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(54) Title: SUBSTITUTED HETEROCYCLIC CARBOXAMINDES AND USE THEREOF

(57) Abstract: The present application relates to novel substituted heterocyclic carboxamides, to processes for preparation thereof, to the use thereof alone or in combinations for treatment and/or prevention of diseases and to the use thereof for producing medicaments for treatment and/or prevention of diseases, in particular for treatment and/or prevention of breathing difficulties including sleep-induced breathing difficulties such as central and obstructive sleep apnoea, snoring (primary and obstructive snoring), dysphagia, peripheral and cardiac vascular disorders including diabetic microangiopathies and disorders of the peripheral and central nervous system including neurodegenerative and neuroinflammatory disorders.

**Substituted heterocyclic carboxamides and use thereof**

The present application relates to novel substituted heterocyclic carboxamides, to processes for preparation thereof, to the use thereof alone or in combinations for treatment and/or prevention of diseases and to the use thereof for producing medicaments for treatment and/or prevention of diseases, in particular for treatment and/or prevention of breathing difficulties including sleep-induced breathing difficulties such as central and obstructive sleep apnoea, snoring (primary and obstructive snoring), dysphagia, peripheral and cardiac vascular disorders including diabetic microangiopathies and disorders of the peripheral and central nervous system including neurodegenerative and neuroinflammatory disorders.

$\alpha_2$-Adrenergic receptors ($\alpha_2$-ARs) belong to the family of the G-protein-coupled receptors. They bind to the pertussis toxin-sensitive inhibitory G proteins $G_i$ and $G_0$ and reduce adenylate cyclase activity. They are involved in the mediation of diverse physiological effects in various tissues following stimulation by endogenous catecholamines (adrenaline, noradrenaline) which are either released by synapses or reach the site of action via the blood.$\alpha_2$-AR play an important physiological role, mainly for the cardiovascular system and in the central nervous system. Biochemical, physiological and pharmacological studies have shown that, in addition to various $\alpha_1$-AR subtypes, there are three $\alpha_2$-AR subtypes ($\alpha_{2A}$, $\alpha_{2B}$ and $\alpha_{2C}$) in many target cells and tissues of cardiovascular relevance and neuronal target cells and tissues, which makes them attractive target proteins for therapeutic interventions. However, the elucidation of the precise physiological task of the receptor subtypes remains difficult to date because of a lack of highly selective ligands and/or antagonists of the respective $\alpha_2$-AR [Gyires *et al., $\alpha_2$-Adrenoceptor subtypes-mediated physiological, pharmacological actions, Neurochemistry International* 55, 447-453, 2009; Tan and Limbird, *The $\alpha_2$-Adrenergic Receptors: Adrenergic Receptors in the 21st Century/Receptors*, 2005, 241-265].

Obstructive sleep apnoea (OSA) is a sleep-related respiratory disorder which is characterized by repeat episodes of obstruction of the upper airways.

When breathing in, the patency of the upper airways is ensured by the interaction of two opposite forces. The dilative effects of the musculature of the upper airways counteract the negative intraluminal pressure, which constricts the lumen. The active contraction of the diaphragm and the other auxiliary respiratory muscles generates a negative pressure in the airways, thus constituting the driving force for breathing. The stability of the upper airways is substantially determined by the coordination and contraction property of the dilating muscles of the upper airways.

It is assumed that collapse of the upper airways in OSA occurs early during sleep, since the activity of several dilator muscles of the upper airways is reduced, which results in anatomically susceptible airways no longer remaining open. However, some dilator muscles of the upper airways including

the genioglossus muscle, which is the most important extensors of the upper airways and is innervated by the hypoglossal nerve, can increase activity during sleep as a reaction to breathing stimuli and possibly counteract some of these changes during early sleep. It has been observed that OSA patients have apnoea-free intervals in which the activity of the genioglossus muscle is only 25-40% higher compared to sleep phases with frequent obstructive apnoea [Jordan AS, *White DP, Lo YL et al., Airway dilator muscle activity and lung volume during stable breathing in obstructive sleep apnea. Sleep 2009*, 32(3): 361-8]. Noradrenaline is a neuromodulator of hypoglossal motor neuron activity [Horner R.L. *Neuromodulation of hypoglossal motoneurons during sleep. Respir Physiol Neurobiol 2008,* 164 (1-2): 179-196]. It is assumed that reduced noradrenergic stimulation leads to sleep-induced reduction of the excitability of hypoglossal motor neurons, which results in a reduced activity of the dilatory muscles of the upper airways, in particular a reduced activity of the genioglossus.

It has been shown that increasing the noradrenaline concentration in the brain by administration of the selective noradrenaline reuptake inhibitor reboxetine improved the severity of sleep apnoea in patients suffering from obstructive sleep apnoea (Altree TJ, Aishah A, Loffler KA, et al. The norepinephrine reuptake inhibitor reboxetine alone reduces obstructive sleep apnea severity: a double-blind, placebo-controlled, randomized crossover trial. J Clin Sleep Med. 2023 Jan 1;19(1):85–96).

Patients suffering from obstructive sleep apnoea have high mortality and morbidity as a result of cardiovascular disorders such as hypertension, myocardial infarction and stroke [Vrints *et al., Acta Clin Belg.*, 68, 169-78 (2013)].

$\alpha_{2C}$-adrenergic receptors regulate release of noradrenaline from central noradrenergic neurons. They are autoreceptors involved in the inhibition of presynaptic feedback of noradrenaline [Hein L. *et al, Two functionally distinct alpha2-adrenergic receptors regulate sympathetic neurotransmission Nature 1999,* 402(6758): 181-184].

Increased activity of the motor neurons of the hypoglossal nerve via alpha2c adrenoceptor antagonism may stabilize the upper airways and protect against collapse and occlusion. In addition, snoring may also be suppressed via stabilisation of the upper airways.

