood as meaning a monovalent, monocyclic or bicyclic hydrocarbon ring system with at least one aromatic ring with the number of ring system atoms as specified and wherein one, two or three ring atoms of the monovalent, monocyclic or bicyclic hydrocarbon ring system is/are replaced by one, two or three heteroatoms or heteroatom-containing groups independently selected from O, S, S(=O), $S(=O)_2$, or N.

"5- to 10-membered heteroaryl" is understood as meaning a heteroaryl having 5, 6, 7, 8, 9 or 10 ring atoms (a "5- to 10-membered heteroaryl") and wherein one, two or three ring atoms of the monovalent, monocyclic or bicyclic hydrocarbon ring system is/are replaced by one, two or three heteroatoms or heteroatom-containing groups independently selected from O, S, S(=O), $S(=O)_2$, or N. Particularly, heteroaryl is selected from thienyl, furanyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, thiadiazolyl, thia-4*H*-pyrazolyl *etc.* and benzo derivatives thereof, such as, for example, benzofuranyl, benzothienyl, benzoxazolyl, benzisoxazolyl, benzimidazolyl, benzotriazolyl, indazolyl, indolyl, isoindolyl, *etc.*; or pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, *etc.*, and benzo derivatives thereof, such as, for example, quinolinyl, quinazolinyl, isoquinolinyl, *etc.*; indolizinyl, and benzo derivatives thereof; or cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, etc.
In case of R^2 of formula (I) or (Ia), said 5- to 10-membered heteroaryl is, unless indicated otherwise, optionally substituted with one or more substituents which are the same or different, and selected from the group consisting of C_1-C_4-alkyl, optionally substituted with 1-5 halogen atoms which are the same or different, a halogen atom, $-NR^aR^b$ and $-COOR^5$.
In case of R^2 of formula (I) or (Ia), said 5- to 10-membered heteroaryl optionally substituted as described above, can be in particular substituted with C_1-C_2-alkyl at any ring N, if present.

In case of A of formula (I) or (Ia), said 5- to 10-membered heteroaryl is, unless indicated otherwise, optionally substituted with one or more substituents, which are the same or different, and selected from the group consisting of a halogen atom, C_1-C_3-alkyl, and C_1-C_3-alkoxy, wherein C_1-C_3-alkyl and C_1-C_3-alkoxy are optionally substituted with 1-5 halogen atoms which are the same or different.

In case of A of formula (I) or (Ia), a "5- or 6-membered heteroaryl" is understood as meaning a heteroaryl having 5 or 6 ring atoms and wherein one, two or three ring atoms of the hydrocarbon ring system is/are replaced by one, two or three heteroatoms or heteroatom-containing groups independently selected from O, S, S(=O), $S(=O)_2$, or N. Said "5- or 6-membered heteroaryl" is, unless indicated otherwise, optionally substituted with one or more substituents, which are the same or different, and selected from the group consisting of a halogen atom, C_1-C_3-alkyl, and C_1-C_3-alkoxy, wherein C_1-C_3-alkyl and C_1-C_3 alkoxy are optionally substituted with 1-5 halogen atoms which are the same or different

A 5-membered heteroaryl group is preferably selected from thienyl, furanyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, thiadiazolyl, thia-4H-pyrazolyl.

A 6-membered heteroaryl group is preferably selected from pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl.

In particular, said 5- or 6-membered heteroaryl is, optionally substituted with preferably one or two substituents, which are the same or different, and selected from a fluorine or chlorine atom, C_1-C_2-alkyl, optionally substituted with 1-5 fluorine atoms, or C_1-C_2-alkoxy, optionally substituted with 1-5 fluorine atoms.

In particular, said 5- or 6-membered heteroaryl is a 6-membered heteroaryl with one or two nitrogen atom(s) and is optionally substituted with one or two substituents, which are the same or different, and selected from a fluorine or chlorine atom, C_1-C_2-alkyl, optionally substituted with 1-5 fluorine atoms, or C_1-C_2-alkoxy, optionally substituted with 1-5 fluorine atoms.

Preferably said 6-membered heteroaryl is CF_3-pyrimidinyl, most preferably 2-CF_3-pyrimidin-5-yl. Also preferred is CF_3-pyridazinyl, most preferably 6-CF_3-pyridazin-3-yl.

In general, and unless otherwise mentioned, the term "heteroaryl" includes all possible isomeric forms thereof, e.g. the positional isomers thereof. Thus, for some illustrative non-restricting example, the term pyridyl includes pyridin-2-yl, pyridin-3-yl, and pyridin-4-yl; or the term pyrimidinyl includes pyrimidin-2-yl, pyrimidin-4-

yl and pyrimidin-5-yl; or the term pyridazinyl includes pyridazin-3-yl and pyridazin-4-yl; or the term thiazolyl includes 1,3-thiazol-5-yl, 1,3-thiazol-4-yl and 1,3-thiazol-2-yl.

The term "C_1-C_4" as used throughout this text is to be understood as meaning a group having a finite number of carbon atoms of 1 to 4, *i.e.* 1, 2, 3 or 4 carbon atoms, *e.g.* in the context of the definition of "C_1-C_4-alkyl", it is to be understood as meaning an alkyl group having a finite number of carbon atoms of 1 to 4, *i.e.* 1, 2, 3 or 4 carbon atoms.

The term "C_2-C_6" as used throughout this text is to be understood as meaning a group having a finite number of carbon atoms of 2 to 6, *i.e.* 2, 3, 4, 5 or 6 carbon atoms, *e.g.* in the context of the definition of "C_2-C_6-alkyl", it is to be understood as meaning an alkyl group having a finite number of carbon atoms of 2 to 6, *i.e.* 2, 3, 4, 5 or 6 carbon atoms. It is to be understood further that said term "C_2-C_6" is to be interpreted as any sub-range comprised therein, *e.g.* C_2-C_6 , C_3-C_5 , C_3-C_4 , C_2-C_3 , C_2-C_4 , C_2-C_5 ; particularly C_2-C_3.

The term "C_1-C_3" as used in the context of the definition "C_1-C_3-alkoxy" is to be understood as meaning an alkoxy group, having a finite number of carbon atoms of 1 to 3, *i.e.* 1, 2 or 3 carbon atoms.

The same applies to other mentioned "alkyl", alkynyl or "alkoxy" as mentioned herein and as it is to be understood by a skilled person.

It is to be understood further that for example a term "C_1-C_6" is to be interpreted as any sub-range comprised therein, *e.g.* C_1-C_6 , C_2-C_3, C_2-C_6 , C_3-C_4 , C_1-C_2 , C_1-C_3 , C_1-C_4 , C_1-C_5 ; particularly C_1-C_2 , C_1-C_3 , C_1-C_4 , C_1-C_5, C_1-C_6; more particularly C_1-C_4.

Similarly, the mentioned above applies to "C_1-C_4-alkyl", "C_1-C_3-alkyl", "C_1-C_3-alkoxy", "C_1-C_2-alkyl" or "C_1-C_2-alkoxy" optionally substituted with 1-5 halogen which are the same or different.

Similarly, as used herein, the term "C_2-C_6", as used throughout this text, *e.g.* in the context of the definitions of "C_2-C_6-alkynyl", is to be understood as meaning an alkynyl group having a finite number of carbon atoms of 2 to 6, *i.e.* 2, 3, 4, 5, or 6

carbon atoms. It is to be understood further that said term "C_2-C_6" is to be interpreted as any sub-range comprised therein, *e.g.* C_2-C_6, C_3-C_5, C_3-C_4, C_2-C_3, C_2-C_4, C_2-C_5; particularly C_2-C_3 and C_2-C_4.

Further, as used herein, the term "C_3-C_7", as used throughout this text, is to be understood as meaning a group having a finite number of carbon atoms of 3 to 7, *i.e.* 3, 4, 5, 6 or 7 carbon atoms, *e.g.* in the context of the definition of "C_3-C_7-cycloalkyl", it is to be understood as meaning a cycloalkyl group having a finite number of carbon atoms of 3 to 7, *i.e.* 3, 4, 5, 6 or 7 carbon atoms. It is to be understood further that said term "C_3-C_7" is to be interpreted as any sub-range comprised therein, *e.g.* C_3-C_6, C_4-C_5, C_3-C_5, C_3-C_4, C_4-C_6, C_5-C_7; particularly C_3-C_6.

The term "substituted" means that one or more hydrogens on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valency under the existing circumstances is not exceeded, and that the substitution results in a stable compound. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

The term "optionally substituted" means that the number of substituents can be zero. Unless otherwise indicated, optionally substituted groups may be 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 atom. Commonly, the number of optional substituents (when present) ranges from 1 to 5, in particular from 1 to 3.

As used herein, the term "one or more", *e.g.* in the definition of the substituents of the compounds of the general formulae of the present invention, is understood as meaning "one, two, three, four or five, particularly one, two, three or four, more particularly one, two or three, even more particularly one or two".

The invention also includes all suitable isotopic variations of a compound of the invention. An isotopic variation of a compound of the invention is defined as one in which at least one atom is replaced by an atom having the same atomic number but an atomic mass different from the atomic mass usually or predominantly found in nature. Examples of isotopes that can be incorporated into a compound of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, sulphur, fluorine and chlorine such as ^{2}H (deuterium), ^{3}H (tritium), ^{11}C, ^{13}C, ^{14}C, ^{15}N, ^{17}O, ^{18}O, ^{33}S, ^{34}S, ^{35}S, ^{36}S, ^{18}F and ^{36}Cl, , respectively. Certain isotopic variations of a compound of the invention, for example, those in which one or more radioactive isotopes such as ^{3}H or ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution studies. Tritiated and carbon-14, i.e., ^{14}C, isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with isotopes such as deuterium may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased in vivo half-life or reduced dosage requirements and hence may be preferred in some circumstances. Isotopic variations of a compound of the invention can generally be prepared by conventional procedures known by a person skilled in the art such as by the illustrative methods or by the preparations described in the examples hereafter using appropriate isotopic variations of suitable reagents.

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.*, chiral HPLC columns), with or without conventional derivatisation, optimally chosen to maximise the separation of the enantiomers. Suitable chiral HPLC columns are manufactured by Daicel, *e.g.*, Chiracel OD and Chiracel OJ among many others, all routinely

selectable. Enzymatic separations, with or without derivatisation, are also useful. The optically active forms of compounds of formula (I) can likewise be obtained by chiral syntheses utilizing optically active starting materials.

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

Further, compounds may exist as tautomers.

The present compounds of formula (I) includes all possible tautomers as single tautomers, or as any mixture of said tautomers, in any ratio.

The present invention also relates to the use of useful forms of compounds of formula (I), such as metabolites, hydrates, solvates, prodrugs, salts, in particular pharmaceutically acceptable salts, and co-precipitates.

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.

Compounds of formula (I) can exist as a hydrate, or as a solvate, wherein compounds of formula (I) contain polar solvents, in particular water, methanol or ethanol for example as structural element of the crystal lattice of the compounds. The amount of polar solvents, in particular water, may 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 compounds include all such hydrates or solvates.

Further, compounds of formula (I) can exist in free form, *e.g.* as a free base, or as a free acid, or as a zwitterion, or can 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, customarily used in pharmacy.

The term "pharmaceutically acceptable salt" refers to a relatively non-toxic, inorganic or organic acid addition salt of compounds of formula (I). 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 compounds of formula (I) 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, such as hydrochloric, hydrobromic, hydroiodic, sulfuric, 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, persulfuric, 3-phenylpropionic, picric, pivalic, 2-hydroxyethanesulfonate, itaconic, sulfamic, trifluoromethanesulfonic, dodecylsulfuric, ethansulfonic, benzenesulfonic, para-toluenesulfonic, methansulfonic, 2-naphthalenesulfonic, naphthalinedisulfonic, camphorsulfonic acid, citric, tartaric, stearic, lactic, oxalic, malonic, succinic, malic, adipic, alginic, maleic, fumaric, D-gluconic, mandelic, ascorbic, glucoheptanoic, glycerophosphoric, aspartic, sulfosalicylic, hemisulfuric, or thiocyanic acid, for example.

Further, another suitably pharmaceutically acceptable salt of a compound of formula (I) 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 or magnesium salt, an ammonium salt or a salt with an organic base which affords a physiologically acceptable cation, for example a salt with N-methyl-glucamine, dimethyl-glucamine, ethyl-glucamine, lysine, dicyclohexylamine, 1,6-hexadiamine, ethanolamine, glucosamine, sarcosine, serinol, tris-hydroxy-methyl-aminomethane,

aminopropandiol, sovak-base, 1-amino-2,3,4-butantriol. Additionally, basic nitrogen containing groups may be quaternised with such agents as lower alkyl halides such as methyl, ethyl, propyl, and butyl chlorides, bromides and iodides ; dialkyl sulfates like dimethyl, diethyl, and dibutyl sulfate ; and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides, aralkyl halides like benzyl and phenethyl bromides and others.

Those skilled in the art will further recognise that acid addition salts of compounds of formula (I) may 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 invention are prepared by reacting the compounds of the invention with the appropriate base via a variety of known methods.

The present invention includes all possible salts of compounds of formula (I) as single salts, or as any mixture of said salts, in any ratio.

Unless otherwise indicated, compounds of formula (I) are also referred to isomers, enantiomers, diastereomers, racemates, hydrates, solvates, or a salt thereof, or a mixture of same.

As used herein, the term "*in vivo* hydrolysable ester" is understood as meaning an *in vivo* hydrolysable ester of a compound of formula (I) containing a carboxy or hydroxy group, for example, a pharmaceutically acceptable ester which is hydrolysed in the human or animal body to produce the parent acid or alcohol. Suitable pharmaceutically acceptable esters for carboxy include for example alkyl, cycloalkyl and optionally substituted phenylalkyl, in particular benzyl esters, C_1-C_6 alkoxymethyl esters, *e.g.* methoxymethyl, C_1-C_6 alkanoyloxymethyl esters, *e.g.* pivaloyloxymethyl, phthalidyl esters, C_3-C_8 cycloalkoxy-carbonyloxy-C_1-C_6 alkyl esters, *e.g.* 1-cyclohexylcarbonyloxyethyl; 1,3-dioxolen-2-onylmethyl esters, *e.g.* 5-methyl-1,3-dioxolen-2-onylmethyl; and C_1-C_6-alkoxycarbonyloxyethyl esters, *e.g.* 1-methoxycarbonyloxyethyl, and may be formed at any carboxy group in the compounds of formula (I) . An *in vivo* hydrolysable ester of a compound of formula (I) containing a hydroxy group includes inorganic esters such as phosphate esters and [alpha]-acyloxyalkyl ethers and related compounds which as a result of the *in vivo* hydrolysis of the ester breakdown to give the parent hydroxy group. Examples of [alpha]-acyloxyalkyl ethers include acetoxymethoxy and

2,2-dimethylpropionyloxymethoxy. A selection of *in vivo* hydrolysable ester forming groups for hydroxy include alkanoyl, benzoyl, phenylacetyl and substituted benzoyl and phenylacetyl, alkoxycarbonyl (to give alkyl carbonate esters), dialkylcarbamoyl and N-(dialkylaminoethyl)-N-alkylcarbamoyl (to give carbamates), dialkylaminoacetyl and carboxyacetyl. The present invention covers all such esters.

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

Heart failure is defined by the European Socient of Cardiology treatment guidelines as a symptomatic clinical manifestation of heart systolic or diastolic functional abnormalities resulting in reduced cardiac output and/ or elevated intracardiac pressures at rest or during stress. Systolic and/or diastolic functional abnormalities can also result from genetic predisposition, abnormalities in the myocardium, valves, endocardium, pericardium and conduction system of the heart. Heart failure with preserved, mid-range, and reduced ejection fraction are defined as ejection fractions ≥50%, 40-49%, and <40% respectively (Ponikowski et al. Eur Heart J. 2016.37:27(2129-200)).

Hypertension is the most common cardiovascular disease comorbidity and is clearly associated with increased event rates in cardiovascular disease and heart failure. Hypertension is defined by the European Society of Hypertension as arterial systolic blood pressure values >140 mmHg and/or diastolic blood pressure values >90 mmHg (Mancia et al. J Hypertens 2013. 31:7(1281-357)).

Cheyne-Stokes respiration is an abnormal breathing pattern that can occur during sleep or wakefulness. Cheyne-Stokes respiration is characterized by a periodic crescendo/decreshendo breathing pattern - gradually increasing speed and depth of breathing followed by a decrease in depth and frequency of breathing. This pattern also results in periodic apnea and cessation of breathing.

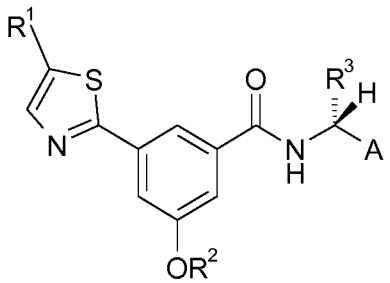
Central sleep apnea is characterized by periodic diminished or lack of respiratory effort during sleep. It is normally associated with symptoms such as frequent arousal during sleep and daytime sleepiness or both.

"Therapeutically effective amount" means an amount of a compound that, when administered to a subject for treating a disease state, is sufficient to effect such treatment for the disease state. The "therapeutically effective amount" will vary depending on the compound, disease state being treated, the severity or the disease treated, the age and relative health of the subject, the route and form of administration, the judgment of the attending medical or veterinary practitioner, and other factors.

"Treating" or "treatment" of a disease state includes: (i) inhibiting the disease state, i.e. arresting the development of the disease state or its clinical symptoms, or (ii) relieving the disease state, i.e. causing temporary or permanent regression of the diseasestate or its clinical symptoms.

"Preventing" or "prevention" of a disease state includes causing the clinical symptoms of the disease state not to develop in a subject that may be exposed to or predisposed to the disease state, but does not yet experience or display symptoms of the disease state. For example, treating or preventing a respiratory disease or disorder includes treating or preventing the symptoms the disorder such as cough and/ or urge to cough associated with a respiratory disease.

Another embodiment of the present invention relates to a method for using compounds of general formula (Ia),



(Ia)

in which A, R^1, R^2 and R^3 have the meanings as defined in formula (I), preferably R^3 represents C_1-C_4-alkyl, more preferably methyl;

or an isomer, enantiomer, diastereomer, racemate, hydrate, solvate, or a salt thereof, or a mixture of same for the treatment or prophylaxis of diseases or disorders which are 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.

Another embodiment of the present invention relates to a method for using compounds of general formula (I), wherein

A represents an optionally substituted 5- or 6-membered heteroaryl, preferably an optionally substituted 6-membered heteroaryl; and

in which R^1, R^2 and R^3 have the same meaning as defined in general formula (I),

or an isomer, enantiomer, diastereomer, racemate, hydrate, solvate, or a salt thereof, or a mixture of same for the treatment or prophylaxis of diseases or disorders which are 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.

Another embodiment of the present invention relates to a method for using compounds of general formula (Ia), wherein

A represents an optionally substituted 5- or 6-membered heteroaryl, preferably an optionally substituted 6-membered heteroaryl; and

in which R^1, R^2 and R^3 have the same meaning as defined in general formula (Ia),

or an isomer, enantiomer, diastereomer, racemate, hydrate, solvate, or a salt thereof, or a mixture of same for the treatment or prophylaxis of diseases or disorders which are 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.

Additionally, an embodiment of the present invention relates to a method for using compounds of general formula (I), wherein

R^1 represents C_1-C_4-alkyl, preferably methyl or ethyl; and

in which A, R^2 and R^3 have the same meaning as defined in general formula (I),

or an isomer, enantiomer, diastereomer, racemate, hydrate, solvate, or a salt thereof, or a mixture of same for the treatment or prophylaxis of diseases or disorders which are 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.

Another embodiment of the present invention relates to a method for using are compounds of general formula (Ia), wherein

R^1 represents C_1-C_4-alkyl, preferably methyl or ethyl; and

in which A, R^2 and R^3 have the same meaning as defined in general formula (Ia),

or an isomer, enantiomer, diastereomer, racemate, hydrate, solvate, or a salt thereof, or a mixture of same for the treatment or prophylaxis of diseases or disorders which are 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.

Another embodiment of the present invention relates to a method for using compounds of general formula (I), wherein

R^1 represents a halogen atom, preferably chloro; and

in which A, R^2 and R^3 have the same meaning as defined in general formula (I),

or an isomer, enantiomer, diastereomer, racemate, hydrate, solvate, or a salt thereof, or a mixture of same for the treatment or prophylaxis of diseases or disorders which are 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.

Another embodiment of the present invention relates to a method for using compounds of general formula (Ia), wherein

R^1 represents a halogen atom, preferably chloro; and

in which A, R^2 and R^3 have the same meaning as defined in general formula (Ia),

or an isomer, enantiomer, diastereomer, racemate, hydrate, solvate, or a salt thereof, or a mixture of same for the treatment or prophylaxis of diseases or disorders which are 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.

Another embodiment of the present invention relates to a method for using compounds of general formula (I), more preferably compounds of general formula (Ia), wherein

R^3 represents C_1-C_4- alkyl, preferably methyl; and

in which R^1, R^2 and A have the same meaning as defined in general formula (I),

or an isomer, enantiomer, diastereomer, racemate, hydrate, solvate, or a salt thereof, or a mixture of same for the treatment or prophylaxis of diseases or

disorders which are 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.

Another embodiment of the present invention relates to a method for using compounds of general formula (I), wherein

R^2 represents -C_2-C_4-alkyl-OR^4, -CH_2-(C_3-C_4-cycloalkyl), C_3-C_4-cycloalkyl, -$(CH_2)_q$-(4- to 6-membered heterocycloalkyl), or -C_2-C_4-alkynyl; and

wherein said -CH_2-(C_3-C_4-cycloalkyl), C_3-C_4-cycloalkyl and -$(CH_2)_q$-(4- to 6-membered heterocycloalkyl) are optionally substituted with one or more substituents which are the same or different, at any ring carbon atom; and

wherein independently any ring nitrogen atom, if present in said -$(CH_2)_q$-(4- to 6-membered heterocycloalkyl) is substituted with R^c;

q represents an integer of 0; and

in which A, R^c, R^1 and R^3 have the same meaning as defined in general formula (I),

or an isomer, enantiomer, diastereomer, racemate, hydrate, solvate, or a salt thereof, or a mixture of same for the treatment or prophylaxis of diseases or disorders which are 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.

Another embodiment of the present invention relates to a method for using compounds of general formula (I), wherein

R^2 represents -C_2-C_3-alkyl-OR^4, -CH_2-(C_3-C_4-cycloalkyl), C_3-C_4-cycloalkyl, -$(CH_2)_q$-(4- to 6-membered heterocycloalkyl), or -C_2-C_4-alkynyl; and

wherein said -CH_2-(C_3-C_4-cycloalkyl), C_3-C_4-cycloalkyl and -$(CH_2)_q$-(4- to 6-membered heterocycloalkyl) are optionally substituted with one or more substituents which are the same or different, at any ring carbon atom; and

wherein independently any ring nitrogen atom, if present in said -$(CH_2)_q$-(4- to 6-membered heterocycloalkyl) is substituted with R^c;

q represents an integer of 0; and

in which A, R^c, R^1 and R^3 have the same meaning as defined in general formula (I),

or an isomer, enantiomer, diastereomer, racemate, hydrate, solvate, or a salt thereof, or a mixture of same for the treatment or prophylaxis of diseases or disorders which are 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.

Another embodiment of the present invention relates to a method for using compounds of general formula (Ia), wherein

R^2 represents -C_2-C_4-alkyl-OR^4, -CH_2-(C_3-C_4-cycloalkyl), C_3-C_4-cycloalkyl, -$(CH_2)_q$-(4- to 6-membered heterocycloalkyl), or -C_2-C_4-alkynyl; and

wherein said -CH_2-(C_3-C_4-cycloalkyl), C_3-C_4-cycloalkyl and -$(CH_2)_q$-(4- to 6-membered heterocycloalkyl) are optionally substituted with one or more substituents which are the same or different, at any ring carbon atom; and

wherein independently any ring nitrogen atom, if present in said -$(CH_2)_q$-(4- to 6-membered heterocycloalkyl) is substituted with R^c;

q represents an integer of 0; and

in which A, R^c, R^1 and R^3 have the same meaning as defined in general formula (Ia),

or an isomer, enantiomer, diastereomer, racemate, hydrate, solvate, or a salt thereof, or a mixture of same for the treatment or prophylaxis of diseases or disorders which are 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.

Another embodiment of the present invention relates to a method for using compounds of general formula (Ia), wherein

R^2 represents -C_2-C_3-alkyl-OR^4, -CH_2-(C_3-C_4-cycloalkyl), C_3-C_4-cycloalkyl, -$(CH_2)_q$-(4- to 6-membered heterocycloalkyl), or -C_2-C_4-alkynyl; and

wherein said -CH_2-(C_3-C_4-cycloalkyl), C_3-C_4-cycloalkyl and -$(CH_2)_q$-(4- to 6-membered heterocycloalkyl) are optionally substituted with one or more substituents which are the same or different, at any ring carbon atom; and

wherein independently any ring nitrogen atom, if present in said -$(CH_2)_q$-(4- to 6-membered heterocycloalkyl) is substituted with R^c;

q represents an integer of 0; and

in which A, R^c, R^1 and R^3 have the same meaning as defined in general formula (Ia),

or an isomer, enantiomer, diastereomer, racemate, hydrate, solvate, or a salt thereof, or a mixture of same for the treatment or prophylaxis of diseases or disorders which are 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.

Another embodiment of the present invention relates to a method for using compounds of general formula (I), wherein

R^2 represents -$(CH_2)_q$-(4- to 6-membered heterocycloalkyl); and wherein $(CH_2)_q$-(4- to 6-membered heterocycloalkyl) is optionally substituted with one or more substituents which are the same or different, at any ring carbon atom; and

wherein independently any ring nitrogen atom, if present in said -$(CH_2)_q$-(4 to 6-membered heterocycloalkyl) is substituted with R^c; and wherein -$(CH_2)_q$-(4- to 6-membered heterocycloalkyl) is preferably -$(CH_2)_q$-morpholinyl; and

q represents an integer of 1; and

in which A, R^c, R^1 and R^3 have the same meaning as defined in general formula (I),

or an isomer, enantiomer, diastereomer, racemate, hydrate, solvate, or a salt thereof, or a mixture of same for the treatment or prophylaxis of diseases or disorders which are 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.

Another embodiment of the present invention relates to a method for using compounds of general formula (I), wherein

R^2 represents-$(CH_2)_q$-morpholinyl, wherein the ring nitrogen atom is substituted with R^c; and

R^c represents methyl;

q represents an integer of 1; and

in which A, R^1 and R^3 have the same meaning as defined in general formula (I),

or an isomer, enantiomer, diastereomer, racemate, hydrate, solvate, or a salt thereof, or a mixture of same for the treatment or prophylaxis of diseases or disorders which are 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.

Another embodiment of the present invention relates to a method for using compounds of general formula (Ia), wherein

R^2 represents -$(CH_2)_q$-(4- to 6-membered heterocycloalkyl); and wherein $(CH_2)_q$-(4- to 6-membered heterocycloalkyl) is optionally substituted with one or more substituents which are the same or different, at any ring carbon atom; and

wherein independently any ring nitrogen atom, if present in said -$(CH_2)_q$-(4 to 6-membered heterocycloalkyl) is substituted with R^c; and wherein -$(CH_2)_q$-(4- to 6-membered heterocycloalkyl) is preferably -$(CH_2)_q$-morpholinyl; and

q represents an integer of 1; and

in which A, R^c, R^1 and R^3 have the same meaning as defined in general formula (Ia),

or an isomer, enantiomer, diastereomer, racemate, hydrate, solvate, or a salt thereof, or a mixture of same for the treatment or prophylaxis of diseases or disorders which are 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.

Another embodiment of the present invention relates to a method for using compounds of general formula (Ia), wherein

R^2 represents-$(CH_2)_q$-morpholinyl, wherein the ring nitrogen atom is substituted with R^c; and

R^c represents methyl;

q represents an integer of 1; and

in which A, R^1 and R^3 have the same meaning as defined in general formula (Ia),

or an isomer, enantiomer, diastereomer, racemate, hydrate, solvate, or a salt thereof, or a mixture of same for the treatment or prophylaxis of diseases or disorders which are 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.

Another embodiment of the present invention relates to a method for using compounds of general formula (I), wherein

R^2 represents -C_2-C_4-alkyl-OH; and

in which A, R^1 and R^3 have the same meaning as defined in general formula (I),

or an isomer, enantiomer, diastereomer, racemate, hydrate, solvate, or a salt thereof, or a mixture of same for the treatment or prophylaxis of diseases or disorders which are 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.

Another embodiment of the present invention relates to a method for using to compounds of general formula (Ia), wherein

R^2 represents -C_2-C_4-alkyl-OH; and

in which A, R^1 and R^3 have the same meaning as defined in general formula (Ia),

or an isomer, enantiomer, diastereomer, racemate, hydrate, solvate, or a salt thereof, or a mixture of same for the treatment or prophylaxis of diseases or disorders which are 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.

Another embodiment of the present invention relates to a method for using compounds of general formula (I), wherein

A represents an optionally substituted 5- or 6-membered heteroaryl, preferably an optionally substituted 6-membered heteroaryl; and

R^1 represents C_1-C_4-alkyl, preferably methyl or ethyl; and

in which R^2 and R^3 have the same meaning as defined in general formula (I),

or an isomer, enantiomer, diastereomer, racemate, hydrate, solvate, or a salt thereof, or a mixture of same for the treatment or prophylaxis of diseases or disorders which are 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.

Another embodiment of the present invention relates to a method for using compounds of general formula (Ia), wherein

A represents an optionally substituted 5- or 6-membered heteroaryl, preferably an optionally substituted 6-membered heteroaryl; and

R^1 represents C_1-C_4-alkyl, preferably methyl or ethyl; and

in which R^2 and R^3 have the same meaning as defined in general formula (Ia),

or an isomer, enantiomer, diastereomer, racemate, hydrate, solvate, or a salt thereof, or a mixture of same for the treatment or prophylaxis of diseases or disorders which are 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.

Another embodiment of the present invention relates to a method for using compounds of general formula (I), wherein

A represents an optionally substituted 5- or 6-membered heteroaryl, preferably an optionally substituted 6-membered heteroaryl; and

R^1 represents a halogen atom, preferably chloro; and

in which R^2 and R^3 have the same meaning as defined in general formula (I),

or an isomer, enantiomer, diastereomer, racemate, hydrate, solvate, or a salt thereof, or a mixture of same for the treatment or prophylaxis of diseases or disorders which are 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.

Another embodiment of the present invention relates to a method for using compounds of general formula (Ia), wherein

A represents an optionally substituted 5- or 6-membered heteroaryl, preferably an optionally substituted 6-membered heteroaryl; and

R^1 represents a halogen atom, preferably chloro; and

in which R^2 and R^3 have the same meaning as defined in general formula (Ia),

or an isomer, enantiomer, diastereomer, racemate, hydrate, solvate, or a salt thereof, or a mixture of same for the treatment or prophylaxis of diseases or disorders which are 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.

Another embodiment of the present invention relates to a method for using compounds of general formula (I), more preferably compounds of general formula (Ia), wherein

A represents an optionally substituted 5- or 6-membered heteroaryl, preferably an optionally substituted 6-membered heteroaryl; and

R^3 represents C_1-C_4-alkyl, preferably methyl; and

in which R^1 and R^2 have the same meaning as defined in general formula (I),

or an isomer, enantiomer, diastereomer, racemate, hydrate, solvate, or a salt thereof, or a mixture of same for the treatment or prophylaxis of diseases or disorders which are 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.

Another embodiment of the present invention relates to a method for using compounds of general formula (I), more preferably compounds of general formula (Ia), wherein

A represents an optionally substituted 5- or 6-membered heteroaryl, preferably an optionally substituted 6-membered heteroaryl;

R^1 represents C_1-C_4-alkyl, preferably methyl or ethyl; and

R^3 represents C_1-C_4-alkyl, preferably methyl; and

in which R^2 has the same meaning as defined in general formula (I),

or an isomer, enantiomer, diastereomer, racemate, hydrate, solvate, or a salt thereof, or a mixture of same for the treatment or prophylaxis of diseases or disorders which are 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.

Another embodiment of the present invention relates to a method for using compounds of general formula (I), more preferably compounds of general formula (Ia), wherein

A represents an optionally substituted 5- or 6-membered heteroaryl, preferably an optionally substituted 6-membered heteroaryl;

R^1 represents a halogen atom, preferably chloro; and

R^3 represents C_1-C_4-alkyl, preferably methyl; and

in which R^2 has the same meaning as defined in general formula (I),

or an isomer, enantiomer, diastereomer, racemate, hydrate, solvate, or a salt thereof, or a mixture of same for the treatment or prophylaxis of diseases or disorders which are 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.

Another embodiment of the present invention relates to a method for using compounds of general formula (I), more preferably compounds of general formula (Ia), wherein

A represents an optionally substituted 5- or 6-membered heteroaryl, preferably an optionally substituted 6-membered heteroaryl;

R^1 represents C_1-C_4-alkyl, preferably methyl or ethyl;

R^2 represents -C_2-C_4-alkyl-OR^4, -CH_2-(C_3-C_4-cycloalkyl), C_3-C_4-cycloalkyl, -$(CH_2)_q$-(4- to 6-membered heterocycloalkyl), or -C_2-C_4-alkynyl; and

wherein said -CH_2-(C_3-C_4-cycloalkyl), C_3-C_4-cycloalkyl and -$(CH_2)_q$-(4- to 6-membered heterocycloalkyl) are optionally substituted with one or more substituents which are the same or different, at any ring carbon atom; and

wherein independently any ring nitrogen atom, if present in said -$(CH_2)_q$-(4- to 6-membered heterocycloalkyl) is substituted with R^c;

R^3 represents C_1-C_4-alkyl, preferably methyl; and

q represents an integer of 0,

wherein R^c is defined as in formula (I),

or an isomer, enantiomer, diastereomer, racemate, hydrate, solvate, or a salt thereof, or a mixture of same for the treatment or prophylaxis of diseases or disorders which are 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.

Another embodiment of the present invention relates to a method for using compounds of general formula (I), more preferably compounds of general formula (Ia), wherein

A represents an optionally substituted 5- or 6-membered heteroaryl, preferably an optionally substituted 6-membered heteroaryl;

R^1 represents C_1-C_4-alkyl, preferably methyl or ethyl;

R^2 represents -C_2-C_3-alkyl-OR^4, -CH_2-(C_3-C_4-cycloalkyl), C_3-C_4-cycloalkyl, -$(CH_2)_q$-(4- to 6-membered heterocycloalkyl), or -C_2-C_4-alkynyl; and

wherein said -CH_2-(C_3-C_4-cycloalkyl), C_3-C_4-cycloalkyl and -$(CH_2)_q$-(4- to 6-membered heterocycloalkyl) are optionally substituted with one or more substituents which are the same or different, at any ring carbon atom; and

wherein independently any ring nitrogen atom, if present in said -$(CH_2)_q$-(4- to 6-membered heterocycloalkyl) is substituted with R^c; and

R^3 represents C_1-C_4-alkyl, preferably methyl; and

q represents an integer of 0,

wherein R^c is defined as in formula (I),

or an isomer, enantiomer, diastereomer, racemate, hydrate, solvate, or a salt thereof, or a mixture of same for the treatment or prophylaxis of diseases or disorders which are 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.

Another embodiment of the present invention relates to a method for using compounds of general formula (I), more preferably compounds of general formula (Ia), wherein

A represents an optionally substituted 5- or 6-membered heteroaryl, preferably an optionally substituted 6-membered heteroaryl;

R^1 represents C_1-C_4-alkyl, preferably methyl or ethyl;

R^2 represents -$(CH_2)_q$-(4- to 6-membered heterocycloalkyl); and wherein $(CH_2)_q$-(4- to 6-membered heterocycloalkyl) is optionally substituted with one or more substituents which are the same or different, at any ring carbon atom; and

wherein independently any ring nitrogen atom, if present in said -$(CH_2)_q$-(4 to 6-membered heterocycloalkyl) is substituted with R^c; wherein -$(CH_2)_q$-(4- to 6-membered heterocycloalkyl) is preferably -$(CH_2)_q$-morpholinyl;

R^3 represents C_1-C_4-alkyl, preferably methyl; and

q represents an integer of 1;

wherein R^c is defined as in formula (I),

or an isomer, enantiomer, diastereomer, racemate, hydrate, solvate, or a salt thereof, or a mixture of same for the treatment or prophylaxis of diseases or disorders which are 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.

Another embodiment of the present invention relates to a method for using compounds of general formula (I), more preferably compounds of general formula (Ia), wherein

A represents an optionally substituted 5- or 6-membered heteroaryl, preferably an optionally substituted 6-membered heteroaryl;

R^1 represents C_1-C_4-alkyl, preferably methyl or ethyl;

R^2 represents -$(CH_2)_q$-morpholinyl, wherein the ring nitrogen atom is substituted with R^c; and

R^c represents methyl;

R^3 represents C_1-C_4-alkyl, preferably methyl; and

q represents an integer of 1;

or an isomer, enantiomer, diastereomer, racemate, hydrate, solvate, or a salt thereof, or a mixture of same for the treatment or prophylaxis of diseases or disorders which are 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.

Another embodiment of the present invention relates to a method for using compounds of general formula (I), more preferably compounds of general formula (Ia), wherein

A represents an optionally substituted 5- or 6-membered heteroaryl, preferably an optionally substituted 6-membered heteroaryl;

R^1 represents a halogen atom, preferably chloro;

R^2 represents -C_2-C_4-alkyl-OH, preferably 3-hydroxybutan-2-yl;

R^3 represents C_1-C_4-alkyl, preferably methyl;

or an isomer, enantiomer, diastereomer, racemate, hydrate, solvate, or a salt thereof, or a mixture of same for the treatment or prophylaxis of diseases or disorders which are 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.

Another embodiment of the present invention relates to a method for using compounds of general formula (I), more preferably compounds of general formula (Ia), wherein

A represents 5- or 6-membered heteroaryl at least containing one or two nitrogen atom(s), preferably a 6-membered heteroaryl with one or two nitrogen atom(s),

wherein said 5- or 6-membered heteroaryl is optionally substituted one or two times, identically or differently, with a substituent selected from a fluorine or chlorine atom, C_1-C_2-alkyl, optionally substituted with 1-5 fluorine atoms, or C_1-C_2-alkoxy, optionally substituted with 1-5 fluorine atoms;

R^1 represents methyl or ethyl;

R^2 represents -C_2-C_3-alkyl-OR^4, unsubstituted -CH_2-(C_3-C_4-cycloalkyl), unsubstituted C_3-C_4-cycloalkyl, unsubstituted $(CH_2)_q$-(4- to 6-membered heterocycloalkyl), or -C_2-C_4-alkynyl;

R^3 represents methyl; and

q represents an integer of 0,

or an isomer, enantiomer, diastereomer, racemate, hydrate, solvate, or a salt thereof, or a mixture of same for the treatment or prophylaxis of diseases or disorders which are 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.

Another embodiment of the present invention relates to a method for using compounds of general formula (I), more preferably compounds of general formula (Ia), wherein

A represents 5- or 6-membered heteroaryl at least containing one or two nitrogen atom(s), preferably a 6-membered heteroaryl with one or two nitrogen atom(s),

wherein said 5- or 6-membered heteroaryl is optionally substituted one or two times, identically or differently, with a substituent selected from a fluorine or chlorine atom, C_1-C_2-alkyl, optionally substituted with 1-5 fluorine atoms, or C_1-C_2-alkoxy, optionally substituted with 1-5 fluorine atoms;

R^1 represents methyl or ethyl;

R^2 represents optionally substituted $(CH_2)_q$-(4- to 6-membered heterocycloalkyl), wherein -$(CH_2)_q$-(4- to 6-membered heterocycloalkyl) is optionally substituted with one or more substituents which are the same or different, at any ring carbon atom; and

wherein independently any ring nitrogen atom, if present in said -$(CH_2)_q$-(4- to 6-membered heterocycloalkyl) is substituted with R^c; wherein -$(CH_2)_q$-(4- to 6-membered heterocycloalkyl) is preferably -$(CH_2)_q$-morpholinyl;

R^3 represents methyl; and

q represents an integer of 1,

wherein R^c is defined as in formula (I),

or an isomer, enantiomer, diastereomer, racemate, hydrate, solvate, or a salt thereof, or a mixture of same for the treatment or prophylaxis of diseases or disorders which are 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.

Another embodiment of the present invention relates to a method for using compounds of general formula (I), more preferably compounds of general formula (Ia), wherein

A represents 5- or 6-membered heteroaryl at least containing one or two nitrogen atom(s), preferably a 6-membered heteroaryl with one or two nitrogen atom(s),

wherein said 5- or 6-membered heteroaryl is optionally substituted one or two times, identically or differently, with a substituent selected from a fluorine or chlorine atom, C_1-C_2-alkyl, optionally substituted with 1-5 fluorine atoms, or C_1-C_2-alkoxy, optionally substituted with 1-5 fluorine atoms;

R^1 represents methyl or ethyl;

R^2 represents -$(CH_2)_q$-morpholinyl, wherein the ring nitrogen atom is substituted with R^c as defined in formula (I), preferably substituted with methyl;

R^3 represents methyl; and

q represents an integer of 1,

or an isomer, enantiomer, diastereomer, racemate, hydrate, solvate, or a salt thereof, or a mixture of same for the treatment or prophylaxis of diseases or disorders which are 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.

Another embodiment of the present invention relates to a method for using compounds of general formula (I), more preferably compounds of general formula (Ia), wherein

A represents 5- or 6-membered heteroaryl at least containing one or two nitrogen atom(s), preferably a 6-membered heteroaryl with one or two nitrogen atom(s),

wherein said 5- or 6-membered heteroaryl is optionally substituted one or two times, identically or differently, with a substituent selected from a fluorine or chlorine atom, C_1-C_2-alkyl, optionally substituted with 1-5 fluorine atoms, or C_1-C_2-alkoxy, optionally substituted with 1-5 fluorine atoms;

R^1 represents a chloro atom;

R^2 represents -C_2-C_4-alkyl-OH, preferably 3-hydroxybutan-2-yl; and

R^3 represents methyl,

or an isomer, enantiomer, diastereomer, racemate, hydrate, solvate, or a salt thereof, or a mixture of same for the treatment or prophylaxis of diseases or disorders which are 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.

Another embodiment of the present invention relates to a method for using compounds of general formula (I), wherein

A represents pyrimidinyl, pyridazinyl, pyridinyl, pyrazinyl, thiazolyl or thiadiazolyl, preferably pyrimidinyl, pyridazinyl, thiazolyl or thiadiazolyl, more preferably pyrimidinyl, pyridazinyl or thiadiazolyl, wherein said pyrimidinyl, pyridazinyl, pyridinyl, pyrazinyl, thiazolyl and thiadiazolyl are optionally substituted; and

in which R^1, R^2 and R^3 have the same meaning as defined in general formula (I),

or an isomer, enantiomer, diastereomer, racemate, hydrate, solvate, or a salt thereof, or a mixture of same for the treatment or prophylaxis of diseases or disorders which are 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.

In another preferred embodiment, the invention relates to use of compounds of general formula (Ia), wherein

A represents pyrimidinyl, pyridazinyl, pyridinyl, pyrazinyl, thiazolyl or thiadiazolyl, preferably pyrimidinyl, pyridazinyl, thiazolyl or thiadiazolyl, more preferably pyrimidinyl, pyridazinyl or thiadiazolyl, wherein said pyrimidinyl, pyridazinyl, pyridinyl, pyrazinyl, thiazolyl and thiadiazolyl are optionally substituted; and

in which R^1, R^2 and R^3 have the same meaning as defined in general formula (Ia),

or an isomer, enantiomer, diastereomer, racemate, hydrate, solvate, or a salt thereof, or a mixture of same for the treatment or prophylaxis of diseases or disorders which are 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.

Another embodiment of the present invention relates to a method for using compounds of general formula (I), wherein

A represents CF_3-pyrimidinyl, preferably 2-CF_3-pyrimidin-5-yl; and

in which R^1, R^2 and R^3 have the same meaning as defined in general formula (I),

or an isomer, enantiomer, diastereomer, racemate, hydrate, solvate, or a salt thereof, or a mixture of same for the treatment or prophylaxis of diseases or disorders which are 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.

In another preferred embodiment, the invention relates to compounds of general formula (Ia), wherein

A represents CF_3-pyrimidinyl, preferably 2-CF_3-pyrimidin-5-yl; and

in which R^1, R^2 and R^3 have the same meaning as defined in general formula (Ia),

or an isomer, enantiomer, diastereomer, racemate, hydrate, solvate, or a salt thereof, or a mixture of same for the treatment or prophylaxis of diseases or disorders which are 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.

Another embodiment of the present invention relates to a method for using compounds of general formula (I), wherein

A represents CF_3-pyridazinyl, preferably 6-CF_3-pyridazin-3-yl; and

in which R^1, R^2 and R^3 have the same meaning as defined in general formula (I),

or an isomer, enantiomer, diastereomer, racemate, hydrate, solvate, or a salt thereof, or a mixture of same for the treatment or prophylaxis of diseases or disorders which are 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.

Another embodiment of the present invention relates to a method for using compounds of general formula (Ia), wherein

A represents CF_3-pyridazinyl, preferably 6-CF_3-pyridazin-3-yl; and

in which R^1, R^2 and R^3 have the same meaning as defined in general formula (Ia),

or an isomer, enantiomer, diastereomer, racemate, hydrate, solvate, or a salt thereof, or a mixture of same for the treatment or prophylaxis of diseases or disorders which are 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.

Another embodiment of the present invention relates to a method for using to compounds of general formula (I), wherein

R^2 represents cyclopropylmethyl, tetrahydrofuran-3-yl, tetrahydrofuran-2-ylmethyl, tetrahydrofuran-3-ylmethyl, prop-2-yn-1-yl, but-2-yn-1-yl, oxetan-3-yl, tetrahydropyran-4-yl, tetrahydro-2H-pyran-4-ylmethyl, pyridin-4-yl, pyridin-3-yl, 1,3,4-thiadiazol-2-yl, 1,3-thiazol-2-yl, 2,2-dimethyl-2-methoxyethyl, methoxyethyl, piperidin-4-yl, pyrrolidin-3-yl or azetidin-3-yl which are optionally substituted, preferably unsubstituted cyclopropylmethyl, unsubstituted oxetan-3-yl, unsubstituted tetrahydrofuran-3-yl; and

in which R^1, A and R^3 have the same meaning as defined in general formula (I),

or an isomer, enantiomer, diastereomer, racemate, hydrate, solvate, or a salt thereof, or a mixture of same for the treatment or prophylaxis of diseases or disorders which are 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.

Another embodiment of the present invention relates to a method for using compounds of general formula (I), wherein

R^2 represents 3-hydroxybutan-2-yl, prop-2-yn-1-yl, but-2-yn-1-yl, 2,2-dimethyl-2-methoxyethyl, methoxyethyl; or

cyclopropylmethyl, tetrahydrofuran-3-yl, tetrahydrofuran-2-ylmethyl, tetrahydrofuran-3-ylmethyl, oxetan-3-yl, tetrahydropyran-4-yl, tetrahydro-2H-pyran-4-ylmethyl, (4-methylmorpholin-2-yl)methyl, pyridin-4-yl, pyridin-3-yl, 1,3,4-thiadiazol-2-yl, 1,3-thiazol-2-yl, piperidin-4-yl, pyrrolidin-3-yl or azetidin-3-yl which are optionally substituted,

preferably unsubstituted cyclopropylmethyl, unsubstituted oxetan-3-yl, unsubstituted (3R)-tetrahydrofuran-3-yl, unsubstituted (3S)-tetrahydrofuran-3-yl, [(2R)-4-methylmorpholin-2-yl]methyl, [(2S)-4-methylmorpholin-2-yl]methyl, (2R,3R)-3-hydroxybutan-2-yl, (2S,3S)-3-hydroxybutan-2-yl, (2S,3R)-3-hydroxybutan-2-yl or (2R,3S)-3-hydroxybutan-2-yl; and

in which R^1, A and R^3 have the same meaning as defined in general formula (I),

or an isomer, enantiomer, diastereomer, racemate, hydrate, solvate, or a salt thereof, or a mixture of same for the treatment or prophylaxis of diseases or disorders which are 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.

Another embodiment of the present invention relates to a method for using compounds of general formula (Ia), wherein

R^2 represents cyclopropylmethyl, tetrahydrofuran-3-yl, tetrahydrofuran-2-ylmethyl, tetrahydrofuran-3-ylmethyl, prop-2-yn-1-yl, but-2-yn-1-yl, oxetan-3-yl, tetrahydropyran-4-yl, tetrahydro-2H-pyran-4-ylmethyl, pyridin-4-yl, pyridin-3-yl, 1,3,4-thiadiazol-2-yl, 1,3-thiazol-2-yl, 2,2-dimethyl-2-methoxyethyl, methoxyethyl, piperidin-4-yl, pyrrolidin-3-yl or azetidin-3-yl which are optionally substituted, preferably unsubstituted cyclopropylmethyl, unsubstituted oxetan-3-yl, unsubstituted tetrahydrofuran-3-yl; and

in which R^1, A and R^3 have the same meaning as defined in general formula (Ia),

or an isomer, enantiomer, diastereomer, racemate, hydrate, solvate, or a salt thereof, or a mixture of same for the treatment or prophylaxis of diseases or disorders which are 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.

Another embodiment of the present invention relates to a method for using compounds of general formula (Ia), wherein

R^2 represents 3-hydroxybutan-2-yl, prop-2-yn-1-yl, but-2-yn-1-yl, 2,2-dimethyl-2-methoxyethyl, methoxyethyl; or

cyclopropylmethyl, tetrahydrofuran-3-yl, tetrahydrofuran-2-ylmethyl, tetrahydrofuran-3-ylmethyl, oxetan-3-yl, tetrahydropyran-4-yl, tetrahydro-2H-pyran-4-ylmethyl, (4-methylmorpholin-2-yl)methyl, pyridin-4-yl, pyridin-3-yl, 1,3,4-thiadiazol-2-yl, 1,3-thiazol-2-yl, piperidin-4-yl, pyrrolidin-3-yl or azetidin-3-yl which are optionally substituted,

preferably unsubstituted cyclopropylmethyl, unsubstituted oxetan-3-yl, unsubstituted (3R)-tetrahydrofuran-3-yl, unsubstituted (3S)-tetrahydrofuran-3-yl, [(2R)-4-methylmorpholin-2-yl]methyl, [(2S)-4-methylmorpholin-2-

yl]methyl, (2R,3R)-3-hydroxybutan-2-yl, (2S,3S)-3-hydroxybutan-2-yl, (2S,3R)-3-hydroxybutan-2-yl or (2R,3S)-3-hydroxybutan-2-yl; and

in which R^1, A and R^3 have the same meaning as defined in general formula (Ia),

or an isomer, enantiomer, diastereomer, racemate, hydrate, solvate, or a salt thereof, or a mixture of same for the treatment or prophylaxis of diseases or disorders which are 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.

Another embodiment of the present invention relates to a method for using compounds of formula (I), wherein

R^2 represents unsubstituted tetrahydrofuran-3-yl or unsubstituted oxetan-3-yl; and

in which R^1, A and R^3 have the same meaning as defined in general formula (I),

or an isomer, enantiomer, diastereomer, racemate, hydrate, solvate, or a salt thereof, or a mixture of same for the treatment or prophylaxis of diseases or disorders which are 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.

Another embodiment of the present invention relates to a method for using compounds of formula (I), wherein

R^2 represents unsubstituted (3R)-tetrahydrofuran-3-yl, (3S)-tetrahydrofuran-3-yl or unsubstituted oxetan-3-yl; and

in which R^1, A and R^3 have the same meaning as defined in general formula (I),

or an isomer, enantiomer, diastereomer, racemate, hydrate, solvate, or a salt thereof, or a mixture of same for the treatment or prophylaxis of diseases or disorders which are 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.

Another embodiment of the present invention relates to a method for using compounds of formula (I), wherein

R^2 represents unsubstituted (3R)-tetrahydrofuran-3-yl; and

in which R^1, A and R^3 have the same meaning as defined in general formula (I),

or an isomer, enantiomer, diastereomer, racemate, hydrate, solvate, or a salt thereof, or a mixture of same for the treatment or prophylaxis of diseases or disorders which are 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.

Another embodiment of the present invention relates to a method for using compounds of formula (I), wherein

R^2 represents [(2R)-4-methylmorpholin-2-yl]methyl, (2R,3R)-3-hydroxybutan-2-yl, or (2S,3S)-3-hydroxybutan-2-yl; and

in which R^1, A and R^3 have the same meaning as defined in general formula (I),

or an isomer, enantiomer, diastereomer, racemate, hydrate, solvate, or a salt thereof, or a mixture of same for the treatment or prophylaxis of diseases or disorders which are 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..

Another embodiment of the present invention relates to a method for using compounds of formula (I), wherein

R^2 represents [(2R)-4-methylmorpholin-2-yl]methyl; and

in which R^1, A and R^3 have the same meaning as defined in general formula (I),

or an isomer, enantiomer, diastereomer, racemate, hydrate, solvate, or a salt thereof, or a mixture of same for the treatment or prophylaxis of diseases or disorders which are 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.

Another embodiment of the present invention relates to a method for using compounds of formula (I), wherein

R^2 represents (2R,3R)-3-hydroxybutan-2-yl, or (2S,3S)-3-hydroxybutan-2-yl; and

in which R^1, A and R^3 have the same meaning as defined in general formula (I),

or an isomer, enantiomer, diastereomer, racemate, hydrate, solvate, or a salt thereof, or a mixture of same for the treatment or prophylaxis of diseases or disorders which are 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.

Another embodiment of the present invention relates to a method for using compounds of formula (Ia), wherein

R^2 represents unsubstituted tetrahydrofuran-3-yl or unsubstituted oxetan-3-yl; and

in which R^1, A and R^3 have the same meaning as defined in general formula (Ia),

or an isomer, enantiomer, diastereomer, racemate, hydrate, solvate, or a salt thereof, or a mixture of same for the treatment or prophylaxis of diseases or disorders which are 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.

Another embodiment of the present invention relates to a method for using compounds of formula (Ia), wherein

R^2 represents unsubstituted (3R)-tetrahydrofuran-3-yl, (3S)-tetrahydrofuran-3-yl or unsubstituted oxetan-3-yl; and

in which R^1, A and R^3 have the same meaning as defined in general formula (Ia),

or an isomer, enantiomer, diastereomer, racemate, hydrate, solvate, or a salt thereof, or a mixture of same for the treatment or prophylaxis of diseases or disorders which are 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.

Another embodiment of the present invention relates to a method for using compounds of formula (Ia), wherein

R^2 represents unsubstituted (3R)-tetrahydrofuran-3-yl; and

in which R^1, A and R^3 have the same meaning as defined in general formula (Ia),

or an isomer, enantiomer, diastereomer, racemate, hydrate, solvate, or a salt thereof, or a mixture of same for the treatment or prophylaxis of diseases or disorders which are 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.

Another embodiment of the present invention relates to a method for using compounds of formula (Ia), wherein

R^2 represents [(2R)-4-methylmorpholin-2-yl]methyl, (2R,3R)-3-hydroxybutan-2-yl or (2S,3S)-3-hydroxybutan-2-yl; and

in which R^1, A and R^3 have the same meaning as defined in general formula (Ia),

or an isomer, enantiomer, diastereomer, racemate, hydrate, solvate, or a salt thereof, or a mixture of same for the treatment or prophylaxis of diseases or disorders which are 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.

Another embodiment of the present invention relates to a method for using compounds of formula (Ia), wherein

R^2 represents [(2R)-4-methylmorpholin-2-yl]methyl; and

in which R^1, A and R^3 have the same meaning as defined in general formula (Ia),

or an isomer, enantiomer, diastereomer, racemate, hydrate, solvate, or a salt thereof, or a mixture of same for the treatment or prophylaxis of diseases or disorders which are 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.

Another embodiment of the present invention relates to a method for using compounds of formula (Ia), wherein

R^2 represents (2R,3R)-3-hydroxybutan-2-yl, or (2S,3S)-3-hydroxybutan-2-yl; and

in which R^1, A and R^3 have the same meaning as defined in general formula (Ia),

or an isomer, enantiomer, diastereomer, racemate, hydrate, solvate, or a salt thereof, or a mixture of same for the treatment or prophylaxis of diseases or disorders which are 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.

Another embodiment of the present invention relates to a method for using compounds of general formula (I), wherein

A represents a 6-membered heteroaryl, in particular pyrimidinyl or pyridazinyl;

wherein said 6-membered heteroaryl is optionally substituted one or two times, identically or differently, with a substituent selected from a fluorine or chlorine atom, C_1-C_2-alkyl, optionally substituted with 1-5 fluorine atoms, or C_1-C_2-alkoxy, optionally substituted with 1-5 fluorine atoms;

R^1 represents methyl or ethyl; and

in which R^2 and R^3 have the meaning as defined in general formula (I),

or an isomer, enantiomer, diastereomer, racemate, hydrate, solvate, or a salt thereof, or a mixture of same for the treatment or prophylaxis of diseases or disorders which are 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.

Another embodiment of the present invention relates to a method for using compounds of general formula (Ia), wherein

A represents a 6-membered heteroaryl, in particular pyrimidinyl or pyridazinyl;

wherein said 6-membered heteroaryl is optionally substituted one or two times, identically or differently, with a substituent selected from a fluorine or chlorine atom, C_1-C_2-alkyl, optionally substituted with 1-5 fluorine atoms, or C_1-C_2-alkoxy, optionally substituted with 1-5 fluorine atoms;

R^1 represents methyl or ethyl; and

in which R^2 and R^3 have the meaning as defined in general formula (Ia),

or an isomer, enantiomer, diastereomer, racemate, hydrate, solvate, or a salt thereof, or a mixture of same for the treatment or prophylaxis of diseases or disorders which are 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.

Another embodiment of the present invention relates to a method for using compounds of general formula (I), more preferably to compounds of general formula (Ia), wherein

A represents a 6-membered heteroaryl, in particular pyrimidinyl or pyridazinyl;

wherein said 6-membered heteroaryl is optionally substituted one or two times, identically or differently, with a substituent selected from a fluorine

or chlorine atom, C_1-C_2-alkyl, optionally substituted with 1-5 fluorine atoms, or C_1-C_2-alkoxy, optionally substituted with 1-5 fluorine atoms;

R^3 represents a methyl group; and

in which R^1 and R^2 have the meaning as defined in general formula (I),

or an isomer, enantiomer, diastereomer, racemate, hydrate, solvate, or a salt thereof, or a mixture of same for the treatment or prophylaxis of diseases or disorders which are 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.

Another embodiment of the present invention relates to a method for using compounds of general formula (I), wherein

A represents a 6-membered heteroaryl, in particular pyrimidinyl or pyridazinyl;

wherein said 6-membered heteroaryl is optionally substituted one or two times, identically or differently, with a substituent selected from a fluorine or chlorine atom, C_1-C_2-alkyl, optionally substituted with 1-5 fluorine atoms, or C_1-C_2-alkoxy, optionally substituted with 1-5 fluorine atoms;

R^2 represents -C_2-C_4-alkyl-OR^4, -CH_2-(C_3-C_4-cycloalkyl), C_3-C_4-cycloalkyl, -$(CH_2)_q$-(4- to 6-membered heterocycloalkyl), or -C_2-C_4- alkynyl;

wherein said -CH_2-(C_3-C_4-cycloalkyl), C_3-C_4-cycloalkyl and -$(CH_2)_q$-(4- to 6-membered heterocycloalkyl) are optionally substituted with one or two substituents which are the same or different, at any ring carbon atom and selected from the group consisting of C_1-C_4-alkyl, optionally substituted with 1-5 halogen atoms which are the same or different, a halogen atom, -NR^aR^b and -$COOR^5$; and wherein independently any ring nitrogen atom, if present in said -$(CH_2)_q$-(4- to 6-membered heterocycloalkyl) is substituted with R^c; and

q represents an integer of 0; and

in which R^c, R^1 and R^3 have the meaning as defined in general formula (I),

or an isomer, enantiomer, diastereomer, racemate, hydrate, solvate, or a salt thereof, or a mixture of same for the treatment or prophylaxis of diseases or disorders which are 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.