In the case of primary snoring, there is no obstruction of the upper airways. However, owing to the constriction of the upper airways, the flow rate of the air that is inhaled and exhaled increases. This, combined with the relaxed musculature, causes the soft tissues of the oral cavity and the pharynx to flutter in the stream of air. This gentle vibration then generates the typical snoring noises.

Obstructive snoring (upper airway resistance syndrome, heavy snoring, hypopnoea syndrome) is caused by repeat partial obstruction of the upper airways during sleep. This results in an increased airway resistance and thus in an increase in work of breathing with considerable fluctuations in intrathoracic pressure. During inspiration, the negative intrathoracic pressure may reach values similar to those that are encountered as a result of complete airway obstruction during obstructive sleep apnea. The pathophysiological consequences for heart, circulation and sleep quality correspond to those of obstructive sleep apnoea. As in obstructive sleep apnoea, the pathogenesis is assumed to be an impaired activity of the pharynx-dilating muscles during inspiration when sleeping. Frequently, obstructive snoring is the preliminary stage of obstructive sleep apnoea [Hollandt *et al., HNO*, 48, 628-634 (2000)].

Central sleep apnoea (CSA) occurs when brain function or control of breathing are impaired. CSA is characterized by lack of breathing stimuli whilst sleeping, resulting in recurring episodes of insufficient breathing or no breathing and impaired gas exchange. There are various manifestations of CSA. These include periodic breathing at high altitudes, idiopathic CSA (ICSA), central apnoea induced by narcotics, hypoventilation syndrome (OHS) and Cheyne-Stokes breathing (CSB). The exact mechanisms in the different types of CSA may vary considerably; however, one main characteristic is unstable breathing stimulation during sleep [Eckert D.J. *et al., Central sleep apnea: Pathophysiology and treatment. Chest 2007,* 131(2): 595-607].

Dysphagia is a difficulty in swallowing which may have various causes. The complex regulation of swallowing takes place in various structures of the brain. The is a two-way connection between the cerebral cortex, the corticobulbar tract, the brain stem and the peripheral swallowing musculature. Regulation and execution of the act of swallowing involves essentially five cranial nerves (the trigeminal nerve (V), the facial nerve (VII), the glossopharyngeal nerve (IX), the vagus nerve (X) and the hypoglossal nerve (XII)) and more than 25 muscle pairs [Arens C., *Position paper of the German Society of Oto-Rhino-Laryngology, Head and Neck Surgery and the German Society of Phoniatrics and Pediatric Audiology - current state of clinical and endoscopic diagnostics, evaluation, and therapy of swallowing disorders in children and adults. Laryngorhinootologie,* 2015 Mar; 94 Suppl 1:306-54].

Dysphagia may have very different causes, for example structural disorders of oral cavity and/or larynx, psychogenic causes and neurological disorders (neurogenic dysphagia), such as, *inter alia*, Parkinson's disease, myotonic dystrophy, amyotrophe lateral sclerosis, cerebral infarction, traumatic brain injury, brain stem laesions, myositides and neuromuscular disorders [Karkos PD, *Current evaluation of the dysphagic patient. Hippokratia.* 2009 Jul;13(3):141-6].

Noradrenergic neurons and $\alpha_2$-AR play a role in the coordination of swallowing and breathing [Yamanishi T., *Alpha2-adrenoceptors coordinate swallowing and respiration. J Dent Res* 2010, 89 (3): 258-2639].

$\alpha_2$-AR also plays an important role in cardiovascular changes. For example, the regulation of the contractility of the heart is regulated, firstly, by the central modulation of the sympathetic efferent nerves. Furthermore, the sympathetic efferent system also regulates direct effects on smooth muscle cells and vascular endothelial cells. Thus, the sympathetic system is involved in the regulation of the output performance of the heart, but also in the control of local perfusion of various vascular beds. This is also controlled via $\alpha_2$-ARs involved in the regulation of the peripheral resistance. Thus, blood vessels are innervated by sympathetic nerve fibres which run in the adventitia and whose endings are provided with varicosities for the release of noradrenaline. Released noradrenaline modulates, via the $\alpha_2$-AR in endothelial cells and smooth muscle cells, the respective local vascular tone.

In addition to the effects on the sympathetic efferent nerves, the peripheral cardiovascular function is also regulated by pre- and postsynaptic $\alpha_2$-AR. Smooth muscle cells and endothelial cells express different $\alpha_2$-AR subtypes. The activation of $\alpha_{2A}$, $\alpha_{2B}$ and $\alpha_{2C}$ receptors on smooth muscle cells leads to contraction with resulting vasoconstriction [Kanagy, *Clinical Science* 109: 431-437, (2005)]. However, the distribution of the respective receptor subtypes varies in the different vascular beds, between the species and between different vessel sizes. Thus, $\alpha_{2A}$-AR appear to be expressed virtually exclusively in large arteries, whereas $\alpha_{2B}$-AR contribute more to the vascular tone in small arteries and veins. AR$\alpha_{2B}$ appears to play a role in salt-induced hypertension [Gyires *et al., $\alpha_2$-Adrenoceptor subtypes-mediated physiological, pharmacological actions, Neurochemistry International* 55, 447-453, (2009)]. The role of AR$\alpha_{2C}$ on haemodynamics is not yet completely understood; however, AR$\alpha_{2C}$ receptors appear to mediate venous vasoconstriction. They are also involved in cold-induced enhancement of adrenoceptor-induced vasoconstriction [Chotani *et al., Silent $\alpha_{2C}$ adrenergic receptors enable cold-induced vasoconstriction in cutaneous arteries. Am J Physiol* 278:H1075-H1083, 2000; Gyires *et al., $\alpha_2$-Adrenoceptor subtypes-mediated physiological, pharmacological actions, Neurochemistry International* 55, 447-453, (2009)]. Cold and other factors (e.g. tissue proteins, oestrogen) regulate the functional coupling of AR$\alpha_{2C}$ to intracellular signal pathways [Chotani *et al., Distinct cAMP signaling pathways differentially regulate $\alpha_{2C}$ adrenenoxceptor expression: role in serum induction in human arteriolar smooth muscle cells. Am J Physiol Heart Circ Physiol* 288: H69-H76, (2005)].