Another embodiment of the present invention relates to a method for using compounds of general formula (I), wherein

A represents a 6-membered heteroaryl, in particular pyrimidinyl or pyridazinyl;

wherein said 6-membered heteroaryl is optionally substituted one or two times, identically or differently, with a substituent selected from a fluorine or chlorine atom, C_1-C_2-alkyl, optionally substituted with 1-5 fluorine atoms, or C_1-C_2-alkoxy, optionally substituted with 1-5 fluorine atoms;

R^2 represents -C_2-C_3-alkyl-OR^4, -CH_2-(C_3-C_4-cycloalkyl), C_3-C_4-cycloalkyl, -$(CH_2)_q$-(4- to 6-membered heterocycloalkyl), or -C_2-C_4- alkynyl;

wherein said -CH_2-(C_3-C_4-cycloalkyl), C_3-C_4-cycloalkyl and -$(CH_2)_q$-(4- to 6-membered heterocycloalkyl) are optionally substituted with one or two substituents which are the same or different, at any ring carbon atom and selected from the group consisting of C_1-C_4-alkyl, optionally substituted with 1-5 halogen atoms which are the same or different, a halogen atom, -NR^aR^b and -$COOR^5$; and wherein independently any ring nitrogen atom, if present in said -$(CH_2)_q$-(4- to 6-membered heterocycloalkyl) is substituted with R^c; and

q represents an integer of 0; and

in which R^c, R^1 and R^3 have the meaning as defined in general formula (I),

or an isomer, enantiomer, diastereomer, racemate, hydrate, solvate, or a salt thereof, or a mixture of same for the treatment or prophylaxis of diseases or disorders which are 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.

Another embodiment of the present invention relates to a method for using compounds of general formula (Ia), wherein

A represents a 6-membered heteroaryl, in particular pyrimidinyl or pyridazinyl;

wherein said 6-membered heteroaryl is optionally substituted one or two times, identically or differently, with a substituent selected from a fluorine or chlorine atom, C_1-C_2-alkyl, optionally substituted with 1-5 fluorine atoms, or C_1-C_2-alkoxy, optionally substituted with 1-5 fluorine atoms;

R^2 represents -C_2-C_4-alkyl-OR^4, -CH_2-(C_3-C_4-cycloalkyl), C_3-C_4-cycloalkyl, -$(CH_2)_q$-(4- to 6-membered heterocycloalkyl), or -C_2-C_4- alkynyl;

wherein said -CH_2-(C_3-C_4-cycloalkyl), C_3-C_4-cycloalkyl and -$(CH_2)_q$-(4- to 6-membered heterocycloalkyl) are optionally substituted with one or two substituents which are the same or different, at any ring carbon atom and selected from the group consisting of C_1-C_4-alkyl, optionally substituted with 1-5 halogen atoms which are the same or different, a halogen atom, -NR^aR^b and -$COOR^5$; and wherein independently any ring nitrogen atom, if present in said -$(CH_2)_q$-(4- to 6-membered heterocycloalkyl) is substituted with R^c; and

q represents an integer of 0; and

in which R^c, R^1 and R^3 have the meaning as defined in general formula (Ia),

or an isomer, enantiomer, diastereomer, racemate, hydrate, solvate, or a salt thereof, or a mixture of same for the treatment or prophylaxis of diseases or disorders which are 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.

Another embodiment of the present invention relates to a method for using compounds of general formula (Ia), wherein

A represents a 6-membered heteroaryl, in particular pyrimidinyl or pyridazinyl;

wherein said 6-membered heteroaryl is optionally substituted one or two times, identically or differently, with a substituent selected from a fluorine or chlorine atom, C_1-C_2-alkyl, optionally substituted with 1-5 fluorine atoms, or C_1-C_2-alkoxy, optionally substituted with 1-5 fluorine atoms;

R^2 represents -C_2-C_3-alkyl-OR^4, -CH_2-(C_3-C_4-cycloalkyl), C_3-C_4-cycloalkyl, -$(CH_2)_q$-(4- to 6-membered heterocycloalkyl), or -C_2-C_4- alkynyl;

wherein said -CH_2-(C_3-C_4-cycloalkyl), C_3-C_4-cycloalkyl and -$(CH_2)_q$-(4- to 6-membered heterocycloalkyl) are optionally substituted with one or two substituents which are the same or different, at any ring carbon atom and selected from the group consisting of C_1-C_4-alkyl, optionally substituted with 1-5 halogen atoms which are the same or different, a halogen atom, -NR^aR^b and -$COOR^5$; and wherein independently any ring nitrogen atom, if present in said -$(CH_2)_q$-(4- to 6-membered heterocycloalkyl) is substituted with R^c ;and

q represents an integer of 0; and

in which R^c, R^1 and R^3 have the meaning as defined in general formula (Ia),

or an isomer, enantiomer, diastereomer, racemate, hydrate, solvate, or a salt thereof, or a mixture of same for the treatment or prophylaxis of diseases or disorders which are 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.

Another embodiment of the present invention relates to a method for using compounds of general formula (I), wherein

A represents a 6-membered heteroaryl, in particular pyrimidinyl or pyridazinyl;

wherein said 6-membered heteroaryl is optionally substituted one or two times, identically or differently, with a substituent selected from a fluorine or chlorine atom, C_1-C_2-alkyl, optionally substituted with 1-5 fluorine atoms, or C_1-C_2-alkoxy, optionally substituted with 1-5 fluorine atoms;

R^2 represents -$(CH_2)_q$-(4- to 6-membered heterocycloalkyl); and wherein $(CH_2)_q$-(4- to 6-membered heterocycloalkyl) is optionally substituted with one or two substituents which are the same or different, at any ring carbon atom and selected from the group consisting of C_1-C_4-alkyl, optionally substituted with 1-5 halogen atoms which are the same or different, a halogen atom, -NR^aR^b and –$COOR^5$; and

wherein independently any ring nitrogen atom, if present in said –$(CH_2)_q$-(4 to 6-membered heterocycloalkyl) is substituted with R^c; and wherein said –$(CH_2)_q$-(4 to 6-membered heterocycloalkyl) is preferably -$(CH_2)_q$-morpholinyl; and

q represents an integer of 1; and

in which R^c, R^1 and R^3 have the meaning as defined in general formula (I),

or an isomer, enantiomer, diastereomer, racemate, hydrate, solvate, or a salt thereof, or a mixture of same for the treatment or prophylaxis of diseases or disorders which are 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.

Another embodiment of the present invention relates to a method for using compounds of general formula (I), wherein

A represents a 6-membered heteroaryl, in particular pyrimidinyl or pyridazinyl;

wherein said 6-membered heteroaryl is optionally substituted one or two times, identically or differently, with a substituent selected from a fluorine

or chlorine atom, C_1-C_2-alkyl, optionally substituted with 1-5 fluorine atoms, or C_1-C_2-alkoxy, optionally substituted with 1-5 fluorine atoms;

R^2 represents -$(CH_2)_q$-morpholinyl, wherein the ring nitrogen atom is substituted with R^c; and

R^c represents methyl; and

q represents an integer of 1; and

in which R^1 and R^3 have the meaning as defined in general formula (I),

or an isomer, enantiomer, diastereomer, racemate, hydrate, solvate, or a salt thereof, or a mixture of same for the treatment or prophylaxis of diseases or disorders which are 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.

Another embodiment of the present invention relates to a method for using compounds of general formula (Ia), wherein

A represents a 6-membered heteroaryl, in particular pyrimidinyl or pyridazinyl;

wherein said 6-membered heteroaryl is optionally substituted one or two times, identically or differently, with a substituent selected from a fluorine or chlorine atom, C_1-C_2-alkyl, optionally substituted with 1-5 fluorine atoms, or C_1-C_2-alkoxy, optionally substituted with 1-5 fluorine atoms;

R^2 represents -$(CH_2)_q$-(4- to 6-membered heterocycloalkyl); and wherein $(CH_2)_q$-(4- to 6-membered heterocycloalkyl) is optionally substituted with one or two substituents which are the same or different, at any ring carbon atom and selected from the group consisting of C_1-C_4-alkyl, optionally substituted with 1-5 halogen atoms which are the same or different, a halogen atom, -NR^aR^b and -$COOR^5$; and

wherein independently any ring nitrogen atom, if present in said -$(CH_2)_q$-(4 to 6-membered heterocycloalkyl) is substituted with R^c; and wherein said -

$(CH_2)_q$-(4 to 6-membered heterocycloalkyl) is preferably -$(CH_2)_q$-morpholinyl; and

q represents an integer of 1; and

in which R^c, R^1 and R^3 have the meaning as defined in general formula (Ia),

or an isomer, enantiomer, diastereomer, racemate, hydrate, solvate, or a salt thereof, or a mixture of same for the treatment or prophylaxis of diseases or disorders which are 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.

Another embodiment of the present invention relates to a method for using compounds of general formula (Ia), wherein

A represents a 6-membered heteroaryl, in particular pyrimidinyl or pyridazinyl;

wherein said 6-membered heteroaryl is optionally substituted one or two times, identically or differently, with a substituent selected from a fluorine or chlorine atom, C_1-C_2-alkyl, optionally substituted with 1-5 fluorine atoms, or C_1-C_2-alkoxy, optionally substituted with 1-5 fluorine atoms;

R^2 represents -$(CH_2)_q$-morpholinyl, wherein the ring nitrogen atom is substituted with R^c; and

R^c represents methyl; and

q represents an integer of 1; and

in which R^1 and R^3 have the meaning as defined in general formula (Ia),

or an isomer, enantiomer, diastereomer, racemate, hydrate, solvate, or a salt thereof, or a mixture of same for the treatment or prophylaxis of diseases or disorders which are 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.

Another embodiment of the present invention relates to a method for using compounds of general formula (I), wherein

A represents a 6-membered heteroaryl, in particular pyrimidinyl or pyridazinyl;

wherein said 6-membered heteroaryl is optionally substituted one or two times, identically or differently, with a substituent selected from a fluorine or chlorine atom, C_1-C_2-alkyl, optionally substituted with 1-5 fluorine atoms, or C_1-C_2-alkoxy, optionally substituted with 1-5 fluorine atoms;

R^2 represents -C_2-C_4-alkyl-OH; and

in which R^1 and R^3 have the meaning as defined in general formula (I),

or an isomer, enantiomer, diastereomer, racemate, hydrate, solvate, or a salt thereof, or a mixture of same for the treatment or prophylaxis of diseases or disorders which are 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.

Another embodiment of the present invention relates to a method for using compounds of general formula (Ia), wherein

A represents a 6-membered heteroaryl, in particular pyrimidinyl or pyridazinyl;

wherein said 6-membered heteroaryl is optionally substituted one or two times, identically or differently, with a substituent selected from a fluorine or chlorine atom, C_1-C_2-alkyl, optionally substituted with 1-5 fluorine atoms, or C_1-C_2-alkoxy, optionally substituted with 1-5 fluorine atoms;

R^2 represents -C_2-C_4-alkyl-OH; and

in which R^1 and R^3 have the meaning as defined in general formula (Ia),

or an isomer, enantiomer, diastereomer, racemate, hydrate, solvate, or a salt thereof, or a mixture of same for the treatment or prophylaxis of diseases or disorders which are 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.

Another embodiment of the present invention relates to a method for using compounds of general formula (I), more preferably to compounds of general formula (Ia), wherein

A represents a 6-membered heteroaryl, in particular pyrimidinyl or pyridazinyl;

wherein said 6-membered heteroaryl is optionally substituted one or two times, identically or differently, with a substituent selected from a fluorine or chlorine atom, C_1-C_2-alkyl, optionally substituted with 1 to 5 fluorine atoms, or C_1-C_2-alkoxy, optionally substituted with 1 to 5 fluorine atoms;

R^1 represents methyl or ethyl;

R^3 represents methyl; and

in which R^2 has the meaning as defined in general formula (I),

or an isomer, enantiomer, diastereomer, racemate, hydrate, solvate, or a salt thereof, or a mixture of same for the treatment or prophylaxis of diseases or disorders which are 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.

In another preferred embodiment, the invention relates to compounds of general formula (I), more preferably to compounds of general formula (Ia), wherein

A represents a 6-membered heteroaryl, in particular pyrimidinyl or pyridazinyl;

wherein said 6-membered heteroaryl is optionally substituted one or two times, identically or differently, with a substituent selected from a fluorine or chlorine atom, C_1-C_2-alkyl, optionally substituted with 1 to 5 fluorine atoms, or C_1-C_2-alkoxy, optionally substituted with 1 to 5 fluorine atoms;

R^1 represents chloro;

R^3 represents methyl; and

in which R^2 has the meaning as defined in general formula (I),

or an isomer, enantiomer, diastereomer, racemate, hydrate, solvate, or a salt thereof, or a mixture of same for the treatment or prophylaxis of diseases or disorders which are 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.

Another embodiment of the present invention relates to a method for using compounds of general formula (I), more preferably to compounds of general formula (Ia), wherein

A represents a 6-membered heteroaryl, in particular pyrimidinyl or pyridazinyl;

wherein said 6-membered heteroaryl is optionally substituted one or two times, identically or differently, with a substituent selected from a fluorine or chlorine atom, C_1-C_2-alkyl, optionally substituted with 1 to 5 fluorine atoms, or C_1-C_2-alkoxy, optionally substituted with 1 to 5 fluorine atoms;

R^3 represents methyl;

R^2 represents -C_2-C_4-alkyl-OR^4, CH_2-(C_3-C_4-cycloalkyl), C_3-C_4-cycloalkyl, -$(CH_2)_q$-(4 to 6-membered heterocycloalkyl), or -C_2-C_4-alkynyl,

wherein said -CH_2-(C_3-C_4-cycloalkyl), C_3-C_4-cycloalkyl and -$(CH_2)_q$-(4- to 6-membered heterocycloalkyl) are optionally substituted one or two times, identically or differently, at any ring carbon atom with a substituent

selected from C_1-C_4-alkyl, optionally substituted with 1-5 halogen atoms which are the same or different, a halogen atom, $-NR^aR^b$ or $-COOR^5$; and wherein independently any ring nitrogen atom, if present in said $-(CH_2)_q$-(4- to 6-membered heterocycloalkyl) is substituted with R^c ; and

q represents an integer of 0; and

in which R^c and R^1 have the meaning as defined in general formula (I),

or an isomer, enantiomer, diastereomer, racemate, hydrate, solvate, or a salt thereof, or a mixture of same for the treatment or prophylaxis of diseases or disorders which are 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.

Another embodiment of the present invention relates to a method for using compounds of general formula (I), more preferably to compounds of general formula (Ia), wherein

A represents a 6-membered heteroaryl, in particular pyrimidinyl or pyridazinyl;

wherein said 6-membered heteroaryl is optionally substituted one or two times, identically or differently, with a substituent selected from a fluorine or chlorine atom, C_1-C_2-alkyl, optionally substituted with 1 to 5 fluorine atoms, or C_1-C_2-alkoxy, optionally substituted with 1 to 5 fluorine atoms;

R^3 represents methyl;

R^2 represents $-C_2$-C_3-alkyl-OR^4, CH_2-(C_3-C_4-cycloalkyl), C_3-C_4-cycloalkyl, $-(CH_2)_q$-(4 to 6-membered heterocycloalkyl), or $-C_2$-C_4-alkynyl,

wherein said $-CH_2$-(C_3-C_4-cycloalkyl), C_3-C_4-cycloalkyl and $-(CH_2)_q$-(4- to 6-membered heterocycloalkyl) are optionally substituted one or two times, identically or differently, at any ring carbon atom with a substituent selected from C_1-C_4-alkyl, optionally substituted with 1-5 halogen atoms which are the same or different, a halogen atom, $-NR^aR^b$ or $-COOR^5$; and

wherein independently any ring nitrogen atom, if present in said -$(CH_2)_q$-(4- to 6-membered heterocycloalkyl) is substituted with R^c ; and

in which R^c and R^1 have the meaning as defined in general formula (I),

or an isomer, enantiomer, diastereomer, racemate, hydrate, solvate, or a salt thereof, or a mixture of same for the treatment or prophylaxis of diseases or disorders which are 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.

Another embodiment of the present invention relates to a method for using compounds of general formula (I), more preferably to compounds of general formula (Ia), wherein

A represents a 6-membered heteroaryl, in particular pyrimidinyl or pyridazinyl;

wherein said 6-membered heteroaryl is optionally substituted one or two times, identically or differently, with a substituent selected from a fluorine or chlorine atom, C_1-C_2-alkyl, optionally substituted with 1 to 5 fluorine atoms, or C_1-C_2-alkoxy, optionally substituted with 1 to 5 fluorine atoms;

R^3 represents methyl;

R^2 represents -$(CH_2)_q$-(4- to 6-membered heterocycloalkyl); and wherein $(CH_2)_q$-(4- to 6-membered heterocycloalkyl) is optionally substituted with one or two substituents which are the same or different, at any ring carbon atom and selected from the group consisting of C_1-C_4-alkyl, optionally substituted with 1-5 halogen atoms which are the same or different, a halogen atom, -NR^aR^b and -$COOR^5$; and

wherein independently any ring nitrogen atom, if present in said -(CH2)q-(4 to 6-membered heterocycloalkyl) is substituted with Rc; and wherein said -

$(CH_2)_q$-(4 to 6-membered heterocycloalkyl) is preferably -$(CH_2)_q$-morpholinyl;

q represents an integer of 1; and

in which R^c and R^1 have the meaning as defined in general formula (I),

or an isomer, enantiomer, diastereomer, racemate, hydrate, solvate, or a salt thereof, or a mixture of same for the treatment or prophylaxis of diseases or disorders which are 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.

Another embodiment of the present invention relates to a method for using compounds of general formula (I), more preferably to compounds of general formula (Ia), wherein

A represents a 6-membered heteroaryl, in particular pyrimidinyl or pyridazinyl;

wherein said 6-membered heteroaryl is optionally substituted one or two times, identically or differently, with a substituent selected from a fluorine or chlorine atom, C_1-C_2-alkyl, optionally substituted with 1 to 5 fluorine atoms, or C_1-C_2-alkoxy, optionally substituted with 1 to 5 fluorine atoms;

R^3 represents methyl;

R^2 represents -$(CH_2)_q$-morpholinyl, wherein the ring nitrogen atom is substituted with R^c; and

R^c represents methyl;

q represents an integer of 1; and

in which R^1 has the meaning as defined in general formula (I),

or an isomer, enantiomer, diastereomer, racemate, hydrate, solvate, or a salt thereof, or a mixture of same for the treatment or prophylaxis of diseases or disorders which are 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.

Another embodiment of the present invention relates to a method for using compounds of general formula (I), more preferably to compounds of general formula (Ia), wherein

A represents a 6-membered heteroaryl, in particular pyrimidinyl or pyridazinyl;

wherein said 6-membered heteroaryl is optionally substituted one or two times, identically or differently, with a substituent selected from a fluorine or chlorine atom, C_1-C_2-alkyl, optionally substituted with 1 to 5 fluorine atoms, or C_1-C_2-alkoxy, optionally substituted with 1 to 5 fluorine atoms;

R^3 represents methyl;

R^2 represents C_2-C_4-alkyl-OH, preferably 3-hydroxybutan-2-yl; and

in which R^1 has the meaning as defined in general formula (I),

or an isomer, enantiomer, diastereomer, racemate, hydrate, solvate, or a salt thereof, or a mixture of same for the treatment or prophylaxis of diseases or disorders which are 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.

Another embodiment of the present invention relates to a method for using compounds of general formula (I), wherein

A represents a 6-membered heteroaryl, in particular pyrimidinyl or pyridazinyl,

wherein said 6-membered heteroaryl is optionally substituted one or two times, identically or differently, with a substituent selected from a fluorine

or chlorine atom, C_1-C_2-alkyl, optionally substituted with 1 to 5 fluorine atoms, or C_1-C_2-alkoxy, optionally substituted with 1 to 5 fluorine atoms;

R^1 represents methyl or ethyl;

R^2 represents -C_2-C_4-alkyl-OR^4, -CH_2-(C_3-C_4-cycloalkyl), C_3-C_4-cycloalkyl, -$(CH_2)_q$-(4 to 6-membered heterocycloalkyl) or -C_2-C_4-alkynyl,

wherein said -CH_2-(C_3-C_4-cycloalkyl), C_3-C_4-cycloalkyl and -$(CH_2)_q$-(4- to 6-membered heterocycloalkyl) are optionally substituted with one or two substituents which are the same or different, at any ring carbon atom and selected from the group consisting of C_1-C_4-alkyl, optionally substituted with 1-5 halogen atoms which are the same or different, a halogen atom, -NR^aR^b and -$COOR^5$; and wherein independently any ring nitrogen atom, if present in said -$(CH_2)_q$-(4- to 6-membered heterocycloalkyl) is substituted with R^c ; and

q represents an integer of 0; and

in which R^c and R^3 have the meaning as defined in general formula (I),

or an isomer, enantiomer, diastereomer, racemate, hydrate, solvate, or a salt thereof, or a mixture of same for the treatment or prophylaxis of diseases or disorders which are 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.

Another embodiment of the present invention relates to a method for using to compounds of general formula (Ia), wherein

A represents a 6-membered heteroaryl, in particular pyrimidinyl or pyridazinyl,

wherein said 6-membered heteroaryl is optionally substituted one or two times, identically or differently, with a substituent selected from a fluorine or chlorine atom, C_1-C_2-alkyl, optionally substituted with 1 to 5 fluorine atoms, or C_1-C_2-alkoxy, optionally substituted with 1 to 5 fluorine atoms;

R^1 represents methyl or ethyl;

R^2 represents -C_2-C_4-alkyl-OR^4, -CH_2-(C_3-C_4-cycloalkyl), C_3-C_4-cycloalkyl, -$(CH_2)_q$-(4 to 6-membered heterocycloalkyl) or -C_2-C_4-alkynyl,

wherein said -CH_2-(C_3-C_4-cycloalkyl), C_3-C_4-cycloalkyl and -$(CH_2)_q$-(4- to 6-membered heterocycloalkyl) are optionally substituted with one or two substituents which are the same or different, at any ring carbon atom and selected from the group consisting of C_1-C_4-alkyl, optionally substituted with 1-5 halogen atoms which are the same or different, a halogen atom, -NR^aR^b and -$COOR^5$; and wherein independently any ring nitrogen atom, if present in said -$(CH_2)_q$-(4- to 6-membered heterocycloalkyl) is substituted with R^c ; and

q represents an integer of 0; and

in which R^c and R^3 have the meaning as defined in general formula (Ia),

or an isomer, enantiomer, diastereomer, racemate, hydrate, solvate, or a salt thereof, or a mixture of same for the treatment or prophylaxis of diseases or disorders which are 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.

Another embodiment of the present invention relates to a method for using compounds of general formula (I), wherein

A represents a 6-membered heteroaryl, in particular pyrimidinyl or pyridazinyl,

wherein said 6-membered heteroaryl is optionally substituted one or two times, identically or differently, with a substituent selected from a fluorine or chlorine atom, C_1-C_2-alkyl, optionally substituted with 1 to 5 fluorine atoms, or C_1-C_2-alkoxy, optionally substituted with 1 to 5 fluorine atoms;

R^1 represents methyl or ethyl;

R^2 represents -C_2-C_3-alkyl-OR^4, -CH_2-(C_3-C_4-cycloalkyl), C_3-C_4-cycloalkyl, -$(CH_2)_q$-(4 to 6-membered heterocycloalkyl) or -C_2-C_4-alkynyl,

wherein said -CH_2-(C_3-C_4-cycloalkyl), C_3-C_4-cycloalkyl and -$(CH_2)_q$-(4- to 6-membered heterocycloalkyl) are optionally substituted with one or two substituents which are the same or different, at any ring carbon atom and selected from the group consisting of C_1-C_4-alkyl, optionally substituted with 1-5 halogen atoms which are the same or different, a halogen atom, -NR^aR^b and -$COOR^5$; and wherein independently any ring nitrogen atom, if present in said -$(CH_2)_q$-(4- to 6-membered heterocycloalkyl) is substituted with R^c ; and

q represents an integer of 0; and

in which R^c and R^3 have the meaning as defined in general formula (I),

or an isomer, enantiomer, diastereomer, racemate, hydrate, solvate, or a salt thereof, or a mixture of same for the treatment or prophylaxis of diseases or disorders which are 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.

Another embodiment of the present invention relates to a method for using compounds of general formula (Ia), wherein

A represents a 6-membered heteroaryl, in particular pyrimidinyl or pyridazinyl,

wherein said 6-membered heteroaryl is optionally substituted one or two times, identically or differently, with a substituent selected from a fluorine or chlorine atom, C_1-C_2-alkyl, optionally substituted with 1 to 5 fluorine atoms, or C_1-C_2-alkoxy, optionally substituted with 1 to 5 fluorine atoms;

R^1 represents methyl or ethyl;

R^2 represents -C_2-C_3-alkyl-OR^4, -CH_2-(C_3-C_4-cycloalkyl), C_3-C_4-cycloalkyl, -$(CH_2)_q$-(4 to 6-membered heterocycloalkyl) or -C_2-C_4-alkynyl,

wherein said -CH_2-(C_3-C_4-cycloalkyl), C_3-C_4-cycloalkyl and -$(CH_2)_q$-(4- to 6-membered heterocycloalkyl) are optionally substituted with one or two substituents which are the same or different, at any ring carbon atom and

selected from the group consisting of C_1-C_4-alkyl, optionally substituted with 1-5 halogen atoms which are the same or different, a halogen atom, -NR^aR^b and -$COOR^5$; and wherein independently any ring nitrogen atom, if present in said -$(CH_2)_q$-(4- to 6-membered heterocycloalkyl) is substituted with R^c ; and

q represents an integer of 0; and

in which R^c and R^3 have the meaning as defined in general formula (Ia),

or an isomer, enantiomer, diastereomer, racemate, hydrate, solvate, or a salt thereof, or a mixture of same for the treatment or prophylaxis of diseases or disorders which are 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.

Another embodiment of the present invention relates to a method for using compounds of general formula (I), wherein

A represents a 6-membered heteroaryl, in particular pyrimidinyl or pyridazinyl,

wherein said 6-membered heteroaryl is optionally substituted one or two times, identically or differently, with a substituent selected from a fluorine or chlorine atom, C_1-C_2-alkyl, optionally substituted with 1 to 5 fluorine atoms, or C_1-C_2-alkoxy, optionally substituted with 1 to 5 fluorine atoms;

R^1 represents methyl or ethyl;

R^2 represents -$(CH_2)_q$-(4- to 6-membered heterocycloalkyl); and wherein $(CH_2)_q$-(4- to 6-membered heterocycloalkyl) is optionally substituted with one or two substituents which are the same or different, at any ring carbon atom and selected from the group consisting of C_1-C_4-alkyl, optionally substituted with 1-5 halogen atoms which are the same or different, a halogen atom, -NR^aR^b and -$COOR^5$; and

wherein independently any ring nitrogen atom, if present in said -$(CH_2)_q$-(4 to 6-membered heterocycloalkyl) is substituted with R^c; and wherein said -

$(CH_2)_q$-(4 to 6-membered heterocycloalkyl) is preferably -$(CH_2)_q$-morpholinyl;

q represents an integer of 1; and

in which R^c and R^3 have the meaning as defined in general formula (I),

or an isomer, enantiomer, diastereomer, racemate, hydrate, solvate, or a salt thereof, or a mixture of same for the treatment or prophylaxis of diseases or disorders which are 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.

Another embodiment of the present invention relates to a method for using compounds of general formula (I), wherein

A represents a 6-membered heteroaryl, in particular pyrimidinyl or pyridazinyl,

wherein said 6-membered heteroaryl is optionally substituted one or two times, identically or differently, with a substituent selected from a fluorine or chlorine atom, C_1-C_2-alkyl, optionally substituted with 1 to 5 fluorine atoms, or C_1-C_2-alkoxy, optionally substituted with 1 to 5 fluorine atoms;

R^1 represents methyl or ethyl;

R^2 represents -$(CH_2)_q$-morpholinyl, wherein the ring nitrogen atom is substituted with R^c; and

R^c represents methyl;

q represents an integer of 1; and

in which R^3 has the meaning as defined in general formula (I),

or an isomer, enantiomer, diastereomer, racemate, hydrate, solvate, or a salt thereof, or a mixture of same for the treatment or prophylaxis of diseases or disorders which are 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.

Another embodiment of the present invention relates to a method for using compounds of general formula (Ia), wherein

A represents a 6-membered heteroaryl, in particular pyrimidinyl or pyridazinyl,

wherein said 6-membered heteroaryl is optionally substituted one or two times, identically or differently, with a substituent selected from a fluorine or chlorine atom, C_1-C_2-alkyl, optionally substituted with 1 to 5 fluorine atoms, or C_1-C_2-alkoxy, optionally substituted with 1 to 5 fluorine atoms;

R^1 represents methyl or ethyl;

R^2 represents -$(CH_2)_q$-(4- to 6-membered heterocycloalkyl); and wherein $(CH_2)_q$-(4- to 6-membered heterocycloalkyl) is optionally substituted with one or two substituents which are the same or different, at any ring carbon atom and selected from the group consisting of C_1-C_4-alkyl, optionally substituted with 1-5 halogen atoms which are the same or different, a halogen atom, -NR^aR^b and -$COOR^5$; and

wherein independently any ring nitrogen atom, if present in said -$(CH_2)_q$-(4 to 6-membered heterocycloalkyl) is substituted with R^c; and wherein said -$(CH_2)_q$-(4 to 6-membered heterocycloalkyl) is preferably -$(CH_2)_q$-morpholinyl;

q represents an integer of 1; and

in which R^c and R^3 have the meaning as defined in general formula (Ia),

or an isomer, enantiomer, diastereomer, racemate, hydrate, solvate, or a salt thereof, or a mixture of same for the treatment or prophylaxis of diseases or disorders which are 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.

Another embodiment of the present invention relates to a method for using compounds of general formula (Ia), wherein

A represents a 6-membered heteroaryl, in particular pyrimidinyl or pyridazinyl,

wherein said 6-membered heteroaryl is optionally substituted one or two times, identically or differently, with a substituent selected from a fluorine or chlorine atom, C_1-C_2-alkyl, optionally substituted with 1 to 5 fluorine atoms, or C_1-C_2-alkoxy, optionally substituted with 1 to 5 fluorine atoms;

R^1 represents methyl or ethyl;

R^2 represents -$(CH_2)_q$-morpholinyl, wherein the ring nitrogen atom is substituted with R^c; and

R^c represents methyl;

q represents an integer of 1; and

in which R^3 has the meaning as defined in general formula (Ia),

or an isomer, enantiomer, diastereomer, racemate, hydrate, solvate, or a salt thereof, or a mixture of same for the treatment or prophylaxis of diseases or disorders which are 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.