Under pathophysiological conditions, the adrenergic system may be activated, which can lead, for example, to hypertension, heart failure, increased platelet activation, endothelial dysfunction, atherosclerosis, angina pectoris, myocardial infarction, thromboses, peripheral circulatory

disturbances, stroke and sexual dysfunction. Thus, for example, the pathophysiology of Raynaud's syndrome and scleroderma is substantially unclear, but is associated with a changed adrenergic activity. Thus, patients suffering from spastic Raynaud's syndrome show, for example, a significantly elevated expression of AR$\alpha_2$ receptoren on their platelets. This may be connected with the vasospastic attacks observed in these patients [Keenan and Porter, *$\alpha_2$-Adrenergic receptors in platelets from patients with Raynaud's syndrome, Surgery,* V94(2), (1983)].

By virtue of the expected high efficiency and low level of side effects, a possible treatment for such disorders targeting the modulation of the activated adrenergic system in organisms is a promising approach. In particular in diabetics, who frequently have elevated catecholamine levels, peripheral circulatory disturbances (microangiopathies) such as diabetic retinopathy, nephropathy or else pronounced wound healing disorders (diabetic foot ulcers) play a large role. In peripheral occlusive disease, diabetes is one of the most important comorbidities and also plays a crucial role in the progression of the disease (micro- and macroangiopathy). Higher expression of the adrenoreceptor $\alpha_{2C}$ receptors associated with elevated catecholamine levels may be involved in these pathophysiological processes in diabetics.

In 2011 there were 350 million diabetics world-wide (≈ 6.6% of the population), and this number is expected to double by 2028. Diabetic foot ulcers are the most frequent cause of hospitalizations of diabetics. The risk of a diabetic developing a diabetic foot ulcer in his or her lifetime is 15-25%, 15% of all diabetic foot ulcers lead to amputation. World-wide, 40-70% of all non-traumatic amputations are carried out on diabetics. Risk factors for diabetic foot ulcers are traumata, poor metabolic control, sensory, motoric and autonomous polyneuropathy, inappropriate footwear, infections and peripheral arterial disorders. The treatment of diabetic foot ulcers requires interdisciplinary teams and employs a multifactor approach: weight loss, revascularization (in the case of peripheral arterial occlusive disease, PAOD), improvements in metabolic control, wound excision, dressings, dalteparin, Regranex (PDGF) and amputation. The treatment costs per diabetic foot ulcer (without amputation) are 7000-10 000 USD. 33% of all diabetic foot ulcers do not heal within 2 years, and there is a high relapse rate (34% within the first year, 61% over 3 years).

Arylpiperazines as α2-adrenoceptor subtype C (alpha-2C) antagonists and the preparation thereof and the use thereof as medicaments are known from WO 03/082866 A1, where the compounds are described as being useful for the treatment of disorders such as stress disorders, Parkinson's disease, depression, schizophrenia, attention deficit hyperactivity disorder, post-traumatic stress disorder, obsessive-compulsive disorder, Tourette's syndrome, blepharospasm or other focal dystonias, temporal lobe epilepsy with psychosis, medicament-induced psychosis, Huntington's disease, a disorder caused by fluctuations in the sexual hormone level, panic disorder, Alzheimer's disease or

slight cognitive impairment. Nothing is known about the use of these compounds in the treatment of sleep-related respiratory disorders, preferably obstructive and central sleep apnoea and snoring.

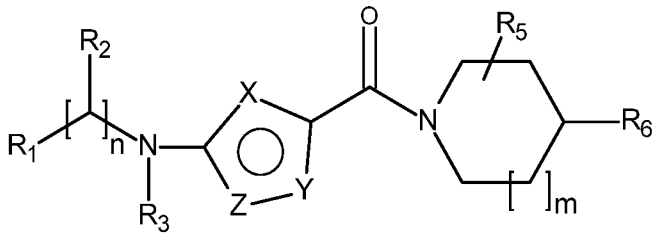
Substituted heterocyclic carboxamides as potent α2 adrenoceptor subtype C inhibitors (alpha-2C) and the preparation thereof are disclosed in WO2021/089683 A1.

The compounds of the present application are suitable for prevention and treatment of diseases caused by activation or by an activated $\alpha_{2C}$-adrenergic receptor, and of diseases secondary to $\alpha_{2C}$-adrenergic receptor-related damage.

Disorders which may be mentioned in this context are in particular breathing difficulties, sleep-induced breathing difficulties such as central and obstructive sleep apnoea, mixed sleep apnoea, Cheyne-Stokes respiration, snoring (primary and obstructive snoring), disrupted central respiratory drive, sudden infant death, postoperative hypoxia and apnoea, muscular respiratory disorders, respiratory disorders following long-term ventilation, respiratory disorders during adaptation in high mountains, dysphagia, acute and chronic pulmonary diseases with hypoxia and hypercapnia, peripheral circulatory disturbances (microangiopathies) such as diabetic retinopathy, diabetic nephropathy and wound healing disorders (diabetic foot ulcers), disorders of the peripheral and central nervous system, in particular dementia, depression, schizophrenia, attention deficit disorder with or without hyperactivity (ADHS), Tourette's syndrome, post-traumatic stress disorder, obsessive-compulsive disorder, blepharospasm or other focal dystonias, drug-induced psychosis, temporal lobe epilepsy with psychosis, panic disorder, disorders caused by changes in sexual hormones, multiple sclerosis, Alzheimer's disease, Parkinson's disease, Huntington's disease.