Another embodiment of the present invention relates to a method for using to compounds of general formula (I), wherein

A represents a 6-membered heteroaryl, in particular pyrimidinyl or pyridazinyl,

wherein said 6-membered heteroaryl is optionally substituted one or two times, identically or differently, with a substituent selected from a fluorine

or chlorine atom, C_1-C_2-alkyl, optionally substituted with 1 to 5 fluorine atoms, or C_1-C_2-alkoxy, optionally substituted with 1 to 5 fluorine atoms;

R^1 represents chloro;

R^2 represents C_2-C_4-alkyl-OH, preferably 3-hydroxybutan-2-yl; and

in which R^3 has the meaning as defined in general formula (I),

or an isomer, enantiomer, diastereomer, racemate, hydrate, solvate, or a salt thereof, or a mixture of same for the treatment or prophylaxis of diseases or disorders which are 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.

Another embodiment of the present invention relates to a method for using compounds of general formula (Ia), wherein

A represents a 6-membered heteroaryl, in particular pyrimidinyl or pyridazinyl,

wherein said 6-membered heteroaryl is optionally substituted one or two times, identically or differently, with a substituent selected from a fluorine or chlorine atom, C_1-C_2-alkyl, optionally substituted with 1 to 5 fluorine atoms, or C_1-C_2-alkoxy, optionally substituted with 1 to 5 fluorine atoms;

R^1 represents chloro;

R^2 represents C_2-C_4-alkyl-OH, preferably 3-hydroxybutan-2-yl; and

in which R^3 has the meaning as defined in general formula (Ia),

or an isomer, enantiomer, diastereomer, racemate, hydrate, solvate, or a salt thereof, or a mixture of same for the treatment or prophylaxis of diseases or disorders which are 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.

Another embodiment of the present invention relates to a method for using compounds of general formula (I), more preferably to compounds of general formula (Ia), wherein

A represents a 6-membered heteroaryl, in particular pyrimidinyl or pyridazinyl;

wherein said 6-membered heteroaryl is optionally substituted with one or two substituents which are the same or different, and selected from a fluorine or chlorine atom, C_1-C_2-alkyl, optionally substituted with 1 to 5 fluorine atoms, or C_1-C_2-alkoxy, optionally substituted with 1 to 5 fluorine atoms;

R^1 represents methyl or ethyl;

R^2 represents -C_2-C_3-alkyl-OR^4, CH_2-(C_3-C_4-cycloalkyl), C_3-C_4-cycloalkyl, -$(CH_2)_q$-(4- to 6-membered heterocycloalkyl), or -C_2-C_4-alkynyl,

wherein said -CH_2-(C_3-C_4-cycloalkyl), C_3-C_4-cycloalkyl and -$(CH_2)_q$-(4- to 6-membered heterocycloalkyl) are optionally substituted with one or two substituents which are the same or different, at any ring carbon atom and selected from the group consisting of C_1-C_4-alkyl, optionally substituted with 1-5 halogen atoms which are the same or different, a halogen atom, -NR^aR^b and -$COOR^5$; and wherein independently any ring nitrogen atom, if present in said -$(CH_2)_q$-(4- to 6-membered heterocycloalkyl) is substituted with R^c; and

R^3 represents methyl; and

q represents an integer of 0,

in which R^c has the meaning as defined in general formula (I),

or an isomer, enantiomer, diastereomer, racemate, hydrate, solvate, or a salt thereof, or a mixture of same for the treatment or prophylaxis of diseases or disorders which are 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.

Another embodiment of the present invention relates to a method for using compounds of general formula (I), more preferably to compounds of general formula (Ia), wherein

A represents a 6-membered heteroaryl, in particular pyrimidinyl or pyridazinyl;

wherein said 6-membered heteroaryl is optionally substituted with one or two substituents which are the same or different, and selected from a fluorine or chlorine atom, C_1-C_2-alkyl, optionally substituted with 1 to 5 fluorine atoms, or C_1-C_2-alkoxy, optionally substituted with 1 to 5 fluorine atoms;

R^1 represents methyl or ethyl;

R^2 represents -$(CH_2)_q$-(4- to 6-membered heterocycloalkyl); and wherein $(CH_2)_q$-(4- to 6-membered heterocycloalkyl) is optionally substituted with one or two substituents which are the same or different, at any ring carbon atom and selected from the group consisting of C_1-C_4-alkyl, optionally substituted with 1-5 halogen atoms which are the same or different, a halogen atom, -NR^aR^b and -$COOR^5$; and

wherein independently any ring nitrogen atom, if present in said -$(CH_2)_q$-(4 to 6-membered heterocycloalkyl) is substituted with R^c; and wherein -$(CH_2)_q$-(4- to 6-membered heterocycloalkyl) is preferably -$(CH_2)_q$-morpholinyl;

R^3 represents methyl; and

q represents an integer of 1,

in which R^c has the meaning as defined in general formula (I),

or an isomer, enantiomer, diastereomer, racemate, hydrate, solvate, or a salt thereof, or a mixture of same for the treatment or prophylaxis of diseases or disorders which are 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.

Another embodiment of the present invention relates to a method for using compounds of general formula (I), more preferably to compounds of general formula (Ia), wherein

A represents a 6-membered heteroaryl, in particular pyrimidinyl or pyridazinyl;

wherein said 6-membered heteroaryl is optionally substituted with one or two substituents which are the same or different, and selected from a fluorine or chlorine atom, C_1-C_2-alkyl, optionally substituted with 1 to 5 fluorine atoms, or C_1-C_2-alkoxy, optionally substituted with 1 to 5 fluorine atoms;

R^1 represents methyl or ethyl;

R^2 represents -$(CH_2)_q$-morpholinyl, wherein the ring nitrogen atom is substituted with R^c; and

R^c represents methyl;

R^3 represents methyl; and

q represents an integer of 1,

or an isomer, enantiomer, diastereomer, racemate, hydrate, solvate, or a salt thereof, or a mixture of same for the treatment or prophylaxis of diseases or disorders which are 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.

Another embodiment of the present invention relates to a method for using compounds of general formula (I), more preferably to compounds of general formula (Ia), wherein

A represents a 6-membered heteroaryl, in particular pyrimidinyl or pyridazinyl;

wherein said 6-membered heteroaryl is optionally substituted with one or two substituents which are the same or different, and selected from a fluorine or chlorine atom, C_1-C_2-alkyl, optionally substituted with 1 to 5 fluorine atoms, or C_1-C_2-alkoxy, optionally substituted with 1 to 5 fluorine atoms;

R^1 represents chloro;

R^2 represents -C_2-C_4-alkyl-OH, preferably 3-hydroxybutan-2-yl; and

R^3 represents methyl,

or an isomer, enantiomer, diastereomer, racemate, hydrate, solvate, or a salt thereof, or a mixture of same for the treatment or prophylaxis of diseases or disorders which are 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.

The use of following compounds for the treatment or prophylaxis of diseases or disorders which are 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, is disclosed, namely use of

1) 3-(cyclopropylmethoxy)-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide
2) 3-(cyclopropylmethoxy)-N-[(6-methylpyridazin-3-yl)methyl]-5-(5-methyl-1,3-thiazol-2-yl)benzamide
3) 3-(cyclopropylmethoxy)-N-[(5-methylpyrazin-2-yl)methyl]-5-(5-methyl-1,3-thiazol-2-yl)benzamide
4) 3-(cyclopropylmethoxy)-N-[(1R)-1-(5-methylpyrazin-2-yl)ethyl]-5-(5-methyl-1,3-thiazol-2-yl)benzamide

5) N-[1-(3-chloro-5-fluoropyridin-2-yl)ethyl]-3-(cyclopropylmethoxy)-5-(5-methyl-1,3-thiazol-2-yl)benzamide

6) N-[1-(5-chloro-3-fluoropyridin-2-yl)ethyl]-3-(cyclopropylmethoxy)-5-(5-methyl-1,3-thiazol-2-yl)benzamide

7) 3-(cyclopropylmethoxy)-N-[(1R)-1-(6-methylpyridazin-3-yl)ethyl]-5-(5-methyl-1,3-thiazol-2-yl)benzamide

8) 3-(cyclopropylmethoxy)-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[6-(trifluoromethyl)pyridazin-3-yl]ethyl}benzamide

9) 3-(cyclopropylmethoxy)-N-[(1R)-1-(2-methylpyrimidin-5-yl)ethyl]-5-(5-methyl-1,3-thiazol-2-yl)benzamide

10) 3-(5-methyl-1,3-thiazol-2-yl)-5-[(3R)-tetrahydrofuran-3-yloxy]-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

11) N-[(5-methylpyrazin-2-yl)methyl]-3-(5-methyl-1,3-thiazol-2-yl)-5-[(3R)-tetrahydrofuran-3-yloxy]benzamide

12) N-[1-(3-chloro-5-fluoropyridin-2-yl)ethyl]-3-(5-methyl-1,3-thiazol-2-yl)-5-[(3R)-tetrahydrofuran-3-yloxy]benzamide

13) N-[1-(5-chloro-3-fluoropyridin-2-yl)ethyl]-3-(5-methyl-1,3-thiazol-2-yl)-5-[(3R)-tetrahydrofuran-3-yloxy]benzamide

14) N-[(1R)-1-(5-chloropyridin-2-yl)ethyl]-3-(5-methyl-1,3-thiazol-2-yl)-5-[(3R)-tetrahydrofuran-3-yloxy]benzamide

15) N-[(1R)-1-(5-methylpyrazin-2-yl)ethyl]-3-(5-methyl-1,3-thiazol-2-yl)-5-[(3R)-tetrahydrofuran-3-yloxy]benzamide

16) N-[(6-methylpyridazin-3-yl)methyl]-3-(5-methyl-1,3-thiazol-2-yl)-5-[(3R)-tetrahydrofuran-3-yloxy]benzamide

17) N-[(1R)-1-(6-methylpyridazin-3-yl)ethyl]-3-(5-methyl-1,3-thiazol-2-yl)-5-[(3R)-tetrahydrofuran-3-yloxy]benzamide

18) 3-(5-methyl-1,3-thiazol-2-yl)-5-[(3R)-tetrahydrofuran-3-yloxy]-N-{(1R)-1-[6-(trifluoromethyl)pyridazin-3-yl]ethyl}benzamide

19) 3-(5-methyl-1,3-thiazol-2-yl)-5-[(3R)-tetrahydrofuran-3-yloxy]-N-{[6-(trifluoromethyl)pyridazin-3-yl]methyl}benzamide

20) 3-(5-methyl-1,3-thiazol-2-yl)-5-[(3R)-tetrahydrofuran-3-yloxy]-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]propyl}benzamide

21) N-[(1R)-1-(2-methylpyrimidin-5-yl)ethyl]-3-(5-methyl-1,3-thiazol-2-yl)-5-[(3R)-tetrahydrofuran-3-yloxy]benzamide

22) N-[(1R)-1-(6-methylpyridin-3-yl)ethyl]-3-(5-methyl-1,3-thiazol-2-yl)-5-[(3R)-tetrahydrofuran-3-yloxy]benzamide

23) N-[(1R)-1-(6-methylpyridazin-3-yl)ethyl]-3-(5-methyl-1,3-thiazol-2-yl)-5-[(3S)-tetrahydrofuran-3-yloxy]benzamide

24) 3-(5-methyl-1,3-thiazol-2-yl)-5-[(3S)-tetrahydrofuran-3-yloxy]-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

25) N-[(1R)-1-(5-chloropyridin-2-yl)ethyl]-3-(5-methyl-1,3-thiazol-2-yl)-5-[(3S)-tetrahydrofuran-3-yloxy]benzamide

26) N-[(1R)-1-(5-methylpyridin-2-yl)ethyl]-3-(5-methyl-1,3-thiazol-2-yl)-5-[(3S)-tetrahydrofuran-3-yloxy]benzamide

27) N-[(1R)-1-(5-methylpyrazin-2-yl)ethyl]-3-(5-methyl-1,3-thiazol-2-yl)-5-[(3S)-tetrahydrofuran-3-yloxy]benzamide

28) N-[(1R)-1-(6-methylpyridin-3-yl)ethyl]-3-(5-methyl-1,3-thiazol-2-yl)-5-[(3S)-tetrahydrofuran-3-yloxy]benzamide

29) N-[(6-methylpyridazin-3-yl)methyl]-3-(5-methyl-1,3-thiazol-2-yl)-5-(prop-2-yn-1-yloxy)benzamide

30) N-[(5-chloro-3-fluoropyridin-2-yl)methyl]-3-(5-methyl-1,3-thiazol-2-yl)-5-(prop-2-yn-1-yloxy)benzamide

31) N-[(1R)-1-(6-methylpyridin-3-yl)ethyl]-3-(5-methyl-1,3-thiazol-2-yl)-5-(prop-2-yn-1-yloxy)benzamide

32) N-[(1R)-1-(5-methylpyrazin-2-yl)ethyl]-3-(5-methyl-1,3-thiazol-2-yl)-5-(prop-2-yn-1-yloxy)benzamide

33) N-[(5-methylpyrazin-2-yl)methyl]-3-(5-methyl-1,3-thiazol-2-yl)-5-(prop-2-yn-1-yloxy)benzamide

34) 3-(5-methyl-1,3-thiazol-2-yl)-5-(prop-2-yn-1-yloxy)-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

35) N-[(1R)-1-(6-methylpyridazin-3-yl)ethyl]-3-(5-methyl-1,3-thiazol-2-yl)-5-(prop-2-yn-1-yloxy)benzamide

36) 3-(5-methyl-1,3-thiazol-2-yl)-5-(prop-2-yn-1-yloxy)-N-{(1R)-1-[6-(trifluoromethyl)pyridazin-3-yl]ethyl}benzamide

37) N-[(1R)-1-(2-methylpyrimidin-5-yl)ethyl]-3-(5-methyl-1,3-thiazol-2-yl)-5-(prop-2-yn-1-yloxy)benzamide

38) 3-(but-2-yn-1-yloxy)-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

39) N-[(1R)-1-(5-methylpyrazin-2-yl)ethyl]-3-(5-methyl-1,3-thiazol-2-yl)-5-(oxetan-3-yloxy)benzamide

40) N-[(1R)-1-(2-methylpyrimidin-5-yl)ethyl]-3-(5-methyl-1,3-thiazol-2-yl)-5-(oxetan-3-yloxy)benzamide

41) N-[1-(5-chloro-3-fluoropyridin-2-yl)ethyl]-3-(5-methyl-1,3-thiazol-2-yl)-5-(oxetan-3-yloxy)benzamide

42) N-[(6-methylpyridazin-3-yl)methyl]-3-(5-methyl-1,3-thiazol-2-yl)-5-(oxetan-3-yloxy)benzamide

43) N-[(1R)-1-(5-chloropyridin-2-yl)ethyl]-3-(5-methyl-1,3-thiazol-2-yl)-5-(oxetan-3-yloxy)benzamide

44) N-[(1R)-1-(6-methylpyridazin-3-yl)ethyl]-3-(5-methyl-1,3-thiazol-2-yl)-5-(oxetan-3-yloxy)benzamide

45) 3-(5-methyl-1,3-thiazol-2-yl)-5-(oxetan-3-yloxy)-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

46) N-[1-(3-chloro-5-fluoropyridin-2-yl)ethyl]-3-(5-methyl-1,3-thiazol-2-yl)-5-(oxetan-3-yloxy)benzamide

47) N-[(1R)-1-(6-methylpyridin-3-yl)ethyl]-3-(5-methyl-1,3-thiazol-2-yl)-5-(oxetan-3-yloxy)benzamide

48) 3-(5-methyl-1,3-thiazol-2-yl)-5-(oxetan-3-yloxy)-N-{[6-(trifluoromethyl)pyridazin-3-yl]methyl}benzamide

49) 3-(5-methyl-1,3-thiazol-2-yl)-5-(oxetan-3-yloxy)-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]propyl}benzamide

50) N-[(6-methylpyridazin-3-yl)methyl]-3-(5-methyl-1,3-thiazol-2-yl)-5-[(2S)-tetrahydrofuran-2-ylmethoxy]benzamide

51) N-[(5-chloro-3-fluoropyridin-2-yl)methyl]-3-(5-methyl-1,3-thiazol-2-yl)-5-[(2S)-tetrahydrofuran-2-ylmethoxy]benzamide

52) N-[(5-methylpyrazin-2-yl)methyl]-3-(5-methyl-1,3-thiazol-2-yl)-5-[(2S)-tetrahydrofuran-2-ylmethoxy]benzamide

53) N-[(1R)-1-(5-methylpyrazin-2-yl)ethyl]-3-(5-methyl-1,3-thiazol-2-yl)-5-[(2S)-tetrahydrofuran-2-ylmethoxy]benzamide

54) 3-(5-methyl-1,3-thiazol-2-yl)-5-[(2S)-tetrahydrofuran-2-ylmethoxy]-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

55) N-[(1R)-1-(6-methylpyridazin-3-yl)ethyl]-3-(5-methyl-1,3-thiazol-2-yl)-5-[(2S)-tetrahydrofuran-2-ylmethoxy]benzamide

56) 3-(5-methyl-1,3-thiazol-2-yl)-5-[(2S)-tetrahydrofuran-2-ylmethoxy]-N-{(1R)-1-[6-(trifluoromethyl)pyridazin-3-yl]ethyl}benzamide

57) N-[(1R)-1-(6-methylpyridazin-3-yl)ethyl]-3-(5-methyl-1,3-thiazol-2-yl)-5-[(2R)-tetrahydrofuran-2-ylmethoxy]benzamide

58) N-[(6-methylpyridazin-3-yl)methyl]-3-(5-methyl-1,3-thiazol-2-yl)-5-[(2R)-tetrahydrofuran-2-ylmethoxy]benzamide

59) 3-(5-methyl-1,3-thiazol-2-yl)-5-[(2R)-tetrahydrofuran-2-ylmethoxy]-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

60) N-[(1R)-1-(5-methylpyrazin-2-yl)ethyl]-3-(5-methyl-1,3-thiazol-2-yl)-5-[(2R)-tetrahydrofuran-2-ylmethoxy]benzamide

61) N-[1-(5-chloro-3-fluoropyridin-2-yl)ethyl]-3-(5-methyl-1,3-thiazol-2-yl)-5-[(3S)-tetrahydrofuran-3-ylmethoxy]benzamide

62) N-[(6-methylpyridazin-3-yl)methyl]-3-(5-methyl-1,3-thiazol-2-yl)-5-[(3S)-tetrahydrofuran-3-ylmethoxy]benzamide

63) N-[(5-methylpyrazin-2-yl)methyl]-3-(5-methyl-1,3-thiazol-2-yl)-5-[(3S)-tetrahydrofuran-3-ylmethoxy]benzamide

64) N-[(1R)-1-(5-methylpyrazin-2-yl)ethyl]-3-(5-methyl-1,3-thiazol-2-yl)-5-[(3S)-tetrahydrofuran-3-ylmethoxy]benzamide

65) N-[1-(3-chloro-5-fluoropyridin-2-yl)ethyl]-3-(5-methyl-1,3-thiazol-2-yl)-5-[(3R)-tetrahydrofuran-3-ylmethoxy]benzamide

66) 3-(5-methyl-1,3-thiazol-2-yl)-5-[(3S)-tetrahydrofuran-3-ylmethoxy]-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

67) N-[(1R)-1-(6-methylpyridazin-3-yl)ethyl]-3-(5-methyl-1,3-thiazol-2-yl)-5-[(3S)-tetrahydrofuran-3-ylmethoxy]benzamide

68) 3-(5-methyl-1,3-thiazol-2-yl)-5-[(3S)-tetrahydrofuran-3-ylmethoxy]-N-{(1R)-1-[6-(trifluoromethyl)pyridazin-3-yl]ethyl}benzamide

69) 3-(5-methyl-1,3-thiazol-2-yl)-5-[(3R)-tetrahydrofuran-3-ylmethoxy]-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

70) N-[(1R)-1-(5-methylpyrazin-2-yl)ethyl]-3-(5-methyl-1,3-thiazol-2-yl)-5-[(3R)-tetrahydrofuran-3-ylmethoxy]benzamide

71) N-[(6-methylpyridazin-3-yl)methyl]-3-(5-methyl-1,3-thiazol-2-yl)-5-[(3R)-tetrahydrofuran-3-ylmethoxy]benzamide

72) N-[(5-methylpyrazin-2-yl)methyl]-3-(5-methyl-1,3-thiazol-2-yl)-5-[(3R)-tetrahydrofuran-3-ylmethoxy]benzamide

73) N-[(1R)-1-(6-methylpyridazin-3-yl)ethyl]-3-(5-methyl-1,3-thiazol-2-yl)-5-[(3R)-tetrahydrofuran-3-ylmethoxy]benzamide

74) N-[1-(5-chloro-3-fluoropyridin-2-yl)ethyl]-3-(5-methyl-1,3-thiazol-2-yl)-5-[(3R)-tetrahydrofuran-3-ylmethoxy] benzamide

75) 3-(5-methyl-1,3-thiazol-2-yl)-5-[(3R)-tetrahydrofuran-3-ylmethoxy]-N-{(1R)-1-[6-(trifluoromethyl)pyridazin-3-yl]ethyl}benzamide

76) N-[1-(3-chloro-5-fluoropyridin-2-yl)ethyl]-3-(5-methyl-1,3-thiazol-2-yl)-5-(tetrahydro-2H-pyran-4-yloxy)benzamide

77) N-[1-(5-chloro-3-fluoropyridin-2-yl)ethyl]-3-(5-methyl-1,3-thiazol-2-yl)-5-(tetrahydro-2H-pyran-4-yloxy)benzamide

78) N-[(6-methylpyridazin-3-yl)methyl]-3-(5-methyl-1,3-thiazol-2-yl)-5-(tetrahydro-2H-pyran-4-yloxy)benzamide

79) N-[(5-methylpyrazin-2-yl)methyl]-3-(5-methyl-1,3-thiazol-2-yl)-5-(tetrahydro-2H-pyran-4-yloxy)benzamide

80) N-[(1R)-1-(5-methylpyrazin-2-yl)ethyl]-3-(5-methyl-1,3-thiazol-2-yl)-5-(tetrahydro-2H-pyran-4-yloxy)benzamide

81) 3-(5-methyl-1,3-thiazol-2-yl)-5-(tetrahydro-2H-pyran-4-yloxy)-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

82) N-[(1R)-1-(6-methoxypyridin-3-yl)ethyl]-3-(5-methyl-1,3-thiazol-2-yl)-5-(tetrahydro-2H-pyran-4-yloxy)benzamide

83) N-[(1R)-1-(6-methylpyridazin-3-yl)ethyl]-3-(5-methyl-1,3-thiazol-2-yl)-5-(tetrahydro-2H-pyran-4-yloxy)benzamide

84) N-[(6-methoxypyridazin-3-yl)methyl]-3-(5-methyl-1,3-thiazol-2-yl)-5-(tetrahydro-2H-pyran-4-yloxy)benzamide

85) 3-(5-methyl-1,3-thiazol-2-yl)-5-(tetrahydro-2H-pyran-4-yloxy)-N-{(1R)-1-[6-(trifluoromethyl)pyridazin-3-yl]ethyl}benzamide

86) 3-(5-methyl-1,3-thiazol-2-yl)-5-(tetrahydro-2H-pyran-4-yloxy)-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]propyl}benzamide

87) N-[(1R)-1-(6-methylpyridin-3-yl)ethyl]-3-(5-methyl-1,3-thiazol-2-yl)-5-(tetrahydro-2H-pyran-4-yloxy)benzamide

88) N-[(6-methylpyridazin-3-yl)methyl]-3-(5-methyl-1,3-thiazol-2-yl)-5-(tetrahydro-2H-pyran-4-ylmethoxy)benzamide

89) N-[(1R)-1-(5-methylpyrazin-2-yl)ethyl]-3-(5-methyl-1,3-thiazol-2-yl)-5-(tetrahydro-2H-pyran-4-ylmethoxy)benzamide

90) N-[1-(5-chloro-3-fluoropyridin-2-yl)ethyl]-3-(5-methyl-1,3-thiazol-2-yl)-5-(tetrahydro-2H-pyran-4-ylmethoxy)benzamide

91) N-[1-(3-chloro-5-fluoropyridin-2-yl)ethyl]-3-(5-methyl-1,3-thiazol-2-yl)-5-(tetrahydro-2H-pyran-4-ylmethoxy)benzamide

92) N-[(5-methylpyrazin-2-yl)methyl]-3-(5-methyl-1,3-thiazol-2-yl)-5-(tetrahydro-2H-pyran-4-ylmethoxy)benzamide

93) 3-(5-methyl-1,3-thiazol-2-yl)-5-(tetrahydro-2H-pyran-4-ylmethoxy)-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

94) N-[(1R)-1-(6-methylpyridazin-3-yl)ethyl]-3-(5-methyl-1,3-thiazol-2-yl)-5-(tetrahydro-2H-pyran-4-ylmethoxy)benzamide

95) N-[(1R)-1-(6-methylpyridazin-3-yl)ethyl]-3-[(2-methylpyridin-4-yl)oxy]-5-(5-methyl-1,3-thiazol-2-yl)benzamide

96) N-[(6-methylpyridazin-3-yl)methyl]-3-[(2-methylpyridin-4-yl)oxy]-5-(5-methyl-1,3-thiazol-2-yl)benzamide

97) N-[(1R)-1-(5-methylpyrazin-2-yl)ethyl]-3-[(2-methylpyridin-4-yl)oxy]-5-(5-methyl-1,3-thiazol-2-yl)benzamide

98) 3-[(2-methylpyridin-4-yl)oxy]-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

99) N-[(5-methylpyrazin-2-yl)methyl]-3-[(2-methylpyridin-4-yl)oxy]-5-(5-methyl-1,3-thiazol-2-yl)benzamide

100) 3-[(2-methylpyridin-4-yl)oxy]-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[6-(trifluoromethyl)pyridazin-3-yl]ethyl}benzamide

101) 3-[(2-methylpyridin-4-yl)oxy]-N-[(1R)-1-(2-methylpyrimidin-5-yl)ethyl]-5-(5-methyl-1,3-thiazol-2-yl)benzamide

102) N-[(1R)-1-(6-methylpyridin-3-yl)ethyl]-3-[(2-methylpyridin-4-yl)oxy]-5-(5-methyl-1,3-thiazol-2-yl)benzamide

103) 3-[(6-methylpyridin-3-yl)oxy]-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

104) N-[(1R)-1-(5-methylpyrazin-2-yl)ethyl]-3-[(5-methyl-1,3,4-thiadiazol-2-yl)oxy]-5-(5-methyl-1,3-thiazol-2-yl)benzamide

105) N-[(1R)-1-(6-methylpyridazin-3-yl)ethyl]-3-[(5-methyl-1,3,4-thiadiazol-2-yl)oxy]-5-(5-methyl-1,3-thiazol-2-yl)benzamide

106) 3-[(5-methyl-1,3,4-thiadiazol-2-yl)oxy]-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

107) N-[(1R)-1-(5-methylpyrazin-2-yl)ethyl]-3-(5-methyl-1,3-thiazol-2-yl)-5-(1,3-thiazol-2-yloxy)benzamide

108) N-[(1R)-1-(6-methylpyridazin-3-yl)ethyl]-3-(5-methyl-1,3-thiazol-2-yl)-5-(1,3-thiazol-2-yloxy)benzamide

109) N-[(1R)-1-(6-methylpyridin-3-yl)ethyl]-3-(5-methyl-1,3-thiazol-2-yl)-5-(1,3-thiazol-2-yloxy)benzamide

110) N-[(1R)-1-(5-chloropyridin-2-yl)ethyl]-3-(5-chloro-1,3-thiazol-2-yl)-5-(2-methoxy-2-methylpropoxy)benzamide

111) 3-(5-chloro-1,3-thiazol-2-yl)-5-(2-methoxy-2-methylpropoxy)-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

112) 3-(5-chloro-1,3-thiazol-2-yl)-5-(2-methoxy-2-methylpropoxy)-N-[(1R)-1-(5-methylpyrazin-2-yl)ethyl]benzamide

113) N-[(6-methylpyridazin-3-yl)methyl]-3-(tetrahydro-2H-pyran-4-ylmethoxy)-5-[5-(trifluoromethyl)-1,3-thiazol-2-yl]benzamide

114) 3-(5-cyclobutyl-1,3-thiazol-2-yl)-N-[(6-methylpyridazin-3-yl)methyl]-5-(tetrahydro-2H-pyran-4-ylmethoxy)benzamide

115) 3-(5-cyclobutyl-1,3-thiazol-2-yl)-5-(tetrahydro-2H-pyran-4-ylmethoxy)-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

116) 3-(5-cyclobutyl-1,3-thiazol-2-yl)-N-[(1R)-1-(5-methylpyrazin-2-yl)ethyl]-5-[(3S)-tetrahydrofuran-3-ylmethoxy]benzamide

117) 3-(5-cyclobutyl-1,3-thiazol-2-yl)-N-[(6-methylpyridazin-3-yl)methyl]-5-[(3S)-tetrahydrofuran-3-ylmethoxy]benzamide

118) 3-(5-cyclobutyl-1,3-thiazol-2-yl)-5-[(3S)-tetrahydrofuran-3-ylmethoxy]-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

119) 3-(5-cyclobutyl-1,3-thiazol-2-yl)-N-[(1R)-1-(2-methylpyrimidin-5-yl)ethyl]-5-(tetrahydro-2H-pyran-4-ylmethoxy)benzamide

120) 3-(5-ethyl-1,3-thiazol-2-yl)-N-[(1R)-1-(2-methylpyrimidin-5-yl)ethyl]-5-(tetrahydro-2H-pyran-4-ylmethoxy)benzamide

121) N-[(1R)-1-(2-methylpyrimidin-5-yl)ethyl]-3-[5-(propan-2-yl)-1,3-thiazol-2-yl]-5-(tetrahydro-2H-pyran-4-ylmethoxy)benzamide

122) 3-(5-cyclobutyl-1,3-thiazol-2-yl)-N-[(1R)-1-(6-methylpyridazin-3-yl)ethyl]-5-(tetrahydro-2H-pyran-4-yloxy)benzamide

123) 3-(5-ethyl-1,3-thiazol-2-yl)-N-[(1R)-1-(6-methylpyridazin-3-yl)ethyl]-5-(tetrahydro-2H-pyran-4-yloxy)benzamide

124) 3-(5-ethyl-1,3-thiazol-2-yl)-5-(tetrahydro-2H-pyran-4-yloxy)-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

125) N-[(1R)-1-(2-methylpyrimidin-5-yl)ethyl]-3-(5-methyl-1,3-thiazol-2-yl)-5-[(3S)-tetrahydrofuran-3-yloxy]benzamide

126) N-[(1R)-1-(5-methylpyrazin-2-yl)ethyl]-3-[(6-methylpyridin-3-yl)oxy]-5-(5-methyl-1,3-thiazol-2-yl)benzamide

127) N-[1-(3-chloro-5-fluoropyridin-2-yl)ethyl]-3-(5-methyl-1,3-thiazol-2-yl)-5-[(3S)-tetrahydrofuran-3-yloxy]benzamide

128) N-[(6-methylpyridazin-3-yl)methyl]-3-(5-methyl-1,3-thiazol-2-yl)-5-[(3S)-tetrahydrofuran-3-yloxy]benzamide

129) N-[1-(5-chloro-3-fluoropyridin-2-yl)ethyl]-3-(5-methyl-1,3-thiazol-2-yl)-5-[(3S)-tetrahydrofuran-3-yloxy]benzamide

130) 3-(5-cyclobutyl-1,3-thiazol-2-yl)-N-[(1R)-1-(6-methylpyridazin-3-yl)ethyl]-5-[(3S)-tetrahydrofuran-3-ylmethoxy]benzamide

131) 3-(2-methoxyethoxy)-N-[(1R)-1-(2-methylpyrimidin-5-yl)ethyl]-5-(5-methyl-1,3-thiazol-2-yl)benzamide

132) tert-butyl 4-[3-(5-methyl-1,3-thiazol-2-yl)-5-({(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}carbamoyl)phenoxy]piperidine-1-carboxylate

133) 3-(5-methyl-1,3-thiazol-2-yl)-5-(piperidin-4-yloxy)-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

134) 3-[(1-methylpiperidin-4-yl)oxy]-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

135) 3-(5-methyl-1,3-thiazol-2-yl)-5-{[1-(propan-2-yl)piperidin-4-yl]oxy}-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

136) 3-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

137) 3-{[(3S)-1-methylpyrrolidin-3-yl]oxy}-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

138) 3-[(1-methylazetidin-3-yl)oxy]-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

139) 3-(5-methyl-1,3-thiazol-2-yl)-5-(prop-2-yn-1-yloxy)-N-{(1S)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

140) 3-(5-methyl-1,3-thiazol-2-yl)-5-(tetrahydro-2H-pyran-4-yloxy)-N-{(1S)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

141) tert-butyl 6-[3-(5-methyl-1,3-thiazol-2-yl)-5-({(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}carbamoyl)phenoxy]-2-azaspiro[3.3]heptane-2-carboxylate

142) 3-(5-methyl-1,3-thiazol-2-yl)-5-[(3R)-tetrahydrofuran-3-yloxy]-N-{(1R)-1-[5-(trifluoromethyl)pyrazin-2-yl]ethyl}benzamide

143) 3-(5-methyl-1,3-thiazol-2-yl)-5-(oxetan-3-yloxy)-N-{(1R)-1-[6-(trifluoromethyl)pyridin-3-yl]ethyl}benzamide

Also disclosed are the following compounds, namely:

144) 3-(1-azabicyclo[2.2.2]oct-4-yloxy)-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

145) 3-[(1-acetylpiperidin-4-yl)oxy]-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

146) N-{(1R)-1-[2-(difluoromethyl)pyrimidin-5-yl]ethyl}-3-(5-methyl-1,3-thiazol-2-yl)-5-[(3S)-tetrahydrofuran-3-yloxy]benzamide

147) N-{(1R)-1-[2-(difluoromethyl)pyrimidin-5-yl]ethyl}-3-(5-methyl-1,3-thiazol-2-yl)-5-(oxetan-3-yloxy)benzamide

148) N-{(1R)-1-[2-(difluoromethyl)pyrimidin-5-yl]ethyl}-3-(5-methyl-1,3-thiazol-2-yl)-5-[(3R)-tetrahydrofuran-3-yloxy]benzamide

149) N-{(1R)-1-[2-(difluoromethyl)pyrimidin-5-yl]ethyl}-3-(5-methyl-1,3-thiazol-2-yl)-5-(tetrahydro-2H-pyran-4-yloxy)benzamide

150) 3-{[(3S)-1-methylpiperidin-3-yl]oxy}-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

151) 3-[(3-methyloxetan-3-yl)oxy]-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

152) 3-(5-methyl-1,3-thiazol-2-yl)-5-[(3R)-tetrahydrofuran-3-yloxy]-N-{(1R)-1-[6-(trifluoromethyl)pyridin-3-yl]ethyl}benzamide

153) 3-{[(3R)-1-methylpiperidin-3-yl]oxy}-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

154) 3-(5-methyl-1,3-thiazol-2-yl)-5-[2-(1H-1,2,4-triazol-1-yl)ethoxy]-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

155) 3-(5-methyl-1,3-thiazol-2-yl)-5-[2-(1H-1,2,4-triazol-1-yl)ethoxy]-N-{(1R)-1-[6-(trifluoromethyl)pyridin-3-yl]ethyl}benzamide

156) 3-(5-methyl-1,3-thiazol-2-yl)-5-(oxetan-3-yloxy)-N-{(1R)-1-[6-(trifluoromethyl)pyridazin-3-yl]ethyl}benzamide

157) Trans Isomer 1; 3-{[3-hydroxybutan-2-yl]oxy}-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

158) Trans Isomer 2; 3-{[3-hydroxybutan-2-yl]oxy}-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

159) N-{(1R)-1-[6-(difluoromethyl)pyridin-3-yl]ethyl}-3-(5-methyl-1,3-thiazol-2-yl)-5-(oxetan-3-yloxy)benzamide

160) 3-{[trans-3-(dimethylamino)cyclobutyl]oxy}-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

161) 3-(5-methyl-1,3-thiazol-2-yl)-5-[(3R)-tetrahydrofuran-3-yloxy]-N-{[2-(trifluoromethyl)pyrimidin-5-yl]methyl}benzamide

162) 3-(5-methyl-1,3-thiazol-2-yl)-5-(oxetan-3-yloxy)-N-{[2-(trifluoromethyl)pyrimidin-5-yl]methyl}benzamide

163) 3-[(3R)-1-azabicyclo[2.2.2]oct-3-yloxy]-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

164) 3-(5-ethyl-1,3-thiazol-2-yl)-5-(oxetan-3-yloxy)-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

165) 3-[(6-methylpyridazin-3-yl)oxy]-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

166) N-{(1R)-1-[6-(difluoromethyl)pyridin-3-yl]ethyl}-3-(5-methyl-1,3-thiazol-2-yl)-5-[(3R)-tetrahydrofuran-3-yloxy]benzamide

167) 3-[(3R)-1-azabicyclo[2.2.2]oct-3-yloxy]-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[6-(trifluoromethyl)pyridin-3-yl]ethyl}benzamide

168) 3-[(3S)-1-azabicyclo[2.2.2]oct-3-yloxy]-5-(5-ethyl-1,3-thiazol-2-yl)-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

169) 3-[(3R)-1-azabicyclo[2.2.2]oct-3-yloxy]-5-(5-ethyl-1,3-thiazol-2-yl)-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

170) 3-[(3S)-1-azabicyclo[2.2.2]oct-3-yloxy]-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[6-(trifluoromethyl)pyridin-3-yl]ethyl}benzamide

171) 3-[(5-methyl-1,3,4-thiadiazol-2-yl)oxy]-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[6-(trifluoromethyl)pyridin-3-yl]ethyl}benzamide

172) 3-[(2R)-1,4-dioxan-2-ylmethoxy]-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[6-(trifluoromethyl)pyridin-3-yl]ethyl}benzamide

173) 3-[(2R)-1,4-dioxan-2-ylmethoxy]-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

174) 3-[(2R)-1,4-dioxan-2-ylmethoxy]-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[6-(trifluoromethyl)pyridazin-3-yl]ethyl}benzamide

175) 3-[(2S)-1,4-dioxan-2-ylmethoxy]-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[6-(trifluoromethyl)pyridin-3-yl]ethyl}benzamide

176) 3-[(2S)-1,4-dioxan-2-ylmethoxy]-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

177) 3-[(2S)-1,4-dioxan-2-ylmethoxy]-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[6-(trifluoromethyl)pyridazin-3-yl]ethyl}benzamide

178) Trans Isomer 1; 3-{[3-hydroxybutan-2-yl]oxy}-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[6-(trifluoromethyl)pyridazin-3-yl]ethyl}benzamide

179) Trans Isomer 1; 3-(5-chloro-1,3-thiazol-2-yl)-5-{[3-hydroxybutan-2-yl]oxy}-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

180) Cis Isomer 1; 3-(5-chloro-1,3-thiazol-2-yl)-5-{[3-hydroxybutan-2-yl]oxy}-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

181) Trans Isomer 1; 3-(5-chloro-1,3-thiazol-2-yl)-5-{[3-hydroxybutan-2-yl]oxy}-N-{(1R)-1-[6-(trifluoromethyl)pyridin-3-yl]ethyl}benzamide

182) Cis Isomer 2; 3-(5-chloro-1,3-thiazol-2-yl)-5-{[3-hydroxybutan-2-yl]oxy}-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

183) Trans Isomer 2; 3-(5-chloro-1,3-thiazol-2-yl)-5-{[3-hydroxybutan-2-yl]oxy}-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

184) Trans Isomer 2; 3-(5-chloro-1,3-thiazol-2-yl)-5-{[3-hydroxybutan-2-yl]oxy}-N-{(1R)-1-[6-(trifluoromethyl)pyridin-3-yl]ethyl}benzamide

185) tert-Butyl (3R)-3-[3-(5-methyl-1,3-thiazol-2-yl)-5-({(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}carbamoyl)phenoxy]piperidine-1-carboxylate, as a mixture of diastereoisomers

186) 3-(but-2-yn-1-yloxy)-N-[(1R)-1-(6-methylpyridazin-3-yl)ethyl]-5-(5-methyl-1,3-thiazol-2-yl)benzamide

187) 3-[(3S)-1-azabicyclo[2.2.2]oct-3-yloxy]-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

188) 3-(5-methyl-1,3-thiazol-2-yl)-5-(piperidin-4-yloxy)-N-{(1R)-1-[6-(trifluoromethyl)pyridazin-3-yl]ethyl}benzamide

189) 3-(2-azaspiro[3.3]hept-6-yloxy)-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

190) 3-(5-methyl-1,3-thiazol-2-yl)-5-[(3S)-pyrrolidin-3-yloxy]-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

191) 3-{[3-fluoropiperidin-4-yl]oxy}-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide, as a mixture of cis isomers

192) Diastereoisomer 1; 3-(5-methyl-1,3-thiazol-2-yl)-5-(piperidin-3-yloxy)-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

193) Diastereoisomer 2; 3-(5-methyl-1,3-thiazol-2-yl)-5-(piperidin-3-yloxy)-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

194) Cis Isomer 1; 3-(5-methyl-1,3-thiazol-2-yl)-5-{[2-(trifluoromethyl)piperidin-4-yl]oxy}-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

195) Cis Isomer 2; 3-(5-methyl-1,3-thiazol-2-yl)-5-{[2-(trifluoromethyl)piperidin-4-yl]oxy}-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

196) 3-{[2-methyl-2-azabicyclo[2.2.1]hept-5-yl]oxy}-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

197) 3-[(1-methylpiperidin-4-yl)oxy]-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[6-(trifluoromethyl)pyridazin-3-yl]ethyl}benzamide

198) 3-[(1-methylazetidin-3-yl)oxy]-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[6-(trifluoromethyl)pyridazin-3-yl]ethyl}benzamide

199) 3-[(3-fluoro-1-methylpiperidin-4-yl)oxy]-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide, as a single unknown isomer

200) 3-{[1-(dimethylamino)cyclopropyl]methoxy}-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

201) 3-[(2-methyl-2-azaspiro[3.3]hept-6-yl)oxy]-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

202) N-{(1R)-1-[2-(difluoromethyl)pyrimidin-5-yl]ethyl}-3-[(1-methylpiperidin-4-yl)oxy]-5-(5-methyl-1,3-thiazol-2-yl)benzamide

203) 3-{[(3-endo)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl]oxy}-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

204) 3-{[(3-exo)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl]oxy}-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

205) 3-{[(4aS,7R,7aR)-4-methyloctahydrocyclopenta[b][1,4]oxazin-7-yl]oxy}-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

206) 3-{[(4aS,7S,7aR)-4-methyloctahydrocyclopenta[b][1,4]oxazin-7-yl]oxy}-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

207) Diastereoisomer 1; 3-[(1-methylpiperidin-3-yl)oxy]-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

208) Diastereoisomer 2; 3-[(1-methylpiperidin-3-yl)oxy]-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

209) Cis Isomer 1; 3-(5-methyl-1,3-thiazol-2-yl)-5-{[1-methyl-2-(trifluoromethyl)piperidin-4-yl]oxy}-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

210) Cis Isomer 2; 3-(5-methyl-1,3-thiazol-2-yl)-5-{[1-methyl-2-(trifluoromethyl)piperidin-4-yl]oxy}-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

211) 3-(5-methyl-1,3-thiazol-2-yl)-5-{[1-(propan-2-yl)piperidin-4-yl]oxy}-N-{(1R)-1-[6-(trifluoromethyl)pyridazin-3-yl]ethyl}benzamide

212) 3-(5-methyl-1,3-thiazol-2-yl)-5-{[(3S)-1-(propan-2-yl)pyrrolidin-3-yl]oxy}-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

213) methyl 4-[3-(5-methyl-1,3-thiazol-2-yl)-5-({(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}carbamoyl)phenoxy]piperidine-1-carboxylate

214) ethyl 4-[3-(5-methyl-1,3-thiazol-2-yl)-5-({(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}carbamoyl)phenoxy]piperidine-1-carboxylate

215) ethyl (3S)-3-[3-(5-methyl-1,3-thiazol-2-yl)-5-({(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}carbamoyl)phenoxy]pyrrolidine-1-carboxylate

216) 3-(5-methyl-1,3-thiazol-2-yl)-5-{[1-(propan-2-yl)azetidin-3-yl]oxy}-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

217) Cis Isomer 1; 3-[(-3-hydroxybutan-2-yl)oxy]-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[6-(trifluoromethyl)pyridazin-3-yl]ethyl}benzamide

218) Cis Isomer 2; 3-[(-3-hydroxybutan-2-yl)oxy]-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[6-(trifluoromethyl)pyridazin-3-yl]ethyl}benzamide

219) 3-[(1,1-dioxidotetrahydro-2H-thiopyran-4-yl)oxy]-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

220) 3-[(1,1-dioxidotetrahydro-2H-thiopyran-4-yl)oxy]-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[6-(trifluoromethyl)pyridin-3-yl]ethyl}benzamide

221) 3-(5-ethyl-1,3-thiazol-2-yl)-N-[(1R)-1-(5-methylpyrazin-2-yl)ethyl]-5-(tetrahydro-2H-pyran-4-yloxy)benzamide

222) 3-(5-ethyl-1,3-thiazol-2-yl)-N-[(6-methylpyridazin-3-yl)methyl]-5-(tetrahydro-2H-pyran-4-yloxy)benzamide

223) 3-(5-cyclobutyl-1,3-thiazol-2-yl)-N-[(1R)-1-(5-methylpyrazin-2-yl)ethyl]-5-(tetrahydro-2H-pyran-4-yloxy)benzamide

224) 3-(5-cyclobutyl-1,3-thiazol-2-yl)-N-[(6-methylpyridazin-3-yl)methyl]-5-(tetrahydro-2H-pyran-4-yloxy)benzamide

225) 3-(5-cyclobutyl-1,3-thiazol-2-yl)-5-(tetrahydro-2H-pyran-4-yloxy)-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

226) 3-(5-cyclobutyl-1,3-thiazol-2-yl)-5-[(3S)-tetrahydrofuran-3-ylmethoxy]-N-{(1S)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

227) 3-(5-ethyl-1,3-thiazol-2-yl)-N-[(1R)-1-(6-methylpyridazin-3-yl)ethyl]-5-[(3R)-tetrahydrofuran-3-yloxy]benzamide

228) 3-(5-ethyl-1,3-thiazol-2-yl)-N-[(1R)-1-(5-methylpyrazin-2-yl)ethyl]-5-[(3R)-tetrahydrofuran-3-yloxy]benzamide

229) 3-(5-ethyl-1,3-thiazol-2-yl)-5-[(3R)-tetrahydrofuran-3-yloxy]-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

230) 3-(5-cyclobutyl-1,3-thiazol-2-yl)-N-[(1R)-1-(6-methylpyridazin-3-yl)ethyl]-5-[(3R)-tetrahydrofuran-3-yloxy]benzamide

231) 3-(5-cyclobutyl-1,3-thiazol-2-yl)-N-[(1R)-1-(5-methylpyrazin-2-yl)ethyl]-5-[(3R)-tetrahydrofuran-3-yloxy]benzamide

232) 3-(5-cyclobutyl-1,3-thiazol-2-yl)-5-[(3R)-tetrahydrofuran-3-yloxy]-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

233) N-[(1R)-1-(6-methylpyridazin-3-yl)ethyl]-3-[5-(propan-2-yl)-1,3-thiazol-2-yl]-5-[(3R)-tetrahydrofuran-3-yloxy]benzamide

234) N-[(1R)-1-(5-methylpyrazin-2-yl)ethyl]-3-[5-(propan-2-yl)-1,3-thiazol-2-yl]-5-[(3R)-tetrahydrofuran-3-yloxy]benzamide

235) 3-[5-(propan-2-yl)-1,3-thiazol-2-yl]-5-[(3R)-tetrahydrofuran-3-yloxy]-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

236) 3-(5-ethyl-1,3-thiazol-2-yl)-N-[(1R)-1-(6-methylpyridazin-3-yl)ethyl]-5-[(3S)-tetrahydrofuran-3-yloxy]benzamide

237) 3-(5-ethyl-1,3-thiazol-2-yl)-N-[(1R)-1-(5-methylpyrazin-2-yl)ethyl]-5-[(3S)-tetrahydrofuran-3-yloxy]benzamide

238) 3-(5-ethyl-1,3-thiazol-2-yl)-5-[(3S)-tetrahydrofuran-3-yloxy]-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

239) 3-(5-cyclobutyl-1,3-thiazol-2-yl)-N-[(1R)-1-(6-methylpyridazin-3-yl)ethyl]-5-[(3S)-tetrahydrofuran-3-yloxy]benzamide

240) 3-(5-cyclobutyl-1,3-thiazol-2-yl)-N-[(1R)-1-(5-methylpyrazin-2-yl)ethyl]-5-[(3S)-tetrahydrofuran-3-yloxy]benzamide

241) 3-(5-cyclobutyl-1,3-thiazol-2-yl)-5-[(3S)-tetrahydrofuran-3-yloxy]-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

242) N-[(1R)-1-(6-methylpyridazin-3-yl)ethyl]-3-[5-(propan-2-yl)-1,3-thiazol-2-yl]-5-[(3S)-tetrahydrofuran-3-yloxy]benzamide

243) N-[(1R)-1-(5-methylpyrazin-2-yl)ethyl]-3-[5-(propan-2-yl)-1,3-thiazol-2-yl]-5-[(3S)-tetrahydrofuran-3-yloxy]benzamide

244) 3-[5-(propan-2-yl)-1,3-thiazol-2-yl]-5-[(3S)-tetrahydrofuran-3-yloxy]-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

245) 3-(5-ethyl-1,3-thiazol-2-yl)-N-[(1R)-1-(6-methylpyridazin-3-yl)ethyl]-5-[(3R)-tetrahydrofuran-3-ylmethoxy]benzamide

246) 3-(5-ethyl-1,3-thiazol-2-yl)-N-[(1R)-1-(5-methylpyrazin-2-yl)ethyl]-5-[(3R)-tetrahydrofuran-3-ylmethoxy]benzamide

247) 3-(5-ethyl-1,3-thiazol-2-yl)-5-[(3R)-tetrahydrofuran-3-ylmethoxy]-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

248) 3-(5-cyclobutyl-1,3-thiazol-2-yl)-N-[(1R)-1-(6-methylpyridazin-3-yl)ethyl]-5-[(3R)-tetrahydrofuran-3-ylmethoxy]benzamide

249) 3-(5-cyclobutyl-1,3-thiazol-2-yl)-N-[(1R)-1-(5-methylpyrazin-2-yl)ethyl]-5-[(3R)-tetrahydrofuran-3-ylmethoxy]benzamide

250) 3-(5-cyclobutyl-1,3-thiazol-2-yl)-5-[(3R)-tetrahydrofuran-3-ylmethoxy]-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

251) N-[(1R)-1-(6-methylpyridazin-3-yl)ethyl]-3-[5-(propan-2-yl)-1,3-thiazol-2-yl]-5-[(3R)-tetrahydrofuran-3-ylmethoxy]benzamide

252) N-[(1R)-1-(5-methylpyrazin-2-yl)ethyl]-3-[5-(propan-2-yl)-1,3-thiazol-2-yl]-5-[(3R)-tetrahydrofuran-3-ylmethoxy]benzamide

253) 3-[5-(propan-2-yl)-1,3-thiazol-2-yl]-5-[(3R)-tetrahydrofuran-3-ylmethoxy]-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

254) 3-(5-ethyl-1,3-thiazol-2-yl)-N-[(1R)-1-(6-methylpyridazin-3-yl)ethyl]-5-[(2R)-tetrahydrofuran-2-ylmethoxy]benzamide

255) 3-(5-ethyl-1,3-thiazol-2-yl)-N-[(1R)-1-(5-methylpyrazin-2-yl)ethyl]-5-[(2R)-tetrahydrofuran-2-ylmethoxy]benzamide

256) 3-(5-ethyl-1,3-thiazol-2-yl)-5-[(2R)-tetrahydrofuran-2-ylmethoxy]-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

257) 3-(5-cyclobutyl-1,3-thiazol-2-yl)-N-[(1R)-1-(6-methylpyridazin-3-yl)ethyl]-5-[(2R)-tetrahydrofuran-2-ylmethoxy]benzamide

258) 3-(5-cyclobutyl-1,3-thiazol-2-yl)-N-[(1R)-1-(5-methylpyrazin-2-yl)ethyl]-5-[(2R)-tetrahydrofuran-2-ylmethoxy]benzamide

259) 3-(5-cyclobutyl-1,3-thiazol-2-yl)-5-[(2R)-tetrahydrofuran-2-ylmethoxy]-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

260) N-[(1R)-1-(6-methylpyridazin-3-yl)ethyl]-3-[5-(propan-2-yl)-1,3-thiazol-2-yl]-5-[(2R)-tetrahydrofuran-2-ylmethoxy]benzamide

261) N-[(1R)-1-(5-methylpyrazin-2-yl)ethyl]-3-[5-(propan-2-yl)-1,3-thiazol-2-yl]-5-[(2R)-tetrahydrofuran-2-ylmethoxy]benzamide

262) 3-[5-(propan-2-yl)-1,3-thiazol-2-yl]-5-[(2R)-tetrahydrofuran-2-ylmethoxy]-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

263) 3-(5-ethyl-1,3-thiazol-2-yl)-N-[(1R)-1-(6-methylpyridazin-3-yl)ethyl]-5-[(3S)-tetrahydrofuran-3-ylmethoxy]benzamide

264) 3-(5-ethyl-1,3-thiazol-2-yl)-N-[(1R)-1-(5-methylpyrazin-2-yl)ethyl]-5-[(3S)-tetrahydrofuran-3-ylmethoxy]benzamide

265) 3-(5-ethyl-1,3-thiazol-2-yl)-5-[(3S)-tetrahydrofuran-3-ylmethoxy]-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

266) N-[(1R)-1-(6-methylpyridazin-3-yl)ethyl]-3-[5-(propan-2-yl)-1,3-thiazol-2-yl]-5-[(3S)-tetrahydrofuran-3-ylmethoxy]benzamide

267) N-[(1R)-1-(5-methylpyrazin-2-yl)ethyl]-3-[5-(propan-2-yl)-1,3-thiazol-2-yl]-5-[(3S)-tetrahydrofuran-3-ylmethoxy]benzamide

268) 3-[5-(propan-2-yl)-1,3-thiazol-2-yl]-5-[(3S)-tetrahydrofuran-3-ylmethoxy]-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

269) 3-(5-ethyl-1,3-thiazol-2-yl)-N-[(1R)-1-(6-methylpyridazin-3-yl)ethyl]-5-[(2S)-tetrahydrofuran-2-ylmethoxy]benzamide

270) 3-(5-ethyl-1,3-thiazol-2-yl)-N-[(1R)-1-(5-methylpyrazin-2-yl)ethyl]-5-[(2S)-tetrahydrofuran-2-ylmethoxy]benzamide

271) 3-(5-ethyl-1,3-thiazol-2-yl)-5-[(2S)-tetrahydrofuran-2-ylmethoxy]-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

272) 3-(5-cyclobutyl-1,3-thiazol-2-yl)-N-[(1R)-1-(6-methylpyridazin-3-yl)ethyl]-5-[(2S)-tetrahydrofuran-2-ylmethoxy]benzamide

273) 3-(5-cyclobutyl-1,3-thiazol-2-yl)-N-[(1R)-1-(5-methylpyrazin-2-yl)ethyl]-5-[(2S)-tetrahydrofuran-2-ylmethoxy]benzamide

274) 3-(5-cyclobutyl-1,3-thiazol-2-yl)-5-[(2S)-tetrahydrofuran-2-ylmethoxy]-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

275) N-[(1R)-1-(6-methylpyridazin-3-yl)ethyl]-3-[5-(propan-2-yl)-1,3-thiazol-2-yl]-5-[(2S)-tetrahydrofuran-2-ylmethoxy]benzamide

276) N-[(1R)-1-(5-methylpyrazin-2-yl)ethyl]-3-[5-(propan-2-yl)-1,3-thiazol-2-yl]-5-[(2S)-tetrahydrofuran-2-ylmethoxy]benzamide

277) 3-[5-(propan-2-yl)-1,3-thiazol-2-yl]-5-[(2S)-tetrahydrofuran-2-ylmethoxy]-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

278) 3-(5-methyl-1,3-thiazol-2-yl)-5-[(3R)-tetrahydrofuran-3-yloxy]-N-{(1S)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

279) 3-(5-ethyl-1,3-thiazol-2-yl)-5-[(3R)-tetrahydrofuran-3-ylmethoxy]-N-{(1R)-1-[6-(trifluoromethyl)pyridazin-3-yl]ethyl}benzamide

280) 3-[5-(propan-2-yl)-1,3-thiazol-2-yl]-5-[(3R)-tetrahydrofuran-3-ylmethoxy]-N-{(1R)-1-[6-(trifluoromethyl)pyridazin-3-yl]ethyl}benzamide

281) 3-[5-(propan-2-yl)-1,3-thiazol-2-yl]-5-[(3R)-tetrahydrofuran-3-yloxy]-N-{(1R)-1-[6-(trifluoromethyl)pyridazin-3-yl]ethyl}benzamide

282) 3-(5-cyclobutyl-1,3-thiazol-2-yl)-5-[(3S)-tetrahydrofuran-3-yloxy]-N-{(1R)-1-[6-(trifluoromethyl)pyridazin-3-yl]ethyl}benzamide

283) 3-(5-ethyl-1,3-thiazol-2-yl)-5-[(3S)-tetrahydrofuran-3-ylmethoxy]-N-{(1R)-1-[6-(trifluoromethyl)pyridazin-3-yl]ethyl}benzamide

284) 3-(5-cyclobutyl-1,3-thiazol-2-yl)-5-[(3R)-tetrahydrofuran-3-ylmethoxy]-N-{(1R)-1-[6-(trifluoromethyl)pyridazin-3-yl]ethyl}benzamide

285) 3-[5-(propan-2-yl)-1,3-thiazol-2-yl]-5-[(3S)-tetrahydrofuran-3-ylmethoxy]-N-{(1R)-1-[6-(trifluoromethyl)pyridazin-3-yl]ethyl}benzamide

286) 3-[5-(propan-2-yl)-1,3-thiazol-2-yl]-5-[(2R)-tetrahydrofuran-2-ylmethoxy]-N-{(1R)-1-[6-(trifluoromethyl)pyridazin-3-yl]ethyl}benzamide

287) 3-(5-cyclobutyl-1,3-thiazol-2-yl)-5-[(2S)-tetrahydrofuran-2-ylmethoxy]-N-{(1R)-1-[6-(trifluoromethyl)pyridazin-3-yl]ethyl}benzamide

288) 3-[5-(propan-2-yl)-1,3-thiazol-2-yl]-5-[(2S)-tetrahydrofuran-2-ylmethoxy]-N-{(1R)-1-[6-(trifluoromethyl)pyridazin-3-yl]ethyl}benzamide

289) 3-(5-ethyl-1,3-thiazol-2-yl)-5-[(2S)-tetrahydrofuran-2-ylmethoxy]-N-{(1R)-1-[6-(trifluoromethyl)pyridazin-3-yl]ethyl}benzamide

290) 3-(5-methyl-1,3-thiazol-2-yl)-5-{[1-(2,2,2-trifluoroethyl)piperidin-4-yl]oxy}-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

291) 3-{[1-(2,2-difluoroethyl)piperidin-4-yl]oxy}-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

292) 3-{[1-(2,2-difluoroethyl)piperidin-4-yl]oxy}-N-[(1R)-1-(6-methylpyridazin-3-yl)ethyl]-5-(5-methyl-1,3-thiazol-2-yl)benzamide

293) 3-{[1-(2,2-difluoroethyl)piperidin-4-yl]oxy}-N-[(1R)-1-(5-methylpyrazin-2-yl)ethyl]-5-(5-methyl-1,3-thiazol-2-yl)benzamide

294) 3-{[1-(2,2-difluoroethyl)piperidin-4-yl]oxy}-N-[(6-methylpyridazin-3-yl)methyl]-5-(5-methyl-1,3-thiazol-2-yl)benzamide

295) 3-{[1-(2,2-difluoroethyl)piperidin-4-yl]oxy}-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1S)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

296) 3-{[1-(2,2-difluoroethyl)piperidin-4-yl]oxy}-N-[(1R)-1-(2-methylpyrimidin-5-yl)ethyl]-5-(5-methyl-1,3-thiazol-2-yl)benzamide