It is an object of the present invention to provide novel substances which act as potent and selective antagonists of the $\alpha_{2C}$-adrenergic receptor and as such are suitable for treatment and/or prevention of breathing difficulties, sleep-induced breathing difficulties such as obstructive and central sleep apnoea, snoring, dysphagia, disorders of the peripheral and central nervous system and peripheral circulatory disturbances (microangiopathies) such as diabetic retinopathy, diabetic nephropathy and wound healing disorders (diabetic foot ulcers).

The present invention provides compounds of the general formula (I)



(I)

in which

X is S, N or O;

Y is N, S or O,

where, when X is S, Z is N;

where, when X is O, Z is N;

Y is $CR_4$, O or $NR_4$,

where, when X is N and Z is N, Y is O;

where, when X is S, Y is $CR_4$ or $NR_4$;

$R_1$ is 5- to 10-membered heteroaryl, phenyl, ($C_4$-$C_{10}$)-heterocycloalkyl or ($C_3$-$C_{10}$)-cycloalkyl,

in which 5- to 10-membered heteroaryl may be substituted by 1 to 3 substituents selected independently from the group of ($C_1$-$C_4$)-alkyl, ($C_1$-$C_4$)-alkoxy, halogen;

where ($C_1$-$C_4$)-alkyl may be up to trisubstituted by halogen,

where ($C_1$-$C_4$)-alkoxy may be up to trisubstituted by halogen,

in which phenyl may be substituted by 1 to 2 substituents selected independently from the group of ($C_1$-$C_4$)-alkyl, ($C_3$-$C_5$)-cycloalkyl, ($C_1$-$C_4$)-alkoxy, cyano, hydroxy, halogen;

where ($C_1$-$C_4$)-alkyl may be up to trisubstituted by halogen,

in which ($C_3$-$C_{10}$)-cycloalkyl and ($C_4$-$C_{10}$)-heterocycloalkyl may be substituted by 1 to 2 substituents selected independently from the group of ($C_1$-$C_4$)-alkyl, ($C_3$-$C_5$)-cycloalkyl, ($C_1$-$C_4$)-alkoxy, cyano, hydroxy, halogen;

where ($C_1$-$C_4$)-alkyl may be up to trisubstituted by halogen,

in which ($C_3$-$C_{10}$)-cycloalkyl and ($C_4$-$C_{10}$)-heterocycloalkyl may be fused to 5- to 10-membered heteroaryl,

where 5- to 10-membered heteroaryl may be substituted by 1 to 2 substituents selected independently from the group of ($C_1$-$C_4$)-alkyl, ($C_1$-$C_4$)-alkoxy and halogen;

$R_2$ is hydrogen, ($C_1$-$C_4$)-alkyl or ($C_3$-$C_5$)-cycloalkyl;

in which ($C_1$-$C_4$)-alkyl may be up to trisubstituted by halogen,

in which ($C_1$-$C_4$)-alkyl may be substituted by cyano or ($C_1$-$C_4$)-alkoxy,

in which ($C_3$-$C_5$)-cycloalkyl may be up to trisubstituted by halogen,

or

together with the carbon atom to which $R_2$ is bonded forms a ($C_3$-$C_4$)-cycloalkyl ring,

or

$R_1$ and $R_2$ together form a ($C_5$-$C_8$)-cycloalkyl or ($C_5$-$C_{10}$)-heterocycloalkyl ring,

in which ($C_5$-$C_8$)-cycloalkyl may be fused to 5- to 10-membered heteroaryl,

where 5- to 10-membered heteroaryl may be substituted by 1 to 2 substituents selected independently from the group of ($C_1$-$C_4$)-alkyl, ($C_1$-$C_4$)-alkoxy and halogen;

in which ($C_3$-$C_{10}$)-heterocycloalkyl may be fused to 5- to 10-membered heteroaryl,

where 5- to 10-membered heteroaryl may be substituted by 1 to 2 substituents selected independently from the group of ($C_1$-$C_4$)-alkyl, ($C_1$-$C_4$)-alkoxy and halogen;

$R_3$ is hydrogen, ($C_1$-$C_4$)-alkyl,

in which ($C_1$-$C_4$)-alkyl may be up to trisubstituted by halogen,

$R_4$ in $CR_4$ is hydrogen, ($C_1$-$C_4$)-alkyl, ($C_3$-$C_4$)-cycloalkyl, phenyl, halogen;

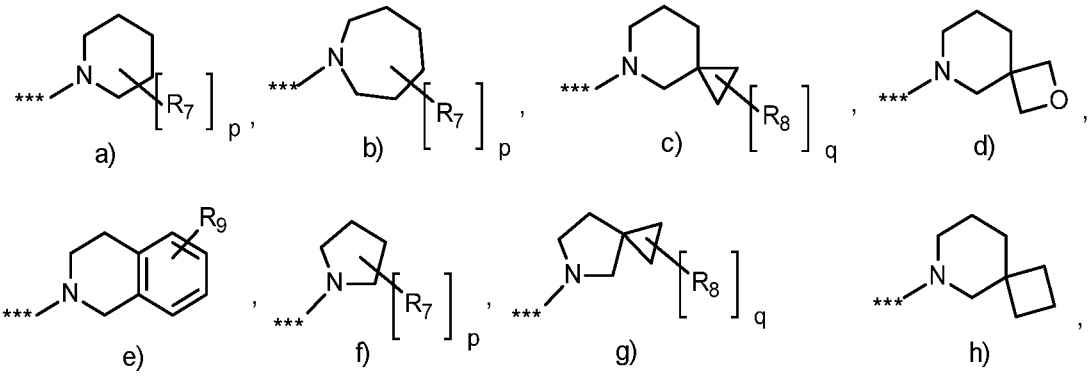
in which ($C_1$-$C_4$)-alkyl may be up to trisubstituted by halogen and phenyl may be substituted by halogen,

in $NR_4$ is absent or is hydrogen, ($C_1$-$C_4$)-alkyl, ($C_3$-$C_4$)-cycloalkyl, phenyl;

in which ($C_1$-$C_4$)-alkyl may be up to trisubstituted by halogen and phenyl may be substituted by halogen,