297) 3-(5-methyl-1,3-thiazol-2-yl)-5-{[1-(2,2,2-trifluoroethyl)piperidin-4-yl]oxy}-N-{(1S)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

298) N-[(1R)-1-(6-methylpyridazin-3-yl)ethyl]-3-(5-methyl-1,3-thiazol-2-yl)-5-{[1-(2,2,2-trifluoroethyl)piperidin-4-yl]oxy}benzamide

299) 3-(5-methyl-1,3-thiazol-2-yl)-5-{[1-(2,2,2-trifluoroethyl)piperidin-4-yl]oxy}-N-{(1R)-1-[6-(trifluoromethyl)pyridazin-3-yl]ethyl}benzamide

300) N-[(1R)-1-(5-methylpyrazin-2-yl)ethyl]-3-(5-methyl-1,3-thiazol-2-yl)-5-{[1-(2,2,2-trifluoroethyl)piperidin-4-yl]oxy}benzamide

301) N-[(6-methylpyridazin-3-yl)methyl]-3-(5-methyl-1,3-thiazol-2-yl)-5-{[1-(2,2,2-trifluoroethyl)piperidin-4-yl]oxy}benzamide

302) N-[(1R)-1-(2-methylpyrimidin-5-yl)ethyl]-3-(5-methyl-1,3-thiazol-2-yl)-5-{[1-(2,2,2-trifluoroethyl)piperidin-4-yl]oxy}benzamide

303) 3-(5-chloro-1,3-thiazol-2-yl)-N-[(1R)-1-(6-methylpyridazin-3-yl)ethyl]-5-[(3S)-tetrahydrofuran-3-ylmethoxy]benzamide

304) 3-(5-chloro-1,3-thiazol-2-yl)-N-[(1R)-1-(6-methylpyridazin-3-yl)ethyl]-5-[(3R)-tetrahydrofuran-3-yloxy]benzamide

305) 3-(5-chloro-1,3-thiazol-2-yl)-5-[(3R)-tetrahydrofuran-3-yloxy]-N-{(1R)-1-[6-(trifluoromethyl)pyridazin-3-yl]ethyl}benzamide

306) 3-(5-chloro-1,3-thiazol-2-yl)-N-[(1R)-1-(5-methylpyrazin-2-yl)ethyl]-5-[(3R)-tetrahydrofuran-3-yloxy]benzamide

307) 3-(5-chloro-1,3-thiazol-2-yl)-5-[(3S)-tetrahydrofuran-3-yloxy]-N-{(1R)-1-[6-(trifluoromethyl)pyridazin-3-yl]ethyl}benzamide

308) 3-(5-chloro-1,3-thiazol-2-yl)-N-[(1R)-1-(5-methylpyrazin-2-yl)ethyl]-5-[(3S)-tetrahydrofuran-3-yloxy]benzamide

309) 3-(5-chloro-1,3-thiazol-2-yl)-N-[(1R)-1-(6-methylpyridazin-3-yl)ethyl]-5-[(3S)-tetrahydrofuran-3-yloxy]benzamide

310) 3-(5-chloro-1,3-thiazol-2-yl)-5-[(3S)-tetrahydrofuran-3-ylmethoxy]-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

311) 3-(5-chloro-1,3-thiazol-2-yl)-N-[(1R)-1-(5-methylpyrazin-2-yl)ethyl]-5-(tetrahydro-2H-pyran-4-yloxy)benzamide

312) 3-(5-chloro-1,3-thiazol-2-yl)-N-[(1R)-1-(6-methylpyridazin-3-yl)ethyl]-5-(tetrahydro-2H-pyran-4-yloxy)benzamide

313) 3-(5-chloro-1,3-thiazol-2-yl)-5-(tetrahydro-2H-pyran-4-yloxy)-N-{(1R)-1-[6-(trifluoromethyl)pyridazin-3-yl]ethyl}benzamide

314) 3-[(3-methyloxetan-3-yl)methoxy]-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

315) 3-(2-hydroxy-2-methylpropoxy)-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

316) 3-[(2-methyltetrahydrofuran-2-yl)methoxy]-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide, as a mixture of two diastereoisomers

317) Diastereoisomer 1; 3-[(2-methyltetrahydrofuran-2-yl)methoxy]-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

318) Diastereoisomer 2; 3-[(2-methyltetrahydrofuran-2-yl)methoxy]-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

319) 3-[(3-methyltetrahydrofuran-3-yl)methoxy]-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide, as a mixture of two diastereoisomers

320) Diastereoisomer 1; 3-[(3-methyltetrahydrofuran-3-yl)methoxy]-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

321) Diastereoisomer 2; 3-[(3-methyltetrahydrofuran-3-yl)methoxy]-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

322) 3-[(1-methyl-6-oxopiperidin-3-yl)oxy]-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide, as a mixture of two diastereoisomers

323) Diastereoisomer 1; 3-[(1-methyl-6-oxopiperidin-3-yl)oxy]-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

324) Diastereoisomer 2; 3-[(1-methyl-6-oxopiperidin-3-yl)oxy]-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

325) 3-[(3-hydroxybutan-2-yl)oxy]-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide, as a mixture of cis isomers

326) Cis Isomer 1; 3-[(3-hydroxybutan-2-yl)oxy]-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

327) Cis Isomer 2; 3-[(3-hydroxybutan-2-yl)oxy]-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

328) 3-[(7-methyl-3-oxa-7-azabicyclo[3.3.1]non-9-yl)oxy]-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide, as a mixture of two stereoisomers

329) Stereoisomer 1; 3-[(7-methyl-3-oxa-7-azabicyclo[3.3.1]non-9-yl)oxy]-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

330) Stereoisomer 2; 3-[(7-methyl-3-oxa-7-azabicyclo[3.3.1]non-9-yl)oxy]-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

331) 3-[(7-isopropyl-3-oxa-7-azabicyclo[3.3.1]non-9-yl)oxy]-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide, as a mixture of two stereoisomers

332) methyl 9-[3-(5-methyl-1,3-thiazol-2-yl)-5-({(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}carbamoyl)phenoxy]-3-oxa-7-azabicyclo[3.3.1]nonane-7-carboxylate, as a mixture of two stereoisomers

333) tert-butyl (2R)-2-{[3-(5-methyl-1,3-thiazol-2-yl)-5-({(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}carbamoyl)phenoxy]methyl}morpholine-4-carboxylate

334) 3-(5-methyl-1,3-thiazol-2-yl)-5-[(2R)-morpholin-2-ylmethoxy]-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

335) 3-{[(2R)-4-methylmorpholin-2-yl]methoxy}-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

336) tert-butyl (2S)-2-{[3-(5-methyl-1,3-thiazol-2-yl)-5-({(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}carbamoyl)phenoxy]methyl}morpholine-4-carboxylate

337) 3-(5-methyl-1,3-thiazol-2-yl)-5-[(2S)-morpholin-2-ylmethoxy]-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

338) 3-{[(2S)-4-methylmorpholin-2-yl]methoxy}-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

339) 3-(5-methyl-1,3-thiazol-2-yl)-5-[morpholin-2-ylmethoxy]-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide, as a mixture of diastereoisomers

340) 3-{[4-methylmorpholin-2-yl]methoxy}-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide, as a mixture of diastereoisomers

341) Diastereoisomer 1; 3-(fluoropiperidin-3-yl)methoxy}-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

342) Diastereoisomer 2; 3-(fluoropiperidin-3-yl)methoxy}-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

343) Diastereoisomer 1; 3-{[3-fluoro-1-methylpiperidin-3-yl]methoxy}-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

344) Diastereoisomer 2; 3-{[3-fluoro-1-methylpiperidin-3-yl]methoxy}-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

345) 3-[(3-fluoroazetidin-3-yl)methoxy]-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

346) 3-{[4,4-difluoropiperidin-3-yl]methoxy}-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide, as a mixture of 2 diastereoisomers

347) 3-{[(3R)-4-methylmorpholin-3-yl]methoxy}-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

348) 3-{[(3S)-4-methylmorpholin-3-yl]methoxy}-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[6-(trifluoromethyl)pyridin-3-yl]ethyl}benzamide

349) 3-{[(3S)-4-methylmorpholin-3-yl]methoxy}-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

350) 3-{[(3R)-4-methylmorpholin-3-yl]methoxy}-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[6-(trifluoromethyl)pyridin-3-yl]ethyl}benzamide

351) 3-{[4-fluoro-1-methylpyrrolidin-2-yl]methoxy}-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide, as a mixture of stereoisomers

352) 3-{[4-fluoro-1-methylpyrrolidin-2-yl]methoxy}-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[6-(trifluoromethyl)pyridin-3-yl]ethyl}benzamide, as a mixture of stereoisomers

353) 3-{[(2R)-4-methylmorpholin-2-yl]methoxy}-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[6-(trifluoromethyl)pyridin-3-yl]ethyl}benzamide

354) 3-(5-chloro-1,3-thiazol-2-yl)-5-{[(2R)-4-methylmorpholin-2-yl]methoxy}-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

355) 3-{[(2S)-4-methylmorpholin-2-yl]methoxy}-5-(5-methyl-1,3-thiazol-2-yl)-N-{[2-(trifluoromethyl)pyrimidin-5-yl]methyl}benzamide

356) N-{(1R)-1-[6-(difluoromethyl)pyridin-3-yl]ethyl}-3-{[(2R)-4-methylmorpholin-2-yl]methoxy}-5-(5-methyl-1,3-thiazol-2-yl)benzamide

357) 3-{[(2S)-4-methylmorpholin-2-yl]methoxy}-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[6-(trifluoromethyl)pyridin-3-yl]ethyl}benzamide

358) 3-[(3-fluoro-1-methylazetidin-3-yl)methoxy]-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

359) 3-{[(2R)-4-methylmorpholin-2-yl]methoxy}-5-(5-methyl-1,3-thiazol-2-yl)-N-{[2-(trifluoromethyl)pyrimidin-5-yl]methyl}benzamide

360) 3-{[(2R)-4-methylmorpholin-2-yl]methoxy}-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[6-(trifluoromethyl)pyridazin-3-yl]ethyl}benzamide

361) 3-{[(2S)-4-methylmorpholin-2-yl]methoxy}-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[6-(trifluoromethyl)pyridazin-3-yl]ethyl}benzamide

362) 3-(5-ethyl-1,3-thiazol-2-yl)-5-{[(2S)-4-methylmorpholin-2-yl]methoxy}-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

363) 3-(5-chloro-1,3-thiazol-2-yl)-5-{[(2S)-4-methylmorpholin-2-yl]methoxy}-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

364) 3-(5-ethyl-1,3-thiazol-2-yl)-5-{[(2R)-4-methylmorpholin-2-yl]methoxy}-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

365) 3-{[(2S)-1-methylpyrrolidin-2-yl]methoxy}-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

366) 3-{[(2R)-1-methylpyrrolidin-2-yl]methoxy}-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

367) 3-[(1-methylpiperidin-4-yl)methoxy]-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

368) 3-(5-methyl-1,3-thiazol-2-yl)-5-{[(2R)-4-(propan-2-yl)morpholin-2-yl]methoxy}-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

369) 3-(5-methyl-1,3-thiazol-2-yl)-5-{[(2S)-4-(propan-2-yl)morpholin-2-yl]methoxy}-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

370) 3-{[4,4-difluoro-1-methylpiperidin-3-yl]methoxy}-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide, as a mixture of 2 diastereoisomers

371) Diastereoisomer 1; 3-{[4,4-difluoro-1-methylpiperidin-3-yl]methoxy}-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

372) Diastereoisomer 2; 3-{[4,4-difluoro-1-methylpiperidin-3-yl]methoxy}-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

373) 3-[(3-fluoro-1-methylazetidin-3-yl)methoxy]-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[6-(trifluoromethyl)pyridin-3-yl]ethyl}benzamide

374) 3-(5-ethyl-1,3-thiazol-2-yl)-5-[(3-fluoro-1-methylazetidin-3-yl)methoxy]-N-{(1R)-1-[6-(trifluoromethyl)pyridin-3-yl]ethyl}benzamide

375) 3-{[(3R)-4-methylmorpholin-3-yl]methoxy}-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[6-(trifluoromethyl)pyridazin-3-yl]ethyl}benzamide

376) 3-{[(3S)-4-methylmorpholin-3-yl]methoxy}-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[6-(trifluoromethyl)pyridazin-3-yl]ethyl}benzamide

377) 3-{[(2R)-4-ethylmorpholin-2-yl]methoxy}-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

378) 3-{[(2R)-4-(2,2-difluoroethyl)morpholin-2-yl]methoxy}-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

379) methyl (2R)-2-{[3-(5-methyl-1,3-thiazol-2-yl)-5-({(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}carbamoyl)phenoxy]methyl}morpholine-4-carboxylate

380) methyl (2S)-2-{[3-(5-methyl-1,3-thiazol-2-yl)-5-({(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}carbamoyl)phenoxy]methyl}morpholine-4-carboxylate

381) 3-(azetidin-3-ylmethoxy)-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

382) 3-{[(3R)-4-methyl-5-oxomorpholin-3-yl]methoxy}-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

383) 3-(5-methyl-1,3-thiazol-2-yl)-5-{[(3R)-5-oxomorpholin-3-yl]methoxy}-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

384) 3-{[(5S)-3-methyl-2-oxo-1,3-oxazolidin-5-yl]methoxy}-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

385) 3-{[(5R)-3-methyl-2-oxo-1,3-oxazolidin-5-yl]methoxy}-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

386) 3-{[(2R)-4-methyl-5-oxomorpholin-2-yl]methoxy}-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

387) 3-(5-methyl-1,3-thiazol-2-yl)-5-{[(2S)-5-oxomorpholin-2-yl]methoxy}-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

388) 3-{[(2S)-4-methyl-5-oxomorpholin-2-yl]methoxy}-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

389) 3-{[(3S)-4-methyl-5-oxomorpholin-3-yl]methoxy}-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

390) 3-(5-methyl-1,3-thiazol-2-yl)-5-{[(3S)-5-oxomorpholin-3-yl]methoxy}-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

391) tert-butyl 1-{[3-(5-methyl-1,3-thiazol-2-yl)-5-({(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}carbamoyl)phenoxy]methyl}-2-oxa-5-azabicyclo[2.2.1]heptane-5-carboxylate, as a mixture of 2 diastereoisomers

392) 3-[(5-isopropyl-2-oxa-5-azabicyclo[2.2.1]hept-1-yl)methoxy]-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide, as a mixture of 2 diastereoisomers

393) 3-[(5-methyl-2-oxa-5-azabicyclo[2.2.1]hept-1-yl)methoxy]-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide, as a mixture of 2 diastereoisomers

394) 3-(5-methyl-1,3-thiazol-2-yl)-5-[(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-1-ylmethoxy]-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide, as a mixture of 2 diastereoisomers

395) 3-(5-methyl-1,3-thiazol-2-yl)-5-[(5-propyl-2-oxa-5-azabicyclo[2.2.1]hept-1-yl)methoxy]-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide, as a mixture of 2 diastereoisomers

396) methyl 1-{[3-(5-methyl-1,3-thiazol-2-yl)-5-({(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}carbamoyl)phenoxy]methyl}-2-oxa-5-azabicyclo[2.2.1]heptane-5-carboxylate, as a mixture of 2 diastereoisomers

397) ethyl 1-{[3-(5-methyl-1,3-thiazol-2-yl)-5-({(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}carbamoyl)phenoxy]methyl}-2-oxa-5-azabicyclo[2.2.1]heptane-5-carboxylate, as a mixture of 2 diastereoisomers

398) 3-{[(2S)-4-ethylmorpholin-2-yl]methoxy}-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

399) tert-butyl (2R)-2-{[3-(5-methyl-1,3-thiazol-2-yl)-5-({(1S)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}carbamoyl)phenoxy]methyl}morpholine-4-carboxylate

400) 3-(5-methyl-1,3-thiazol-2-yl)-5-[(2R)-morpholin-2-ylmethoxy]-N-{(1S)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

401) 3-(5-ethyl-1,3-thiazol-2-yl)-5-[(2S)-morpholin-2-ylmethoxy]-N-{(1R)-1-[6-(trifluoromethyl)pyridazin-3-yl]ethyl}benzamide

402) 3-(5-ethyl-1,3-thiazol-2-yl)-5-[(2R)-morpholin-2-ylmethoxy]-N-{(1R)-1-[6-(trifluoromethyl)pyridazin-3-yl]ethyl}benzamide

403) 3-{[(2R)-4-methylmorpholin-2-yl]methoxy}-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1S)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

404) 3-{[(2S)-4-methylmorpholin-2-yl]methoxy}-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1S)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

405) 3-(5-ethyl-1,3-thiazol-2-yl)-5-{[(2S)-4-methylmorpholin-2-yl]methoxy}-N-{(1R)-1-[6-(trifluoromethyl)pyridazin-3-yl]ethyl}benzamide

406) 3-(5-ethyl-1,3-thiazol-2-yl)-5-{[(2R)-4-methylmorpholin-2-yl]methoxy}-N-{(1R)-1-[6-(trifluoromethyl)pyridazin-3-yl]ethyl}benzamide.

Also disclosed is the use of following compounds for the treatment or prophylaxis of diseases or disorders which are 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,

3-(5-Methyl-1,3-thiazol-2-yl)-5-[(3R)-tetrahydrofuran-3-yloxy]-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide;

3-(5-Methyl-1,3-thiazol-2-yl)-5-[(3S)-tetrahydrofuran-3-yloxy]-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide;

3-(5-Methyl-1,3-thiazol-2-yl)-5-(oxetan-3-yloxy)-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide;

3-(5-Ethyl-1,3-thiazol-2-yl)-5-[(3R)-tetrahydrofuran-3-yloxy]-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide;

3-(5-Ethyl-1,3-thiazol-2-yl)-5-[(3S)-tetrahydrofuran-3-yloxy]-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide;

3-(5-Ethyl-1,3-thiazol-2-yl)-5-(oxetan-3-yloxy)-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide;

3-(5-Methyl-1,3-thiazol-2-yl)-5-[(3R)-tetrahydrofuran-3-yloxy]-N-{(1R)-1-[6-(trifluoromethyl)pyridazin-3-yl]ethyl}benzamide;

3-(5-Methyl-1,3-thiazol-2-yl)-5-[(3S)-tetrahydrofuran-3-yloxy]-N-{(1R)-1-[6-(trifluoromethyl)pyridazin-3-yl]ethyl}benzamide.

Preferred embodiment of the present invention is the use of following compounds for the treatment or prophylaxis of diseases or disorders which are 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, namely

3-(5-methyl-1,3-thiazol-2-yl)-5-[(3R)-tetrahydrofuran-3-yloxy]-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide;

3-(5-methyl-1,3-thiazol-2-yl)-5-[(3S)-tetrahydrofuran-3-yloxy]-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide.

An even more preferred embodiment of the present invention is the use of 3-(5-methyl-1,3-thiazol-2-yl)-5-[(3R)-tetrahydrofuran-3-yloxy]-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide for the treatment or prophylaxis of diseases or disorders which are 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.

Another preferred embodiment of the present invention is the use of the following compounds, namely

3-(5-ethyl-1,3-thiazol-2-yl)-5-{[(2R)-4-methylmorpholin-2-yl]methoxy}-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide;

3-{[(2R)-4-methylmorpholin-2-yl]methoxy}-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide;

3-(5-ethyl-1,3-thiazol-2-yl)-5-{[(2R)-4-methylmorpholin-2-yl]methoxy}-N-{(1R)-1-[6-(trifluoromethyl)pyridazin-3-yl]ethyl}benzamide

for the treatment or prophylaxis of diseases or disorders which are 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.

An even more preferred embodiment of the present invention is the use of 3-{[(2R)-4-methylmorpholin-2-yl]methoxy}-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide for the treatment or prophylaxis of diseases or disorders which are 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.

Another preferred embodiment of the present invention is the use of the following compounds, namely

Trans Isomer 2; 3-{[3-hydroxybutan-2-yl]oxy}-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide;

Trans Isomer 1; 3-{[3-hydroxybutan-2-yl]oxy}-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[6-(trifluoromethyl)pyridazin-3-yl]ethyl}benzamide;

Trans Isomer 1; 3-(5-chloro-1,3-thiazol-2-yl)-5-{[3-hydroxybutan-2-yl]oxy}-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide;

Cis Isomer 1; 3-(5-chloro-1,3-thiazol-2-yl)-5-{[3-hydroxybutan-2-yl]oxy}-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide;

Cis Isomer 2; 3-(5-chloro-1,3-thiazol-2-yl)-5-{[3-hydroxybutan-2-yl]oxy}-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide;

Trans Isomer 2; 3-(5-chloro-1,3-thiazol-2-yl)-5-{[3-hydroxybutan-2-yl]oxy}-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide;

Cis Isomer 1; 3-[(-3-hydroxybutan-2-yl)oxy]-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[6-(trifluoromethyl)pyridazin-3-yl]ethyl}benzamide;

Cis Isomer 2; 3-[(-3-hydroxybutan-2-yl)oxy]-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[6-(trifluoromethyl)pyridazin-3-yl]ethyl}benzamide;

Cis Isomer 1; 3-[(3-hydroxybutan-2-yl)oxy]-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide;

Cis Isomer 2; 3-[(3-hydroxybutan-2-yl)oxy]-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide

for the treatment or prophylaxis of diseases or disorders which are 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.

An even more preferred embodiment of the present invention is the use of Cis Isomer 1; 3-(5-chloro-1,3-thiazol-2-yl)-5-{[3-hydroxybutan-2-yl]oxy}-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide for the treatment or prophylaxis of diseases or disorders which are 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.

It is to be understood that the present invention relates also to the use of any combination of the preferred embodiments described above.

The synthesis of the compounds of formula (I) is described in WO2016/091776.

Pharmaceutical compositions of the compounds of the invention

This invention also relates to the use of pharmaceutical compositions containing one or more compounds of the general formula (I). These compositions can be utilised to achieve the desired pharmacological effect by administration to a patient in need thereof. A patient, for the purpose of the present invention, is a mammal, including a human, in need of treatment for the particular condition or disease. Therefore, the present invention includes pharmaceutical compositions that are comprised of a pharmaceutically acceptable carrier and a pharmaceutically effective amount of a compound, or salt thereof, of the present invention. A pharmaceutically acceptable carrier is preferably a carrier that is relatively non-toxic and innocuous to a patient at concentrations consistent with effective activity of the active ingredient so that any side effects ascribable to the carrier do not vitiate the beneficial effects of the active ingredient. A pharmaceutically effective amount of compound is preferably that amount which produces a result or exerts an influence on the particular condition being treated. The present compounds can be administered with pharmaceutically acceptable carriers well known in the art using any effective conventional dosage unit forms, including immediate, slow and timed release preparations, orally, parenterally, topically, inhaled, nasally, sublingually, intravescially, rectally, vaginally, and the like.

For oral administration, the compounds can be formulated into solid or liquid preparations such as capsules, pills, tablets, troches, lozenges, melts, powders, solutions, suspensions, or emulsions, and may be prepared according to methods known in the art for the manufacture of pharmaceutical compositions. The solid unit dosage forms can be a capsule that can be of the ordinary hard- or soft-shelled gelatine type containing, for example, surfactants, lubricants, and inert fillers such as lactose, sucrose, calcium phosphate, and corn starch.

In another embodiment, the present compounds may be tableted with conventional tablet bases such as lactose, sucrose and cornstarch in combination with binders such as acacia, corn starch or gelatine, disintegrating agents intended to assist the break-up and dissolution of the tablet following administration such as potato

starch, alginic acid, corn starch, and guar gum, gum tragacanth, acacia, lubricants intended to improve the flow of tablet granulation and to prevent the adhesion of tablet material to the surfaces of the tablet dies and punches, for example talc, stearic acid, or magnesium, calcium or zinc stearate, dyes, colouring agents, and flavouring agents such as peppermint, oil of wintergreen, or cherry flavouring, intended to enhance the aesthetic qualities of the tablets and make them more acceptable to the patient. Suitable excipients for use in oral liquid dosage forms include dicalcium phosphate and diluents such as water and alcohols, for example, ethanol, benzyl alcohol, and polyethylene alcohols, either with or without the addition of a pharmaceutically acceptable surfactant, suspending agent or emulsifying agent. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance tablets, pills or capsules may be coated with shellac, sugar or both.

Dispersible powders and granules are suitable for the preparation of an aqueous suspension. They provide the active ingredient in admixture with a dispersing or wetting agent, a suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example those sweetening, flavouring and colouring agents described above, may also be present.

The pharmaceutical compositions containing the present compounds may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil such as liquid paraffin or a mixture of vegetable oils. Suitable emulsifying agents may be (1) naturally occurring gums such as gum acacia and gum tragacanth, (2) naturally occurring phosphatides such as soy bean and lecithin, (3) esters or partial esters derived form fatty acids and hexitol anhydrides, for example, sorbitan monooleate, (4) condensation products of said partial esters with ethylene oxide, for example, polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavouring agents.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil such as, for example, arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent such as, for example, beeswax, hard paraffin, or cetyl alcohol. The suspensions may also contain one or more preservatives, for example, ethyl or

n-propyl p-hydroxybenzoate ; one or more colouring agents ; one or more flavouring agents ; and one or more sweetening agents such as sucrose or saccharin.

Syrups and elixirs may be formulated with sweetening agents such as, for example, glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, and preservative, such as methyl and propyl parabens and flavouring and colouring agents.

The present compounds may also be administered parenterally, that is, subcutaneously, intravenously, , intravescially, , intramuscularly, or interperitoneally, as injectable dosages of the compound in preferably a physiologically acceptable diluent with a pharmaceutical carrier which can be a sterile liquid or mixture of liquids such as water, saline, aqueous dextrose and related sugar solutions, an alcohol such as ethanol, isopropanol, or hexadecyl alcohol, glycols such as propylene glycol or polyethylene glycol, glycerol ketals such as 2,2-dimethyl-1,1-dioxolane-4-methanol, ethers such as poly(ethylene glycol) 400, an oil, a fatty acid, a fatty acid ester or, a fatty acid glyceride, or an acetylated fatty acid glyceride, with or without the addition of a pharmaceutically acceptable surfactant such as a soap or a detergent, suspending agent such as pectin, carbomers, methylcellulose, hydroxypropylmethylcellulose, or carboxymethylcellulose, or emulsifying agent and other pharmaceutical adjuvants.

Illustrative of oils which can be used in the parenteral formulations of the present invention are those of petroleum, animal, vegetable, or synthetic origin, for example, peanut oil, soybean oil, sesame oil, cottonseed oil, corn oil, olive oil, petrolatum and mineral oil. Suitable fatty acids include oleic acid, stearic acid, isostearic acid and myristic acid. Suitable fatty acid esters are, for example, ethyl oleate and isopropyl myristate. Suitable soaps include fatty acid alkali metal, ammonium, and triethanolamine salts and suitable detergents include cationic detergents, for example dimethyl dialkyl ammonium halides, alkyl pyridinium halides, and alkylamine acetates ; anionic detergents, for example, alkyl, aryl, and olefin sulfonates, alkyl, olefin, ether, and monoglyceride sulfates, and sulfosuccinates ; non-ionic detergents, for example, fatty amine oxides, fatty acid alkanolamides, and poly(oxyethylene-oxypropylene)s or ethylene oxide or propylene oxide copolymers ; and amphoteric detergents, for example,

alkyl-beta-aminopropionates, and 2-alkylimidazoline quarternary ammonium salts, as well as mixtures.

Illustrative of surfactants used in parenteral formulations are the class of polyethylene sorbitan fatty acid esters, for example, sorbitan monooleate and the high molecular weight adducts of ethylene oxide with a hydrophobic base, formed by the condensation of propylene oxide with propylene glycol.

The pharmaceutical compositions may be in the form of sterile injectable aqueous suspensions. Such suspensions may be formulated according to known methods using suitable dispersing or wetting agents and suspending agents such as, for example, sodium carboxymethylcellulose, methylcellulose, hydroxylpropylmethyl-cellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia ; dispersing or wetting agents which may be a naturally occurring phosphatide such as lecithin, a condensation product of an alkylene oxide with a fatty acid, for example, polyoxyethylene stearate, a condensation product of ethylene oxide with a long chain aliphatic alcohol, for example, heptadeca-ethyleneoxycetanol, a condensation product of ethylene oxide with a partial ester derived from a fatty acid and a hexitol such as polyoxyethylene sorbitol monooleate, or a condensation product of an ethylene oxide with a partial ester derived from a fatty acid and a hexitol anhydride, for example polyoxyethylene sorbitan monooleate.

The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent. Diluents and solvents that may be employed are, for example, water, Ringer's solution, isotonic sodium chloride solutions and isotonic glucose solutions. In addition, sterile fixed oils are conventionally employed as solvents or suspending media. For this purpose, any bland, fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid can be used in the preparation of injectables.

A composition containing the present compounds may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritation excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are, for example, cocoa butter and polyethylene glycol.

Another formulation employed in the methods of the present invention employs transdermal delivery devices ("patches"). Such transdermal patches may be used to provide continuous or discontinuous infusion of the present compounds in controlled amounts. The construction and use of transdermal patches for the delivery of pharmaceutical agents is well known in the art (see, e.g., US Patent No. 5,023,252, issued June 11, 1991, incorporated herein by reference). Such patches may be constructed for continuous, pulsatile, or on demand delivery of pharmaceutical agents.

Controlled release formulations for parenteral and intravesical administration include liposomal, polymeric microsphere and polymeric gel formulations that are known in the art.

A composition containing a compound of general formula (I) may also be administered in the form of Prolonged release, implant, or depot formulation.

Another formulation employed in the methods of the present invention employs an aerosol, which enables the delivery of the compound of the general formula (I) to the airways with minimal systemic drug exposure. There are several aerosol formulations known, which can be used for that purpose, like for example liquid or dry particles generated by nebulizers or dry powder inhalers.

It may be desirable or necessary to introduce the pharmaceutical composition to the patient via a mechanical delivery device. The construction and use of mechanical delivery devices for the delivery of pharmaceutical agents is well known in the art. Direct techniques for, for example, administering a drug directly to the brain usually involve placement of a drug delivery catheter into the patient's ventricular system to bypass the blood-brain barrier. One such implantable delivery system, used for the transport of agents to specific anatomical regions of the body, is described in US Patent No. 5,011,472, issued April 30, 1991.

The compositions containing present compounds can also contain other conventional pharmaceutically acceptable compounding ingredients, generally referred to as carriers or diluents, as necessary or desired. Conventional procedures for preparing such compositions in appropriate dosage forms can be utilized.

Such ingredients and procedures include those described in the following

references, each of which is incorporated herein by reference: Powell, M.F. *et al.*, "Compendium of Excipients for Parenteral Formulations" PDA Journal of Pharmaceutical Science & Technology **1998**, 52(5), 238-311 ; Strickley, R.G "Parenteral Formulations of Small Molecule Therapeutics Marketed in the United States (1999)-Part-1" PDA Journal of Pharmaceutical Science & Technology **1999**, 53(6), 324-349 ; and Nema, S. *et al.*, "Excipients and Their Use in Injectable Products" PDA Journal of Pharmaceutical Science & Technology **1997**, 51(4), 166-171.

Commonly used pharmaceutical ingredients that can be used as appropriate to formulate the composition for its intended route of administration include:

acidifying agents (examples include but are not limited to acetic acid, citric acid, fumaric acid, hydrochloric acid, nitric acid);

alkalinizing agents (examples include but are not limited to ammonia solution, ammonium carbonate, diethanolamine, monoethanolamine, potassium hydroxide, sodium borate, sodium carbonate, sodium hydroxide, triethanolamine, trolamine);

adsorbents (examples include but are not limited to powdered cellulose and activated charcoal);

aerosol propellants (examples include but are not limited to carbon dioxide, CCl_2F_2, $F_2ClC\text{-}CClF_2$ and $CClF_3$);

air displacement agents (examples include but are not limited to nitrogen and argon);

antifungal preservatives (examples include but are not limited to benzoic acid, butylparaben, ethylparaben, methylparaben, propylparaben, sodium benzoate);

antimicrobial preservatives (examples include but are not limited to benzalkonium chloride, benzethonium chloride, benzyl alcohol, cetylpyridinium chloride, chlorobutanol, phenol, phenylethyl alcohol, phenylmercuric nitrate and thimerosal);

antioxidants (examples include but are not limited to ascorbic acid, ascorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, hypophosphorus acid, monothioglycerol, propyl gallate, sodium ascorbate, sodium bisulfite, sodium formaldehyde sulfoxylate, sodium metabisulfite);

binding materials (examples include but are not limited to block polymers, natural and synthetic rubber, polyacrylates, polyurethanes, silicones, polysiloxanes and styrene-butadiene copolymers);

buffering agents (examples include but are not limited to potassium metaphosphate, dipotassium phosphate, sodium acetate, sodium citrate anhydrous and sodium citrate dihydrate);

carrying agents (examples include but are not limited to acacia syrup, aromatic syrup, aromatic elixir, cherry syrup, cocoa syrup, orange syrup, syrup, corn oil, mineral oil, peanut oil, sesame oil, bacteriostatic sodium chloride injection and bacteriostatic water for injection);

chelating agents (examples include but are not limited to edetate disodium and edetic acid);

colourants (examples include but are not limited to FD&C Red No. 3, FD&C Red No. 20, FD&C Yellow No. 6, FD&C Blue No. 2, D&C Green No. 5, D&C Orange No. 5, D&C Red No. 8, caramel and ferric oxide red);

clarifying agents (examples include but are not limited to bentonite);

emulsifying agents (examples include but are not limited to acacia, cetomacrogol, cetyl alcohol, glyceryl monostearate, lecithin, sorbitan monooleate, polyoxyethylene 50 monostearate);

encapsulating agents (examples include but are not limited to gelatin and cellulose acetate phthalate);

flavourants (examples include but are not limited to anise oil, cinnamon oil, cocoa, menthol, orange oil, peppermint oil and vanillin);

humectants (examples include but are not limited to glycerol, propylene glycol and sorbitol);

levigating agents (examples include but are not limited to mineral oil and glycerin);

oils (examples include but are not limited to arachis oil, mineral oil, olive oil, peanut oil, sesame oil and vegetable oil);

ointment bases (examples include but are not limited to lanolin, hydrophilic ointment, polyethylene glycol ointment, petrolatum, hydrophilic petrolatum, white ointment, yellow ointment, and rose water ointment);

penetration enhancers (transdermal delivery) (examples include but are not limited to monohydroxy or polyhydroxy alcohols, mono-or polyvalent alcohols, saturated or unsaturated fatty alcohols, saturated or unsaturated fatty esters, saturated or unsaturated dicarboxylic acids, essential oils, phosphatidyl derivatives, cephalin, terpenes, amides, ethers, ketones and ureas);

plasticizers (examples include but are not limited to diethyl phthalate and glycerol);

solvents (examples include but are not limited to ethanol, corn oil, cottonseed oil, glycerol, isopropanol, mineral oil, oleic acid, peanut oil, purified water, water for injection, sterile water for injection and sterile water for irrigation);

stiffening agents (examples include but are not limited to cetyl alcohol, cetyl esters wax, microcrystalline wax, paraffin, stearyl alcohol, white wax and yellow wax);

suppository bases (examples include but are not limited to cocoa butter and polyethylene glycols (mixtures));

surfactants (examples include but are not limited to benzalkonium chloride, nonoxynol 10, oxtoxynol 9, polysorbate 80, sodium lauryl sulfate and sorbitan mono-palmitate);

suspending agents (examples include but are not limited to agar, bentonite, carbomers, carboxymethylcellulose sodium, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, kaolin, methylcellulose, tragacanth and veegum);

sweetening agents (examples include but are not limited to aspartame, dextrose, glycerol, mannitol, propylene glycol, saccharin sodium, sorbitol and sucrose);

tablet anti-adherents (examples include but are not limited to magnesium stearate and talc);

tablet binders (examples include but are not limited to acacia, alginic acid, carboxymethylcellulose sodium, compressible sugar, ethylcellulose, gelatin, liquid

glucose, methylcellulose, non-crosslinked polyvinyl pyrrolidone, and pregelatinized starch);

tablet and capsule diluents (examples include but are not limited to dibasic calcium phosphate, kaolin, lactose, mannitol, microcrystalline cellulose, powdered cellulose, precipitated calcium carbonate, sodium carbonate, sodium phosphate, sorbitol and starch);

tablet coating agents (examples include but are not limited to liquid glucose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, methylcellulose, ethylcellulose, cellulose acetate phthalate and shellac);

tablet direct compression excipients (examples include but are not limited to dibasic calcium phosphate);

tablet disintegrants (examples include but are not limited to alginic acid, carboxymethylcellulose calcium, microcrystalline cellulose, polacrillin potassium, cross-linked polyvinylpyrrolidone, sodium alginate, sodium starch glycollate and starch);

tablet glidants (examples include but are not limited to colloidal silica, corn starch and talc);

tablet lubricants (examples include but are not limited to calcium stearate, magnesium stearate, mineral oil, stearic acid and zinc stearate);

tablet/capsule opaquants (examples include but are not limited to titanium dioxide);

tablet polishing agents (examples include but are not limited to carnuba wax and white wax);

thickening agents (examples include but are not limited to beeswax, cetyl alcohol and paraffin);

tonicity agents (examples include but are not limited to dextrose and sodium chloride);

viscosity increasing agents (examples include but are not limited to alginic acid, bentonite, carbomers, carboxymethylcellulose sodium, methylcellulose, polyvinyl pyrrolidone, sodium alginate and tragacanth); and

wetting agents (examples include but are not limited to heptadecaethylene oxycetanol, lecithins, sorbitol monooleate, polyoxyethylene sorbitol monooleate, and polyoxyethylene stearate).

Combination therapies

The term "combination" in the present invention is used as known to persons skilled in the art and may be present as a fixed combination, a non-fixed combination or 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 the said first active ingredient and the said second active ingredient are present together in one unit dosage or in a single entity. One example of a "fixed combination" is a pharmaceutical composition wherein the said first active ingredient and the said second 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 the said first active ingredient and the said second 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 the said first active ingredient and the said second 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 said first active ingredient and the said second active ingredient are present separately. The components of the non-fixed combination or kit-of-parts may be administered separately, sequentially, simultaneously, concurrently or chronologically staggered.

The present compounds can be administered as the sole pharmaceutical agent or in combination with one or more other pharmaceutical agents where the combination causes no unacceptable adverse effects. The present invention relates also to the

use of such combinations containing the present compounds for the use in treating and/ or for prophylaxis of diseases or disorders which are 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.

The present compounds 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 cardiovascular disease, hypertension, resistant hypertension, and heart failure, the compounds of formula (I) may be administered in combination or as co-medication with antithrombotic agents, for example and preferably from the group of platelet aggregation inhibitors, anticoagulants and profibrinolytic substances;
- blood pressure lowering agents, for example and preferably from the group of calcium antagonists, angiotensin AII antagonists, ACE inhibitors, vasopeptidase inhibitors, endothelin antagonists, renin inhibitors, alpha-blockers, beta-blockers, mineralocorticoid receptor antagonists such as for example eplerenone, spironolactone and finerenone and diuretics;
- sympatholytic agents, for example and preferably from the group of centrally acting sympatholytic agents such as for examples moxonidine, clonidine and alpha-methyldopa.
- Vasopressin receptor antagonists, such as for example and preferable Conivaptan, Tolvaptan, Lixivaptan, Mozavaptan, Satavaptan, SR-121463, RWJ 676070 or BAY 86-8050, and also the compounds described in WO 2010/105770, WO2011/104322 und WO 2016/071212,

- antiarrhythmic agents, for example and preferably from the group of sodium channel blockers, beta-blockers, potassium channel blockers, calcium channel blockers, I_f- channels blockers, Digitalis, parasympathatolytics, sympathomimetics and vernakalant.
- antidiabetic agents (hypoglycemic or antihyperglycemic agents), such as for example and preferably insulin and derivatives, sulfonylureas, biguanides, thiazolidinediones, acarbose, DPP4 inhibitors, GLP-1 analogues, or SGLT inhibitors (gliflozins).
- organic nitrates and NO-donors, for example sodium nitroprusside, nitroglycerin, isosorbide mononitrate, isosorbide dinitrate, molsidomine or SIN-1, and inhalational NO;
- compounds that inhibit the degradation of cyclic guanosine monophosphate (cGMP), for example inhibitors of phosphodiesterases (PDE) 1, 2, 5 and/or 9, in particular PDE-5 inhibitors such as sildenafil, vardenafil, tadalafil, udenafil, dasantafil, avanafil, mirodenafil, lodenafil or PF-00489791;
- positive-inotropic agents, such as for example cardiac glycosides (digoxin, digitoxin) and beta-adrenergic and dopaminergic agonists such as isoproterenol, adrenalin, noradrenalin, dopamine or dobutamine and serelaxin
- natriuretic peptides, such as for example atrial natriuretic peptide (ANP, anaritide), B-type natriuretic peptide or brain natriuretic peptide (BNP, nesiritide), C-type natriuretic peptide (CNP) or urodilatin;
- calcium sensitizers, such as for example and preferably levosimendan;
- NO- and heme-independent activators of soluble guanylate cyclase (sGC), such as in particular cinaciguat and also the compounds described in WO01/19355, WO01/19776, WO01/19778, WO01/19780, WO02/070462, WO02/070510; WO2013/157528, WO2015/056663, WO2009/123316, WO2016/001875, WO2016/001876, WO2016/001878, WO2000/02851, WO2012/122340, WO2013/025425, WO2014/039434, WO2016/014463, WO2009/068652, WO2009/071504, WO2010/015652, WO2010/015653, WO2015/033307, WO2016/042536, WO2009/032249, WO2010/099054, WO2012/058132, US2010/0216764, WO02/070459, WO02/070460, WO2007/045366, WO2007/045369, WO2007/045433, WO2007/045370, WO2007/045367,

WO2014/012935, WO2014/012934, WO2011/141409, WO2008/119457, WO2008/119458, WO2009/127338, WO2010/102717, WO2011/051165, WO2012/076466, WO2012/139888 and WO2013/174736,

- NO-independent, but heme-dependent stimulators of guanylate cyclase (sGC), such as in particular riociguat, vericiguat and also the compounds described in WO00/06568, WO00/06569, WO02/42301, WO03/095451, WO2011/147809, WO2012/004258, WO2012/028647, WO2012/059549, WO2016/081668, WO2015/187470, WO2015/088885, WO2015/088886, WO2011/149921, WO2011119518, WO2010/065275, WO2016/04445, WO2016/044447, WO2016/044446, WO2016/044441, WO2015/089182, WO2014/047111, WO2014/047325, WO2013/101830, WO2012/064559, WO2012/003405, WO2011/115804, WO2014/084312, WO2012/165399, WO03/097063, WO03/09545, WO04/009589, WO03/004503, WO2007/124854, WO2008/031513, WO2008/061657, WO2010/079120, WO2010/102717, WO2012/004259, WO2012/059548, WO2012/152630, WO2014/068099, WO2014/068104, WO2012/143510, WO2012/152629, WO2013/004785, WO2013/104598, WO2013/104597, WO2013/030288, WO2013/104703, WO2013/131923, WO2014/068095, WO2014/195333, WO2014/128109, WO2014/131760, WO2014/131741, WO2015/018808, WO2015/004105, WO2015/018814, WO98/16223, WO98/16507, WO98/23619, WO02/042299, WO02/092596, WO02/042300, WO02/042301, WO02/036120, WO02/042302, WO02/070461, WO2012/165399, WO2014/084312, WO2011115804, WO2012003405, WO2012064559, WO2014/047111, WO2014/047325, WO2011/149921, WO2010/065275 and WO2011/119518,
- inhibitors of human neutrophil elastase (HNE), such as for example sivelestat or DX-890 (reltran);
- compounds inhibiting the signal transduction cascade, in particular tyrosine and/or serine/threonine kinase inhibitors, such as for example nintedanib, dasatinib, nilotinib, bosutinib, regorafenib, sorafenib, sunitinib, cediranib, axitinib, telatinib, imatinib, brivanib, pazopanib, vatalanib, gefitinib, erlotinib, lapatinib, canertinib, lestaurtinib, pelitinib, semaxanib or tandutinib;
- compounds influencing the energy metabolism of the heart, such as for example and preferably etomoxir, dichloroacetate, ranolazine or trimetazidine,

bendavia/ elamipritide or full or partial adenosine A1 receptor agonists as GS-9667 (previously known as CVT-3619), capadenoson and neladenoson;

- compounds influencing the heart rate, such as for example and preferably ivabradine;
- cardiac myosin activators, such as for example and preferably omecamtiv mecarbil (CK-1827452);
- HIF-PH Inhibitors, for example and preferably Molidustat, Daprodustat, Roxadustat,
- bronchodilatory agents, for example and preferably from the group of beta-adrenergic receptor agonists, such as for example Albuterol, Isoproterenol, Metaproterenol, Terbutalin, Formoterol or Salmeterol, and from the group of anticholinergic agents such as for example Ipratropiumbromide;
- anti-inflammatory drugs such as non-steroidal anti-inflammatory drugs (NSAIDs) including acetylsalicylic acid (aspirin), ibuprofen and naproxen, glucocorticoids, 5-aminosalicylic acid derivatives leukotriene antagonists ,alpha inhibit-TNF ,ors and chemokine receptor antagonists such as CCR1, 2 and/or 5 inhibitors;
- fat metabolism altering agents, for example and preferably from the group of thyroid receptor agonists, cholesterol synthesis inhibitors, such as for example and preferably HMG-CoA-reductase or squalene synthesis inhibitors, ACAT inhibitors, CETP inhibitors, MTP inhibitors, PPAR-alpha, PPAR-gamma and/or PPAR-delta agonists, cholesterol absorption inhibitors, lipase inhibitors, polymeric bile acid adsorbers, bile acid reabsorption inhibitors, lipoprotein(a) antagonists and agents that inhibit the soluble epoxidhydrolase (sEH) such as for example N,N'-Di-cyclohexylurea, 12-(3-Adamantan-1-yl-ureido)-dodecanacid or 1-Adamantan-1-yl-3-{5-[2-(2-ethoxyethoxy)ethoxy]pentyl}-urea,
- Prostacyclin analogs, for example and preferable Iloprost, Beraprost, Treprostinil or Epoprostenol;
- agents that mediate the remodeling of extracellular matrix, for example and preferable, matrix-metalloproteinase inhibitors such as inhibitors of MMP-1, MMP-3, MMP-8, MMP-9, MMP-10, MMP-11 and MMP-13, inhibitor of metallo-elastase (MMP-12), Chymase-Inhibitors as disclosed in WO2013/167495, Inhibitors

of stromelysin, collagenases, gelatinases und aggrecanases (such as and preferable neutrophil-elastase (HNE), such as Sivelestat or DX-890;

- antiepileptic agents for example and preferable of the group of classical and new antiepileptic agents, such as Carbamazepin, Diazepam/ Clonazepam, Ethosuximide, Phenobarbital, Primidon, Phenytoin, Valproat, Gabapentin, Labotrigin, Levetiracetam, Oxcarbazepin, Pregabalin, Tiagabin, Topiramat, Vigabatrin.

- analgetic agents for example and preferable of the group of non-opiod analgetics for example and preferable of the group of antipyretic analgetics such as ASS, paracetamol, phenacetin, metamizol, propyphenazon, phenylbutazon, and of the group of antiphlogistic analgetics such as diclofenac, indomethacin, piroxica, meloxicam and COX2 inhibitors such as celecoxib, etoricoxib, parecoxib, rofecoxib and valdecoxib, and centrally acting agents such as katadolon, and of the group of opioids such as morphin, heroin, fentanyl, alfentanil, sufentanil, remifentanil, levomethadon, pritramid, pethidin, tramadol, dihydrocodein, tilidin, nalbuphin, pentazocin, buprenorphine, of the group of 5HT1 receptor agonists such as Sumatriptan, Naratriptan, Rizatriptan, Zolmitriptan, Almotriptan, Eletriptan and Frovatriptan.

Antithrombotic agents are preferably to be understood as compounds from the group of platelet aggregation inhibitors, anticoagulants and profibrinolytic substances.

In a preferred embodiment of the invention, the compounds of formula (I) are administered in combination with a platelet aggregation inhibitor, for example and preferably aspirin, clopidogrel, ticlopidine or dipyridamole.

In a preferred embodiment of the invention, the compounds of formula (I) are administered in combination with a thrombin inhibitor, for example and preferably ximelagatran, dabigatran, melagatran, bivalirudin or enoxaparin.

In a preferred embodiment of the invention, the compounds of formula (I) are administered in combination with a GPIIb/IIIa antagonist, for example and preferably tirofiban or abciximab.

In a preferred embodiment of the invention, the compounds of formula (I) are administered in combination with a factor Xa inhibitor, for example and preferably rivaroxaban, apixaban, otamixaban, fidexaban, razaxaban, fondaparinux, idraparinux, DU-176b, PMD-3112, YM-150, KFA-1982, EMD-503982, MCM-17, MLN-1021, DX 9065a, DPC 906, JTV 803, SSR-126512 or SSR-128428.

In a preferred embodiment of the invention, the compounds of formula (I) are administered in combination with a factor XIa inhibitor.

In a preferred embodiment of the invention, the compounds of formula (I) are administered in combination with heparin or a low molecular weight (LMW) heparin derivative.

In a preferred embodiment of the invention, the compounds of formula (I) are administered in combination with a vitamin K antagonist, for example and preferably coumarin or warfarin.

Blood pressure lowering agents are preferably to be understood as compounds from the group of calcium antagonists, angiotensin AII antagonists, ACE inhibitors, vasopeptidase inhibitors, endothelin antagonists, renin inhibitors, alpha-blockers, centrally acting sympatholytics beta-blockers, mineralocorticoid receptor antagonists and diuretics.

In a preferred embodiment of the invention, the compounds of formula (I) are administered in combination with a calcium antagonist, for example and preferably nifedipine, amlodipine, verapamil or diltiazem.

In a preferred embodiment of the invention, the compounds of formula (I) are administered in combination with an alpha-1-receptor blocker, for example and preferably prazosin,tamsulosin, bunazosin, doxazosin, phenoxybenzamin, terazosin or urapidil,

In a preferred embodiment of the invention, the compounds of formula (I) are administered in combination with a centrally acting sympatholytic agent, for example and preferably alpha-methydopa, moxonidine or clonidine.

In a preferred embodiment of the invention, the compounds of formula (I) are administered in combination with a beta-blocker, for example and preferably propranolol, atenolol, timolol, pindolol, alprenolol, oxprenolol, penbutolol, bupranolol, metipranolol, nadolol, mepindolol, carazolol, sotalol, metoprolol,

betaxolol, celiprolol, bisoprolol, carteolol, esmolol, labetalol, carvedilol, adaprolol, landiolol, nebivolol, epanolol or bucindolol.

In a preferred embodiment of the invention, the compounds of formula (I) are administered in combination with an angiotensin AII receptor antagonist, for example and preferably losartan, candesartan, valsartan, telmisartan, irbesartan, olmesartan, eprosartan or azilsartan.

In a preferred embodiment of the invention, the compounds of formula (I) are administered in combination with a vasopeptidase inhibitor or inhibitor of neutral endopeptidase (NEP), such as for example and preferably sacubitril, omapatrilat or AVE-7688.

In a preferred embodiment of the invention, the compounds of formula (I) are administered in combination with a dual angiotensin AII receptor antagonist/NEP inhibitor (ARNI), for example and preferably LCZ696 (Entresto).

In a preferred embodiment of the invention, the compounds of formula (I) are administered in combination with an ACE inhibitor, for example and preferably enalapril, captopril, lisinopril, ramipril, delapril, fosinopril, quinopril, perindopril or trandopril.

In a preferred embodiment of the invention, the compounds of formula (I) are administered in combination with an endothelin antagonist, for example and preferably bosentan, darusentan, ambrisentan, tezosentan, sitaxsentan or atrasentan.

In a preferred embodiment of the invention, the compounds of formula (I) are administered in combination with a renin inhibitor, for example and preferably aliskiren, SPP-600 or SPP-800.

In a preferred embodiment of the invention, the compounds of formula (I) are administered in combination with a mineralocorticoid receptor antagonist, for example and preferably finerenone, spironolactone, canrenone, potassium canrenoate, eplerenone, CS-3150, or MT-3995.

In a preferred embodiment of the invention, the compounds of formula (I) are administered in combination with a diuretic, such as for example and preferably furosemide, bumetanide, piretanide, torsemide, bendroflumethiazide, chlorothiazide, hydrochlorothiazide, xipamide, indapamide, hydroflumethiazide,

methyclothiazide, polythiazide, trichloromethiazide, chlorothalidone, metolazone, quinethazone, acetazolamide, dichlorophenamide, methazolamide, glycerine, isosorbide, mannitol, amiloride or triamterene.

sGC modulating agents are preferably to be understood as compounds from the group of NO- and heme-independent activators of soluble guanylate cyclase (sGC) and NO-independent, but heme-dependent stimulators of guanylate cyclase (sGC).

In a preferred embodiment of the invention, the compounds of formula (I) are administered in combination with a NO- and heme-independent activators of soluble guanylate cyclase (sGC), such as in particular cinaciguat.

In a preferred embodiment of the invention, the compounds of formula (I) are administered in combination with a NO-independent, but heme-dependent stimulators of guanylate cyclase (sGC), such as in particular riociguat, vericiguat.

Antiarrhythmic agents are preferably to be understood as compounds from the group of sodium channel blockers, beta-blockers, potassium channel blockers, calcium channel blockers, If- channels blockers, Digitalis, parasympathatolytics, sympathomimetics and vernakalant.

In a preferred embodiment of the invention, the compounds of formula (I) are administered in combination with a sodium channel blocker (class I antiarrhythmic agent) such as Chinidin, Ajmalin, Prajmalin, Disopyramid, Lidocain, Mexiletin, Tocainind, Phenytoin, Aprinidin, Propafenon, Flecainid, Lorcainid.

In a preferred embodiment of the invention, the compounds of formula (I) are administered in combination with a beta receptor blocker (class II antiarrhythmic agent) such as Acebutulol, Atenolol, Betaxolol, Bisoprolol, Metoprolol, Oxprenolol, Pindolol, Propanolol, Sotalol, Timolol.

In a preferred embodiment of the invention, the compounds of formula (I) are administered in combination with a potassium channel blocker (class III antiarrhythmic agent) such as Sotalol, Amiodaron, Dronedaron.

In a preferred embodiment of the invention, the compounds of formula (I) are administered in combination with a potassium channel blocker (class IV antiarrhythmic agent) such as Diltiazem, Gallopramil, Verapamil.

In a preferred embodiment of the invention, the compounds of formula (I) are administered in combination with Digoxin or Vernakalant.

Antiepileptic agents are preferably to be understood as compounds from the group of classic and new antiepileptic agents.

In a preferred embodiment of the invention, the compounds of formula (I) are administered in combination with classic antiepileptic agents such as Carbamazepin, Diazepam/ Clonazepam, Ethosuximide, Phenobarbital, Primidon, Phenytoin, Valproat.

In a preferred embodiment of the invention, the compounds of formula (I) are administered in combination with new antiepileptic agents such as Gabapentin, Labotrigin, Levetiracetam, Oxcarbazepin, Pregabalin, Tiagabin, Topiramat, Vigabatrin.

Analgetic agents are preferably to be understood as compounds from the group of non-opiod analgetics, antiphlogistic analgetics, COX2 inhibitors, centrally acting analgetics, opioids and 5HT1 Receptor Agonists.

In a preferred embodiment of the invention, the compounds of formula (I) are administered in combination with non-opiod analgetics such as ASS, paracetamol, phenacetin, metamizol, propyphenazon, phenylbutazon.

In a preferred embodiment of the invention, the compounds of formula (I) are administered in combination with antiphlogistic analgetics such as diclofenac, indomethacin, piroxica, meloxicam.

In a preferred embodiment of the invention, the compounds of formula (I) are administered in combination with COX2 inhibitors such as celecoxib, etoricoxib, parecoxib, rofecoxib and valdecoxib.

In a preferred embodiment of the invention, the compounds of formula (I) re administered in combination with centrally acting agents such as katadolon.

In a preferred embodiment of the invention, the compounds of formula (I) dministered in combination with opioids such as morphin, heroin, fentanyl, alfentanil, sufentanil, remifentanil, levomethadon, pritramid, pethidin, tramadol, dihydrocodein, tilidin, nalbuphin, pentazocin, buprenorphine.

In a preferred embodiment of the invention, the compounds of formula (I) are administered in combination with receptor agonists such as Sumatriptan, Naratriptan, Rizatriptan, Zolmitriptan, Almotriptan, Eletriptan and Frovatriptan.

Blood hematocrit increasing agents are preferably to be understood as compounds from the group of HIF-PH Inhibitors.

In a preferred embodiment of the invention, the compounds of formula (I) are administered in combination with HIF-PH Inhibitors such as Molidustat, Daprodustat, Roxadustat..Fat metabolism altering agents are preferably to be understood as compounds from the group of CETP inhibitors, thyroid receptor agonists, cholesterol synthesis inhibitors such as HMG-CoA-reductase or squalene synthesis inhibitors, ACAT inhibitors, MTP inhibitors, PPAR-alpha, PPAR-gamma and/or PPAR-delta agonists, cholesterol absorption inhibitors, polymeric bile acid adsorbers, bile acid reabsorption inhibitors, lipase inhibitors and lipoprotein(a) antagonists.

In a preferred embodiment of the invention, the compounds of formula (I) are administered in combination with a CETP inhibitor, for example and preferably dalcetrapib, anacetrapib, BAY 60-5521 or CETP-vaccine (Avant).

In a preferred embodiment of the invention, the compounds of formula (I) are administered in combination with a thyroid receptor agonist, for example and preferably D-thyroxin, 3,5,3'-triiodothyronin (T3), CGS 23425 or axitirome (CGS 26214).

In a preferred embodiment of the invention, the compounds of formula (I) are administered in combination with an HMG-CoA-reductase inhibitor from the class of statins, for example and preferably lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin, rosuvastatin or pitavastatin.

In a preferred embodiment of the invention, the compounds of formula (I) administered in combination with a squalene synthesis inhibitor, for example and preferably BMS-188494 or TAK-475.

In a preferred embodiment of the invention, the compounds of formula (I) are administered in combination with an ACAT inhibitor, for example and preferably avasimibe, melinamide, pactimibe, eflucimibe or SMP-797.

In a preferred embodiment of the invention, the compounds of formula (I) are administered in combination with an MTP inhibitor, for example and preferably implitapide, R-103757, BMS-201038 or JTT-130.

In a preferred embodiment of the invention, the compounds of formula (I) are administered in combination with a PPAR-gamma agonist, for example and preferably pioglitazone or rosiglitazone.

In a preferred embodiment of the invention, the compounds of formula (I) are administered in combination with a PPAR-delta agonist, for example and preferably GW 501516 or BAY 68-5042.

In a preferred embodiment of the invention, the compounds of formula (I) are administered in combination with a cholesterol absorption inhibitor, for example and preferably ezetimibe, tiqueside or pamaqueside.

In a preferred embodiment of the invention, the compounds of formula (I) are administered in combination with a lipase inhibitor, for example and preferably orlistat.

In a preferred embodiment of the invention, the compounds of formula (I) are administered in combination with a polymeric bile acid adsorber, for example and preferably cholestyramine, colestipol, colesolvam, CholestaGel or colestimide.

In a preferred embodiment of the invention, the compounds of formula (I) are administered in combination with a bile acid reabsorption inhibitor, for example and preferably ASBT (= IBAT) inhibitors such as AZD-7806, S-8921, AK-105, BARI-1741, SC-435 or SC-635.

In a preferred embodiment of the invention, the compounds of formula (I) e administered in combination with a lipoprotein(a) antagonist, for example and preferably gemcabene calcium (CI-1027) or nicotinic acid.

In a preferred embodiment of the invention, the compounds of formula (I) are administered in combination with antidiabetics (hypoglycemic or antihyperglycemic agents), such as for example and preferably insulin and derivatives, sulfonylureas such as tolbutamide, carbutamide, acetohexamide, chlorpropamide, glipizide, gliclazide, glibenclamide, glyburide, glibornuride, gliquidone, glisoxepide, glyclopyramide, glimepiride, JB253 and JB558, meglitinides such as repaglinide and nateglinide, biguanides such as metformin and buformin, thiazolidinediones such as

rosiglitazone and pioglitazone, alpha-glucosidase inhibitors such as miglitol, acarbose and voglibose, DPP4 inhibitors such as vildagliptin, sitagliptin, saxagliptin, linagliptin, alogliptin, septagliptin and teneligliptin, GLP-1 analogues such as exenatide (also exendin-4, liraglutide, lixisenatide and taspoglutide, or SGLT inhibitors (gliflozins) such as canagliflozin, dapagliflozin and empagliflozin.