$R_5$ is hydrogen, ($C_1$-$C_4$)-alkyl, ($C_1$-$C_4$)-alkoxy, halogen,

$R_6$ is a group of formula a), b), c), d), e), f) or g)




,

in which *** marks the attachment to the adjacent piperidine ring,

in which $R_7$ is hydrogen, ($C_1$-$C_4$)-alkyl, ($C_3$-$C_4$)-cycloalkyl, ($C_1$-$C_4$)-alkoxy, ($C_3$-$C_4$)-cycloalkoxy, phenyl,

where ($C_1$-$C_4$)-alkyl may be substituted by ($C_3$-$C_4$)-cycloalkyl, ($C_1$-$C_4$)-alkoxy, ($C_3$-$C_4$)-cycloalkoxy and up to trisubstituted by halogen,

where ($C_1$-$C_4$)-alkoxy may be substituted by ($C_3$-$C_4$)-cycloalkyl and up to trisubstituted by halogen,

where ($C_3$-$C_4$)-cycloalkyl may be substituted by monofluoromethyl, difluoromethyl or trifluoromethyl and up to disubstituted by halogen,

where ($C_1$-$C_4$)-alkoxy may be substituted by ($C_3$-$C_4$)-cycloalkyl and up to trisubstituted by halogen,

where ($C_3$-$C_4$)-cycloalkyl may be mono- or disubstituted by halogen,

where ($C_3$-$C_4$)-cycloalkoxy may be up to disubstituted by halogen,

in which $R_8$ is hydrogen or fluorine,

in which $R_9$ is hydrogen, ($C_1$-$C_4$)-alkyl, ($C_1$-$C_4$)-alkoxy, halogen;

where ($C_1$-$C_4$)-alkyl may be substituted by ($C_1$-$C_4$)-alkoxy,

n represents 0 or 1,

m represents 0, 1 or 2,

p represents 0, 1 or 2 and

q represents 0, 1 or 2,

and the salts, solvates and solvates of the salts thereof.

Compounds of the invention are the compounds of the formula (I) and the salts, solvates and solvates of the salts thereof, the compounds that are encompassed by formula (I) and are of the formulae mentioned below and the salts, solvates and solvates of the salts thereof and the compounds that are encompassed by formula (I) and are cited below as working examples and the salts, solvates and solvates of the salts thereof if the compounds that are encompassed by formula (I) and are mentioned below are not already salts, solvates and solvates of the salts.

Compounds of the invention are likewise *N*-oxides and *S*-oxides of the compounds of the formula (I) and the salts, solvates and solvates of the salts thereof.

Preferred salts in the context of the present invention are physiologically acceptable salts of the compounds of the invention. Also encompassed are salts which are not themselves suitable for pharmaceutical applications but can be used, for example, for the isolation, purification or storage of the compounds of the invention.

A suitable pharmaceutically acceptable salt of the compounds of the present invention may be, for example, an acid addition salt of a compound of the present invention bearing a sufficiently basic nitrogen atom in a chain or in a ring, such as an acid addition salt with an inorganic acid, or "mineral acid", such as hydrochloric acid, hydrobromic acid, hydriodic acid, sulfuric acid, sulfamic acid, disulfuric acid, phosphoric acid or nitric acid, for example, or with an organic acid, for example formic acid, acetic acid, acetoacetic acid, pyruvic acid, trifluoroacetic acid, propionic acid, butyric acid, hexanoic acid, heptanoic acid, undecanoic acid, lauric acid, benzoic acid, salicylic acid, 2-(4-

hydroxybenzoyl)benzoic acid, camphoric acid, cinnamic acid, cyclopentanepropionic acid, digluconic acid, 3-hydroxy-2-naphthoic acid, nicotinic acid, pamoic acid, pectinic acid, 3-phenylpropionic acid, pivalic acid, 2-hydroxyethanesulfonic acid, itaconic acid, trifluoromethanesulfonic acid, dodecylsulfuric acid, ethanesulfonic acid, benzenesulfonic acid, para-toluenesulfonic acid, methanesulfonic acid, 2-naphthalenesulfonic acid, naphthalenedisulfonic acid, camphorsulfonic acid, citric acid, tartaric acid, stearic acid, lactic acid, oxalic acid, malonic acid, succinic acid, malic acid, adipic acid, alginic acid, maleic acid, fumaric acid, D-gluconic acid, mandelic acid, ascorbic acid, glucoheptanoic acid, glycerophosphoric acid, aspartic acid, sulfosalicylic acid or thiocyanic acid.

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

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

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

In the present text, in particular in the Experimental Section, for the synthesis of intermediates and of examples of the present invention, when a compound is mentioned as a salt form with the corresponding base or acid, the exact stoichiometric composition of said salt form, as obtained by the respective preparation and/or purification process, is, in most cases, unknown. Unless stated otherwise, suffixes to chemical names or structural formulae relating to salts, such as "hydrochloride", "trifluoroacetate", "sodium salt", or "x HCl", "x $CF_3COOH$", "x $Na^+$", for example,

mean a salt form, without specification of the stoichiometry of this salt. This applies analogously to cases in which synthesis intermediates or example compounds or salts thereof have been obtained as solvates, for example hydrates, by the preparation and/or purification processes described.

Solvates in the context of the invention are described as those forms of the compounds of the invention which form a complex in the solid or liquid state by coordination with solvent molecules. Hydrates are a specific form of the solvates in which the coordination is with water. Solvates preferred in the context of the present invention are hydrates.