In a particularly preferred embodiment, the compounds of formula (I) are administered in combination with one or more additional therapeutic agents selected from the group consisting of diuretics, angiotensin AII antagonists, ACE inhibitors, beta-receptor blockers, mineralocorticoid receptor antagonists, antidiabetics, organic nitrates and NO donors, activators and stimulators of the soluble guanylate cyclase (sGC), and positive-inotropic agents.

Thus, in a further embodiment, the present invention relates to pharmaceutical compositions comprising at least one of the compounds of formula (I) according to the invention and one or more additional therapeutic agents for the treatment and/or prevention of diseases, especially of the aforementioned diseases.

Methods of treating

The present invention relates to a method for using the present compounds and compositions thereof, to inhibit the P2X3 receptor and therefore achieve an efficacious treatment of breathing disorders, Cheyne Stokes respiration, central and obstructive sleep apnea, cardiovascular disease, hypertension, resistant hypertension, and heart failure.The present invention also provides a method for using the compounds of formula (I) and compositions thereof, to selectively inhibit the P2X3 receptor over the P2X2/3 receptor which means at least 10-fold selectivity over the P2X2/3 receptor.The advantage of having such selective compounds results in a is the access to a method of treating breathing disorders, Cheyne Stokes respiration, central and obstructive sleep apnea, cardiovascular disease, hypertension, resistant hypertension, and heart failure with less or no effect to the taste sensitivity of the patient in need of a chronic treatment of breathing disorders, Cheyne Stokes respiration, central and obstructive sleep apnea, cardiovascular disease, hypertension, resistant hypertension, and heart

failure. This provides the advantage of having an effective treatment for breathing disorders, Cheyne Stokes respiration, central and obstructive sleep apnea, cardiovascular disease, hypertension, resistant hypertension, and heart failure with less or no effect to the taste sensitivity of the patient in need of a treatment of breathing disorders, Cheyne Stokes respiration, central and obstructive sleep apnea, cardiovascular disease, hypertension, resistant hypertension, and heart failure available which may be used as chronic treatment if necessary.

Therefore, the quality of life of patients with breathing disorders, Cheyne Stokes respiration, central and obstructive sleep apnea, cardiovascular disease, hypertension, resistant hypertension, and heart failure with less or no effect to the taste sensitivity of the patient in need of a treatment of breathing disorders, Cheyne Stokes respiration, central and obstructive sleep apnea, cardiovascular disease, hypertension, resistant hypertension, and heart failure may be highly improved.

The compounds of formula (I) are also useful in a method for using the present compounds and compositions thereof, to selectively inhibit the P2X3 receptor over the P2X2/3 receptor with at least 10-fold selectivity over the P2X2/3 receptor. In addition to that, the present invention also provides a method of treating mammalian including human disorders and diseases, i.e. breathing disorders, Cheyne Stokes respiration, central and obstructive sleep apnea, cardiovascular disease, hypertension, resistant hypertension, and heart failure may be highly improved.

The present invention relates to a method for using the present compounds and compositions thereof, to treat mammalian, including human, disorders and diseases which include but are not limited to:

cardiovascular diseases including but not limited to acute and chronic heart failure in¬cluding worsening chronic heart failure (or hospitalization for heart failure) and congestive heart failure, heart failure with reduced ejection fraction, systolic heart failure, heart failure with preserved ejection fraction, diastolic heart failure, heart failure with normal ejection fraction, post-myocardial infarction heart failure, right heart failure, left heart failure, ischemic cardiomyopathy, dilatative cardiomyopathy,

hypertrophic cardiomyopathy, valvular heart failure, diabetic cardiomyopathy, augmented chemoreflex, autonomic imbalance, arterial hypertension, resistant hypertension, arterial pul¬mo¬nary hyper¬tension, coronary heart disease, stable and unstable angina pectoris, acute coronary syndrome (ACS), acute myocardial infarction, STEMI, NSTEMI, disturbances of atrial and ventricular rhythm and conduction disturbances, for example atrioventricular blocks of degree I-III (AVB I-III), supraventricular tachyarrhythmia, atrial fibrillation, paroxysmal atrial fibrillation, persistant atrial fibrillation, permanent atrial fibrillation, atrial flutter, sinus arrhythmia, ven¬tricular fibrillation, ventricular flutter, ventricular tachy¬arrhyth¬mia, torsade-de-pointes tachy¬cardia, atrial and ventricular extrasystoles, AV-junction extrasystoles, sick-sinus syndrome, syncopes, cardiac death, AV-node re-entry tachycardia and Wolff-Parkinson-White syn¬drome, autoimmune heart diseases, pericarditis, endocarditis, valvu¬litis, aortitis, cardiomyo¬pathies, myocarditis, shock such as cardiogenic shock, septic shock and ana¬phy¬lactic shock, aneurysms, Boxer cardiomyopathy (premature ventricular contraction), further¬more thromboembolic diseases and ischaemias such as peripheral perfusion disturbances, reperfusion injury, arterial and venous throm¬boses, myocardial insufficiency, endothelial dys¬function, micro- and macrovascular damage (vasculitis) and for preventing restenoses such as after thrombolysis therapies, percutaneous trans¬luminal angioplasty (PTA), percutaneous transluminal coronary angio¬plasty (PTCA), heart trans¬plan¬tation and bypass opera¬tions, arterio¬sclerosis, disturbances of lipid metabolism, hypo¬lipo¬protein¬aemias, dyslipidemias, hypertriglyceridemias, hyperlipid¬emias and combined hyperlipid-emias, hyper¬cholesterolaemias, abetalipoproteinaemia, sitosterol¬emia, xantho-matosis, Tangier disease, adipositas, obesity, metabolic syndrome, diabetes, insulin resistance, transi¬tory ischemic attacks, stroke, inflam¬ma¬tory cardiovascular diseases, myocarditis, peripheral and cardiac vascular diseases, peri¬pheral circulation disorders, peripheral artery disease, spas¬ms of the coronary arteries and peripheral arteries, and edema such as, for example, pulmonary edema, cerebral edema, renal edema and heart failure-related edema, periodic breathing disorders, central sleep apnea,

obstructive sleep apnea, combined central and obstructive sleep apnea, Cheyne-Stokes respiration, and Chaga's disease.

An embodiment of the present invention relates to a method for using the compounds of formula (I) and compositions thereof, to treat breathing disorders, Cheyne Stokes respiration, central and obstructive sleep apnea, cardiovascular disease, hypertension, resistant hypertension, and heart failure.

These 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 stated throughout this document is used conventionally, *e.g.*, the management or care of a subject for the purpose of combating, alleviating, reducing, relieving, improving a condition, disease or disorder such as a gynaecological disease, urinary tract disease, respiratory disorder or arthritis.

In the sense of the present invention, the term heart failure also includes more specific or related disease forms such as right heart failure, left heart failure, global insufficiency, ischemic cardio¬myopathy, dilatative cardiomyopathy, congenital heart defects, heart valve defects, heart failure with heart valve defects, mitral valve stenosis, mitral valve insufficiency, aortic valve stenosis, aortic valve insufficiency, tricuspidal stenosis, tricuspidal¬ insufficiency, pulmonary valve stenosis, pulmonary valve insufficiency, combined heart valve defects, heart muscle inflammation (myo¬carditis), chronic myocarditis, acute myocarditis, viral myocarditis, diabetic heart failure, alcohol-toxic cardiomyopathy, cardiac storage diseases, heart failure with preserved ejection fraction (HFpEF or dia¬stolic heart failure), and heart failure with reduced ejection fraction (HFrEF or systolic heart failure) and heart failure with normal ejection fraction (HFnEF).

Dose and administration

Based upon standard laboratory techniques known to evaluate compounds useful for the treatment of disorders and/ or disease which are mediated by the P2X3 receptor, 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 medicaments that are used to treat these conditions, the effective dosage of the present compounds 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, preferably from about 0.01 mg/kg to about 20 mg/kg body weight per day. A preferred administration of present compounds includes but is not limited to 0.1 mg/kg to about 10 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, "drug holidays" in which a patient is not dosed with a drug for a certain period of time, may be beneficial to the overall balance between pharmacological effect and tolerability. A unit dosage may contain from about 0.5 mg to about 1500 mg of active ingredient, and can be administered one or more times per day or less than once a day. A preferred oral unit dosage for an administration of the present compounds includes but is not limited to 0.1 mg/kg to about 10 mg/kg body weight one to three times a day to once a week. The average daily dosage for administration by injection, including intravenous, intravesical, 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 the present compounds 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.

Biological assays

Examples were tested in selected biological assays one or more times. Unless stated otherwise, when tested more than once, data are reported as either average values or as median values, wherein

- the average value, also referred to as the arithmetic mean value, represents the sum of the values obtained divided by the number of times tested, and
- the median value represents the middle number of the group of values when ranked in ascending or descending order. If the number of values in the data set is odd, the median is the middle value. If the number of values in the data set is even, the median is the arithmetic mean of the two middle values.

Examples were synthesized one or more times. When synthesized more than once, data from biological assays represent average values or median values calculated utilizing data sets obtained from testing of one or more synthetic batch.

Data of compounds of formula (I) obtained from intracellular calcium measurement to assess antagonist activity at human P2X3 and human P2X2/3 receptors are described in WO2016/091776.

<u>In vivo assay for ventilatory response under anesthesia</u>

The aim of this study is to test the effect of P2X3 antagonism on chemoreflex sensitivity in anesthetized animals. Reduction in breathing rate increase in response to hypoxic challenge is interpreted as a reduction in chemoreflex sensitivity.

Figure 1 illustrates the breathing rate response of anesthetized adult male Sprague Dawley rats to acute hypocapnic hypoxia. Rats are treated with compounds and exposed to acute hypocapnic hypoxia (12% O_2 balanced with N_2) under anesthesia. Animals can be additionally instrumented with ECG electrodes, invasive arterial blood pressure catheters, pulse oximeters and esophageal catheters as a surrogate for pleural pressure. Changes in pleural pressure measured by esophageal catheter are used to approximate breathing rate. Blood pressure, heart rate, and breathing

rate were monitored during baseline conditions (21% O_2 balanced with N_2) and during exposure to hypoxia. Response to hypoxia in vehicle treated rats is shown in Figure 1.

This model system is used to evaluate the tonic activity of the peripheral chemoreflex, as well as the sensitivity of the peripheral chemoreflex to isocapnic hypoxia, hypocapnic hypoxia, hypercapnic hypoxia, normoxic hypercapnia, or hyperoxia.

<u>In vivo assay for ventilatory response in conscious animals by whole-body plethysmography</u>

The aim of this study is to test the effect of P2X3 inhibitors on the chemoreflex sensitivity in awake animals. Reduction in ventilation at rest is interpreted as a reduction in chemoreflex sensitivity. In addition, reduction in ventilatory response (as measured by minute ventilation) to an acute hypoxic challenge is interpreted as a reduction in chemoreflex sensitivity. Using this system, we demonstrate reduced minute ventilation in spontaneously hypertensive rats treated for three weeks with P2X3 inhibitor patent example 11 as described in WO2016/091776 (Figure 2) and after single administration in Sprague dawley rats with P2X3 inbibitor patent example 348 as described in WO2016/091776 (Figure 3).

Whole body plethysmography involves measuring the flow from breathing of animals in a closed chamber. Animals are placed in small chambers with controlled atmosphere and their breathing is measured in response to changing air composition. In this case, a small animal whole body plethysmography system purchaced from Data Sciences International was used. With this method the breathing rate, inhalation and exhalation volume can be measured simultaneously. The minute ventilation, calculated as the product of tidal volume and breathing rate, is a measurement of the respiratory drive of the subject. Whole body plethysmography can be combined with exposure to defined mixtures of gas to measure the response of the subject to specific atmospheric conditions. For example, “normoxia” represents a normal atmospheric oxygen concentration from sea level of 21 %. “Hypoxia” represents oxygen concentrations under 21%. Generally for testing physiological responses to hypoxia concentrations of 10-12%

oxygen are used. These conditions can be achieved either with an oxygen scrubber to remove oxygen from room air, or by controlling the flow of nitrogen and oxygen to specific concentrations.

5

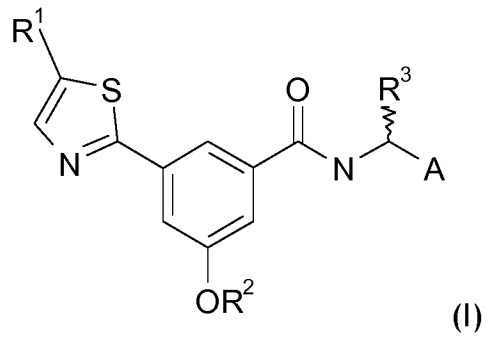
In vivo assay for blood pressure monitoring in conscious animals by radiotelemetry

The aim of this study is to evaluate the effect of P2X3 inhibitors on the systemic
10 blood pressure of experimental animals. For P2X3 inhibitors are reported to lower the blood pressure in animal models of hypertension (spontaneously hypertensive rats, SHR). Therefore, a reduction in blood pressure in SHR but not in healthy normotensive animals is interpreted as an on-target antihypertensive effect.

15 Female SHR or healthy control Wistar Kyoto rats are instrumented with radiotelemetric devices measuring systemic blood pressure by pressure catheters permanently fixed in the abdominal aorta of the animals. Blood pressure is monitored continuously for 24 hours prior to substance application and 48 hours post substance application. Animals are treated p.o. with substance or placebo.
20 Reference to In these experiments we observed a slight reduction in blood pressure in spontaneously hypertensive rats, indicating a mild on-target antihypertensive effect (Figure 4).

Claims

1. Use of compounds of general formula (I):



(I)

in which

R^1 represents a halogen atom, C_1-C_4-alkyl or C_3-C_6-cycloalkyl, wherein C_1-C_4-alkyl is optionally substituted with 1-5 halogen atoms which are the same or different;

R^2 represents -C_2-C_6-alkyl-OR^4, -$(CH_2)_q$-(C_3-C_7-cycloalkyl), -$(CH_2)_q$-(6- to 12-membered heterobicycloalkyl), -$(CH_2)_q$-(4- to 7-membered heterocycloalkyl), -$(CH_2)_q$-(5- to 10-membered heteroaryl) or -C_2-C_6-alkynyl; and

wherein said -$(CH_2)_q$-(C_3-C_7-cycloalkyl), -$(CH_2)_q$-(6- to 12-membered heterobicycloalkyl) and -$(CH_2)_q$-(4- to 7-membered heterocycloalkyl) are optionally substituted with one or more substituents which are the same or different, at any ring carbon atom and selected from the group consisting of

C_1-C_4 alkyl, optionally substituted with 1-5 halogen atoms which are the same or different, a halogen atom, -NR^aR^b, $COOR^5$ and oxo (=O); and

wherein independently any ring nitrogen atom, if present in said

-$(CH_2)_q$-(6- to 12-membered heterobicycloalkyl) and -$(CH_2)_q$-(4- to 7-membered heterocycloalkyl) is substituted with R^c; and

wherein said -$(CH_2)_q$-(5- to 10-membered heteroaryl) is optionally substituted with one or more substituents which are the same or different, and selected from the group consisting of C_1-C_4-alkyl, optionally substituted with 1-5 halogen atoms which are the same or different, a halogen atom, -NR^aR^b and -$COOR^5$;

R^3 represents hydrogen or C_1-C_4-alkyl, which is optionally substituted with 1-5 halogen atoms which are the same or different;

R^4 and R^5 represent hydrogen or C_1-C_4-alkyl;

R^a and R^b represent hydrogen or C_1-C_4-alkyl;

R^c represents hydrogen, C_1-C_4-alkyl, optionally substituted with 1-5 halogen atoms which are the same or different, -C(O)O-C_1-C_4-alkyl, or -C(O)-C_1-C_4-alkyl;

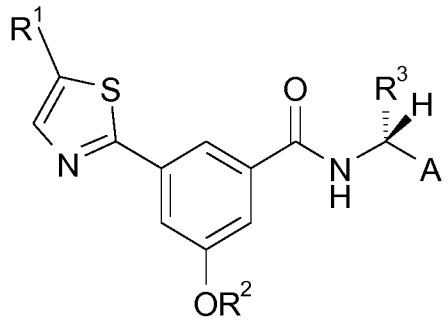
A represents 5- to 10-membered heteroaryl which is optionally substituted with one or more substituents, which are the same or different, and selected from the group consisting of a halogen atom, C_1-C_3-alkyl, and C_1-C_3-alkoxy, wherein C_1-C_3-alkyl and C_1-C_3-alkoxy are optionally substituted with 1-5 halogen atoms which are the same or different;

q represents an integer of 0, 1, or 2;

or an isomer, enantiomer, diastereomer, racemate, hydrate, solvate, or a salt thereof, or a mixture of same for the treatment or prophylaxis of

diseases or disorders which are 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.

2. Use according to claim 1, wherein the compounds have general formula (Ia):



(Ia)

in which A, R^1, R^2 and R^3 have the meanings as defined in claim 1, and R^3 preferably represents C_1-C_4-alkyl, more preferably methyl.

3. Use according to claim 1 or 2, namely

3-(5-methyl-1,3-thiazol-2-yl)-5-[(3R)-tetrahydrofuran-3-yloxy]-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide;

3-(5-methyl-1,3-thiazol-2-yl)-5-[(3S)-tetrahydrofuran-3-yloxy]-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide.

4. Use according to claim 3, namely 3-(5-methyl-1,3-thiazol-2-yl)-5-[(3R)-tetrahydrofuran-3-yloxy]-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide.

5. Use according according to any one of claims 1 or 2, namely 3-{[(2S)-4-methylmorpholin-2-yl]methoxy}-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[2-(trifluoromethyl)pyrimidin-5-yl]ethyl}benzamide; 3-{[(2R)-4-methylmorpholin-2-yl]methoxy}-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[2-(trifluoromethyl)-pyrimidin-5-yl]ethyl}benzamide.

6. Use according according to claim 5, namely 3-{[(2R)-4-methylmorpholin-2-yl]methoxy}-5-(5-methyl-1,3-thiazol-2-yl)-N-{(1R)-1-[2-(trifluoromethyl)-pyrimidin-5-yl]ethyl}benzamide.

7. Use of a pharmaceutical composition comprising a compound according to any one of claims 1 to 6, or an isomer, enantiomer, diastereomer, racemate, hydrate, solvate, or salt thereof, particularly a pharmaceutically acceptable salt thereof, or a mixture of same, and a pharmaceutically acceptable diluent or carrier.

8. Use according to any one claim 1 to 7 whereby the use is a long-term use.

9. Use according to any one claim 1 to 8 whereby the use is related to oral administration of a compound of general formula (I) or a composition containing such.

Figure 1:

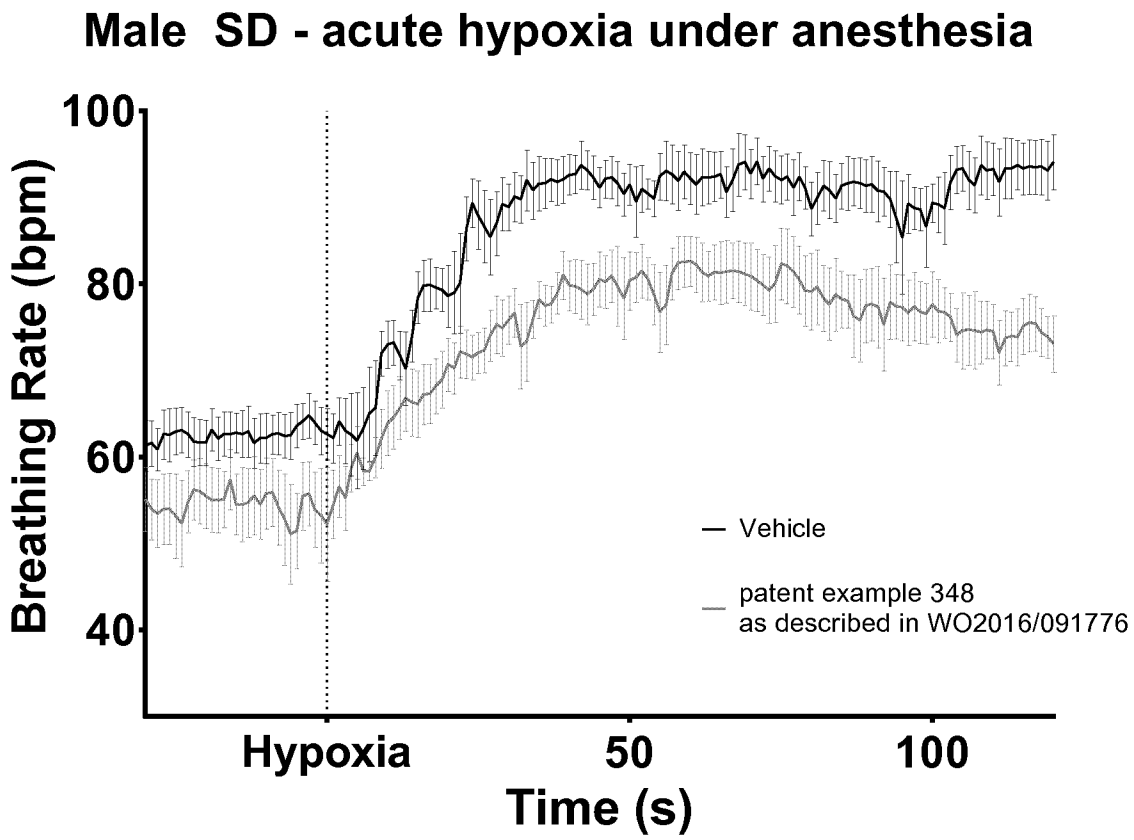

Male SD - acute hypoxia under anesthesia
Breathing Rate (bpm)
100
80
60
40
Hypoxia
50
100
Time (s)
Vehicle
patent example 348
as described in WO2016/091776

Figure 2

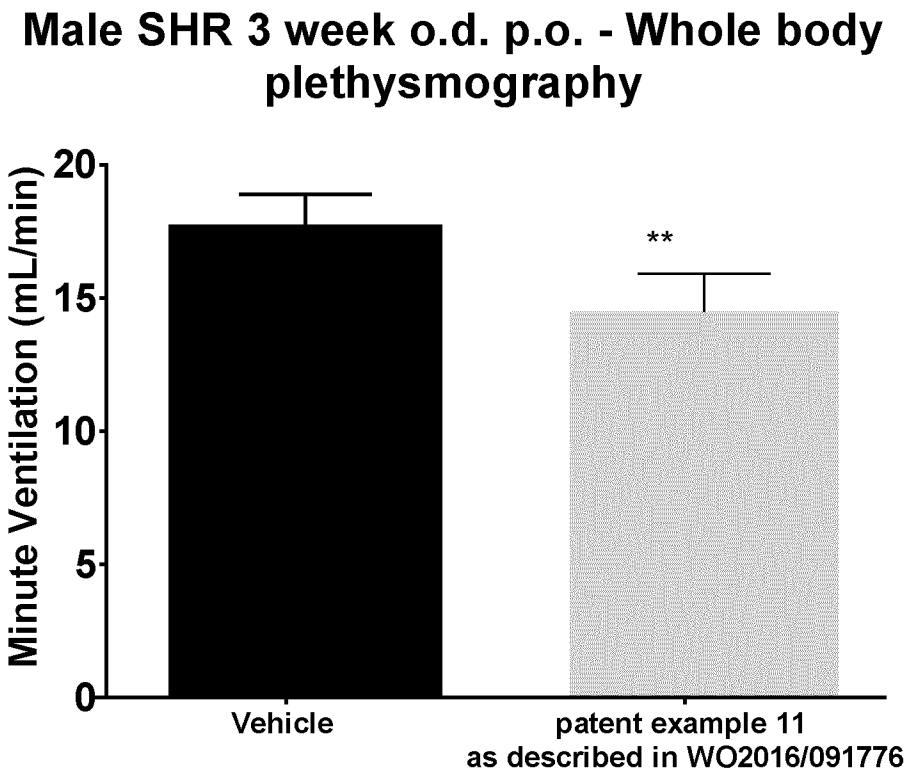
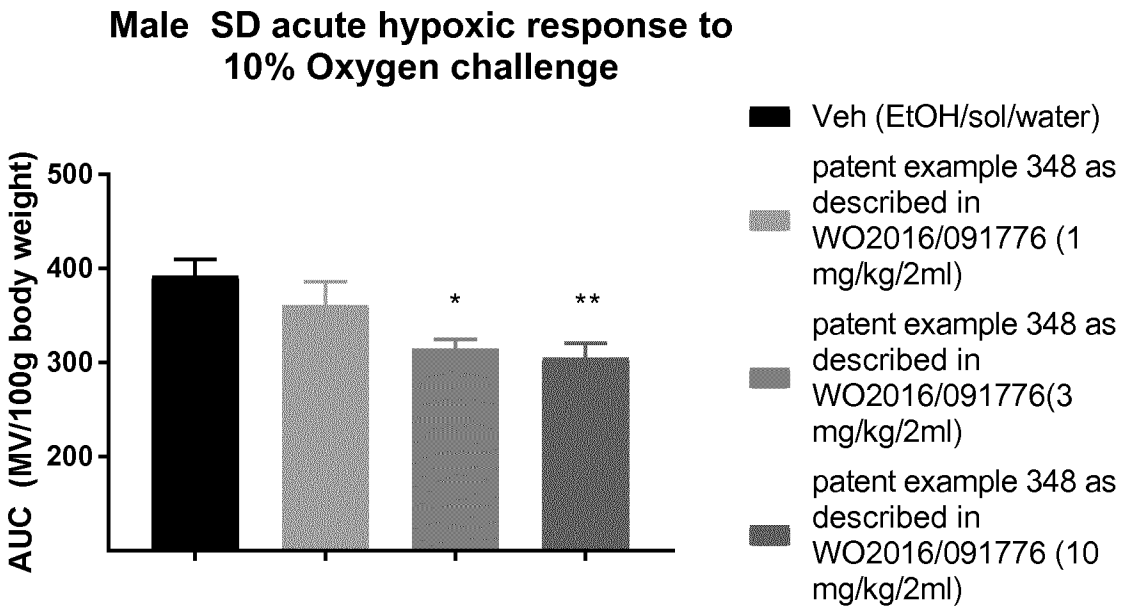
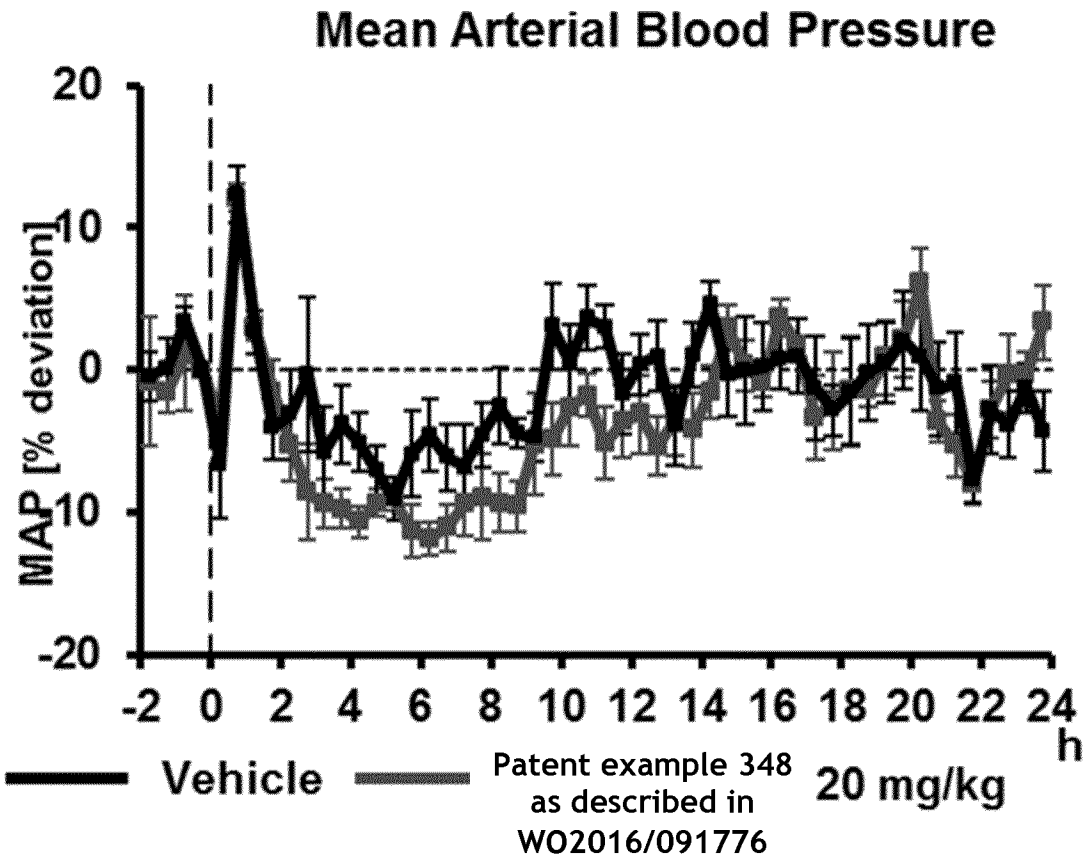

Male SHR 3 week o.d. p.o. - Whole body plethysmography
Minute Ventilation (mL/min)
20
15
10
5
0
**
Vehicle
patent example 11
as described in WO2016/091776

Figure 3:



n = 7-8 per group
data shown are mean ± SEM
One way ANOVA vs. Vehicle control with Tukey's post-hoc test

Figure 4:


Mean Arterial Blood Pressure
MAP [% deviation]
20
10
0
-10
-20
-2 0 2 4 6 8 10 12 14 16 18 20 22 24
h
Vehicle
Patent example 348
as described in
WO2016/091776
20 mg/kg

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2019/062329

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/427 A61P9/10 A61P9/04 A61P25/28 A61P9/12
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K 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, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2016/091776 A1 (EVOTEC AG [DE]) 16 June 2016 (2016-06-16) cited in the application example 11 claims 1-32, 34 page 640 - paragraph 1 page 645, line 16 - page 664, line 1 -----	1-9

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

☒ See patent family annex.

* Special categories of cited documents :

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Date of the actual completion of the international search	Date of mailing of the international search report
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INTERNATIONAL SEARCH REPORT

Information on patent family members

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