The compounds of the invention may, depending on their structure, exist in different stereoisomeric forms, i.e. in the form of configurational isomers or else, if appropriate, as conformational isomers (enantiomers and/or diastereomers, including those in the case of atropisomers). The present invention therefore encompasses the enantiomers and diastereomers, and the respective mixtures thereof. It is possible to isolate the stereoisomerically homogeneous constituents from such mixtures of enantiomers and/or diastereomers in a known manner. Preference is given to employing chromatographic methods for this purpose, especially HPLC chromatography on achiral or chiral separation phases. In the case of carboxylic acids as intermediates or end products, separation is alternatively also possible via diastereomeric salts using chiral amine bases.

In the context of the present invention, the term "enantiomerically pure" is understood to the effect that the compound in question with respect to the absolute configuration of the chiral centers is present in an enantiomeric excess of more than 95%, preferably more than 98%. The enantiomeric excess, ee, is calculated here by evaluating an HPLC analysis chromatogram on a chiral phase using the formula below:

$$ee = \left| \frac{\text{Enantiomer 1 (area per cent)} - \text{Enantiomer 2 (area per cent)}}{\text{Enantiomer 1 (area per cent)} + \text{Enantiomer 2 (area per cent)}} \right| \times 100\%.$$

If the compounds of the invention can occur in tautomeric forms, the present invention encompasses all the tautomeric forms.

The present invention also encompasses all suitable isotopic variants of the compounds of the invention. An isotopic variant of a compound of the invention is understood here to mean a compound in which at least one atom within the compound of the invention has been exchanged for another atom of the same atomic number, but with a different atomic mass from the atomic mass which usually or predominantly occurs in nature (“unnatural fraction”). The expression “unnatural fraction” is understood to mean a proportion of such an isotope higher than its natural frequency. The natural frequencies of isotopes to be employed in this connection can be found in "Isotopic Compositions of the Elements 1997", Pure Appl. Chem., 70(1), 217-235, 1998. Examples of isotopes

which can be incorporated into a compound of the invention are those of hydrogen, carbon, nitrogen, oxygen, phosphorus, sulfur, fluorine, chlorine, bromine and iodine, such as $^{2}H$ (deuterium), $^{3}H$ (tritium), $^{13}C$, $^{14}C$, $^{15}N$, $^{17}O$, $^{18}O$, $^{32}P$, $^{33}P$, $^{33}S$, $^{34}S$, $^{35}S$, $^{36}S$, $^{18}F$, $^{36}Cl$, $^{82}Br$, $^{123}I$, $^{124}I$, $^{129}I$ and $^{131}I$. Particular isotopic variants of a compound of the invention, especially those in which one or more radioactive isotopes have been incorporated, may be beneficial, for example, for the examination of the mechanism of action or of the active ingredient distribution in the body; due to the comparatively easy preparability and detectability, especially compounds labelled with $^{3}H$ or $^{14}C$ isotopes are suitable for this purpose. In addition, the incorporation of isotopes, for example of deuterium, can lead to particular therapeutic benefits as a consequence of greater metabolic stability of the compound, for example an extension of the half-life in the body or a reduction in the active dose required; such modifications of the compounds of the invention may therefore possibly also constitute a preferred embodiment of the present invention. With regard to the treatment and/or prophylaxis of the disorders specified here, the isotopic variant(s) of the compounds of the general formula (I) preferably contain deuterium ("deuterium-containing compounds of the general formula (I)"). Isotopic variants of the compounds of the general formula (I) into which one or more radioactive isotopes such as $^{3}H$ or $^{14}C$ have been incorporated are beneficial, for example, in medicament and/or substrate tissue distribution studies. Because of their easy incorporability and detectability, these isotopes are particularly preferred. It is possible to incorporate positron-emitting isotopes such as $^{18}F$ or $^{11}C$ into a compound of the general formula (I). These isotopic variants of the compounds of the general formula (I) are suitable for use in in vivo imaging applications. Deuterium-containing and $^{13}C$-containing compounds of the general formula (I) can be used within the scope of preclinical or clinical studies in mass spectrometry analyses (H. J. Leis *et al., Curr. Org. Chem.,* **1998**, *2*, 131). Isotopic variants of the compounds of the invention can be prepared by commonly used processes known to those skilled in the art, for example by the methods described further down and the procedures described in the working examples, by using corresponding isotopic modifications of the respective reagents and/or starting compounds.

Isotopic variants of the compounds of the general formula (I) can generally be prepared by processes known to those skilled in the art as described in the schemes and/or examples described here, by replacing a reagent with an isotopic variant of the reagent, preferably a deuterium-containing reagent. According to the deuteration sites desired, it is possible in some cases to incorporate deuterium from $D_2O$ either directly into the compounds or into reagents which can be used for the synthesis of such compounds (Esaki *et al.*, *Tetrahedron*, **2006**, *62*, 10954; Esaki *et al.*, *Chem. Eur. J.*, **2007**, *13*, 4052). A photochemical deuteration and tritiation method has also been described (Y. Y. Loh et al., Science 10.1126/science.aap9674 (2017). Another useful reagent for incorporation of deuterium into molecules is deuterium gas. A rapid route for incorporation of deuterium is the catalytic deuteration of olefinic bonds (H. J. Leis *et al.*, *Curr. Org. Chem.*, **1998**, *2*, 131; J. R. Morandi *et al.*, *J. Org. Chem.*, **1969**, *34* (*6*), 1889) and acetylenic bonds (N. H. Khan, *J. Am. Chem. Soc.*, **1952**, *74* (*12*),

3018; S. Chandrasekhar *et al.*, *Tetrahedron*, **2011**, *52*, 3865). For direct exchange of hydrogen for deuterium in hydrocarbons containing functional groups, it is also possible to use metal catalysts (i.e. Pd, Pt and Rh) in the presence of deuterium gas (J. G. Atkinson *et al.*, US Patent 3966781). Various deuterated reagents and synthesis units are commercially available from companies like, for example, C/D/N Isotopes, Quebec, Canada; Cambridge Isotope Laboratories Inc., Andover, MA, USA; and CombiPhos Catalysts, Inc., Princeton, NJ, USA. Further information relating to the prior art with regard to deuterium-hydrogen exchange can be found, for example, in Hanzlik *et al.*, *J. Org. Chem.*, **1990**, *55*, 3992-3997; R. P. Hanzlik *et al.*, *Biochem. Biophys. Res. Commun.*, **1989**, *160*, 844; P. J. Reider *et al.*, *J. Org. Chem.*, **1987**, *52*, 3326-3334; M. Jarman *et al.*, *Carcinogenesis* ,**1993**, *16*(4), 683-688; J. Atzrodt *et al.*, *Angew. Chem., Int. Ed.* **2007**, *46*, 7744; K. Matoishi *et al.*, **2000**, *J. Chem. Soc, Chem. Commun.*, 1519−1520; K. Kassahun *et al.*, WO 2012/112363.

The term "deuterium-containing compound of the general formula (I)" is defined as a compound of the general formula (I) in which one or more hydrogen atoms have been replaced by one or more deuterium atoms and in which the frequency of deuterium in every deuterated position in the compound of the general formula (I) is higher than the natural frequency of deuterium, which is about 0.015%. More particularly, in a deuterium-containing compound of the general formula (I), the frequency of deuterium in every deuterated position in the compound of the general formula (I) is higher than 10%, 20%, 30%, 40%, 50%, 60%, 70% or 80%, preferably higher than 90%, 95%, 96% or 97%, even further preferably higher than 98% or 99%, in this position or these positions. It will be apparent that the frequency of deuterium in every deuterated position is independent of the frequency of deuterium in other deuterated positions.

The selective incorporation of one or more deuterium atoms into a compound of the general formula (I) can alter the physicochemical properties (for example acidity [A. Streitwieser *et al.*, J. Am. Chem. Soc., **1963**, *85*, 2759; C. L. Perrin *et al.*, J. Am. Chem. Soc., **2007**, *129*, 4490], basicity [C. L. Perrin, et al., J. Am. Chem. Soc., 2003, 125, 15008; C. L. Perrin in Advances in Physical Organic Chemistry, 44, 144; C. L. Perrin et al., J. Am. Chem. Soc., 2005, 127, 9641], lipophilicity [B. Testa et al., Int. J. Pharm., 1984, 19(3), 271]) and/or the metabolic profile of the molecule, and cause changes in the ratio of parent compound to metabolites or the amounts of metabolites formed. Such changes may lead to particular therapeutic benefits and therefore be preferable under particular circumstances. Reduced rates of metabolism and metabolic switching, where the ratio of metabolites is changed, have been reported (D. J. Kushner et al., Can. J. Physiol. Pharmacol., 1999, 77, 79; A. E. Mutlib et al., Toxicol. Appl. Pharmacol., 2000, 169, 102). These changes in the exposure to parent compound and metabolites can have important consequences with respect to the pharmacodynamics, tolerability and efficacy of a deuterium-containing compound of the general formula (I). In some cases deuterium substitution reduces or eliminates the formation of an undesired or toxic metabolite and enhances the formation of a desired metabolite (e.g. Nevirapine: A. M. Sharma et al., Chem. Res. Toxicol., 2013,

26, 410; Uetrecht et al., Chemical Research in Toxicology, 2008, 21, 9, 1862; Efavirenz: A. E. Mutlib et al., Toxicol. Appl. Pharmacol., 2000, 169, 102). In other cases the major effect of deuteration is to reduce the rate of systemic clearance. As a result, the biological half-life of the compound is increased. The potential clinical benefits would include the ability to maintain similar systemic exposure with decreased peak levels and increased trough levels. This could result in lower side effects and enhanced efficacy, depending on the particular compound's pharmacokinetic/pharmacodynamic relationship. Examples of this deuterium effect are indiplon (A. J. Morales et al., Abstract 285, The 15th North American Meeting of the International Society of Xenobiotics, San Diego, CA, October 12-16, 2008), ML-337 (C. J. Wenthur et al., J. Med. Chem., 2013, 56, 5208), and Odanacatib (K. Kassahun et al., WO2012/112363) are examples for this deuterium effect. Still other cases have been reported in which reduced rates of metabolism result in an increase in exposure of the drug without changing the rate of systemic clearance (e.g. Rofecoxib: F. Schneider et al., Arzneim. Forsch. Drug. Res., 2006, 56, 295; Telaprevir: F. Maltais et al., J. Med. Chem., 2009, 52, 7993). Deuterated drugs showing this effect may have reduced dosing requirements (e.g. lower number of doses or lower dosage to achieve the desired effect) and/or may produce lower metabolite loads.

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

The present invention additionally also encompasses prodrugs of the compounds of the invention. The term "prodrugs" refers here to compounds which may themselves be biologically active or inactive, but are converted while present in the body, for example by a metabolic or hydrolytic route, to compounds of the invention.

In the context of the present invention, unless specified otherwise, the substituents are defined as follows:

Alkyl in the context of the invention is a straight-chain or branched alkyl radical having the particular number of carbon atoms specified. Examples include: methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, 1-methylpropyl, tert-butyl, n-pentyl, isopentyl, 1-ethylpropyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, n-hexyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 3,3-dimethylbutyl, 1-ethylbutyl, 2-ethylbutyl, 1,4-dimethylpentyl, 4,4-dimethylpentyl and 1,4,4-trimethylpentyl.

Alkoxy in the context of the invention is a straight-chain or branched alkoxy radical having the particular number of carbon atoms specified. Examples include: methoxy, ethoxy, n-propoxy, isopropoxy, 1-methylpropoxy, n-butoxy, isobutoxy and tert-butoxy.

Cycloalkoxy in the context of the invention is a cyclic alkoxy radical having 3 to 4 carbon atoms. Examples include: cyclopropoxy or cyclobutoxy.

Cycloalkyl or carbocycle in the context of the invention is a mono-, poly- or spirocyclic, preferably mono- or bicyclic, saturated carbocycle having the respectively specified number of ring atoms. A monocyclic saturated carbocycle is referred to synonymously as cycloalkyl. Examples include: cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclopentenyl, cyclohexenyl, cyclohexadienyl, cycloheptenyl, cycloheptadienyl, spiro[2.3]hexyl, spiro[2.4]heptyl, spiro[2.5]octyl, bicyclo[1.1.1]pentyl, bicyclo[2.2.1]heptyl, bicyclo[4.1.0]heptyl, bicyclo[2.2.2]octyl, tricyclo[3.3.1.13,7]decyl. Monocyclic cycloalkyl having 3 to 5 carbon atoms is preferred. Examples include: cyclopropyl, cyclobutyl or cyclopentyl.

Heterocycle or heterocyclyl in the context of the invention is a monocyclic or bicyclic, saturated heterocycle which has the particular number of ring atoms specified, contains one or two ring heteroatoms from the group of N, O, S, SO and/or $SO_2$ and is joined via a ring carbon atom or optionally a ring nitrogen atom. Examples include: azetidinyl, oxetanyl, pyrrolidinyl, pyrazolidinyl, tetrahydrofuranyl, thiolanyl, piperidinyl, piperazinyl, tetrahydropyranyl, tetrahydrothiopyranyl, morpholinyl, thiomorpholinyl, hexahydroazepinyl and hexahydro-1,4-diazepinyl. Preference is given to azetidinyl, oxetanyl, pyrrolidinyl, tetrahydrofuranyl, piperidinyl, piperazinyl, tetrahydropyranyl and morpholinyl.

Heteroaryl in the context of the invention is a monocyclic or bicyclic aromatic heterocycle (heteroaromatic) which has the particular number of ring atoms specified, contains up to four identical or different ring heteroatoms from the group of N, O and S and is joined via a ring carbon atom or optionally via a ring nitrogen atom. Preferred examples include: furyl, pyrrolyl, thienyl, pyrazolyl, imidazolyl, quinolinyl, thiazolyl, oxazolyl, isoxazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl and triazinyl.

In general, and unless stated otherwise, the heteroaryl groups include all possible isomeric forms, for example tautomers and positional isomers in relation to the attachment point to the rest of the molecule. Thus, the term pyridyl embraces, as non-limiting examples, 2-pyridyl, 3-pyridyl and 4-pyridyl, or the term thienyl embraces 2-thienyl and 3-thienyl.

Halogen in the context of the invention includes fluorine, chlorine, bromine and iodine. Preference is given to chlorine or fluorine.

When radicals in the compounds of the invention are substituted, the radicals may be mono- or polysubstituted, unless specified otherwise. In the context of the present invention, all radicals which occur more than once are defined independently of one another. When radicals in the compounds of the invention are substituted, the radicals may be mono- or polysubstituted, unless specified otherwise. Substitution by one substituent or by two identical or different substituents is preferred.

In the context of the present invention, the term "treatment" or "treating" includes inhibition, retardation, checking, alleviating, attenuating, restricting, reducing, suppressing, repelling or healing of a disease, a condition, a disorder, an injury or a health problem, or the development, the course or the progression of such states and/or the symptoms of such states. The term “therapy” is understood here to be synonymous with the term “treatment”.

The terms “prevention” and “prophylaxis” are used synonymously in the context of the present invention and refer to the avoidance or reduction of the risk of contracting, experiencing, suffering from or having a disease, a condition, a disorder, an injury or a health problem or a development or progression of such states and/or the symptoms of such states.

The treatment or prevention of a disease, a condition, a disorder, an injury or a health problem may be partial or complete.

Preference is given in the context of the present invention to compounds of the formula (I) in which

X is S or N;

Y is N, S or O,

where, when X is S, Z is N;

where, when X is O, Z is N;

Y is $CR_4$, N or O,

where, when X is N and Z is N, Y is O;

where, when X is S, Y is N or $CR_4$;

$R_1$ is pyridinyl, pyrazolyl, thiazolyl, thienyl, phenyl, heterocyclohexyl or cyclohexyl,

in which pyridinyl may be substituted by 1 to 2 substituents selected independently from the group of ($C_1$-$C_2$)-alkyl, fluorine, chlorine, trifluoromethyl, trifluoromethoxy,

in which pyrazolyl may be substituted by 1 to 2 substituents selected independently from the group of ($C_1$-$C_2$)-alkyl, fluorine, chlorine, trifluoromethyl,

in which thiazolyl may be substituted by 1 to 2 substituents selected independently from the group of fluorine, chlorine,

in which thienyl may be substituted by 1 to 2 substituents selected independently from the group of fluorine, chlorine,

in which phenyl may be substituted by 1 to 2 substituents selected independently from the group of ($C_1$-$C_2$)-alkyl, ($C_3$-$C_4$)-cycloalkyl, methoxy, cyano, hydroxy, fluorine, chlorine, trifluoromethyl;

in which heterocyclohexyl and cyclohexyl may be fused to 5- to 6-membered heteroaryl,

$R_2$ is hydrogen, ($C_1$-$C_2$)-alkyl or cyclopropyl,

in which ($C_1$-$C_2$)-alkyl may be substituted by cyano or ($C_1$-$C_2$)-alkoxy,

or

together with the carbon atom to which $R_2$ is bonded forms a cyclopropyl ring,

or

$R_1$ and $R_2$ together form a cyclohexyl or ($C_6$)-heterocycloalkyl ring,

in which cyclohexyl may be fused to 6-membered heteroaryl,

in which ($C_6$)-heterocycloalkyl may be fused to 6-membered heteroaryl,

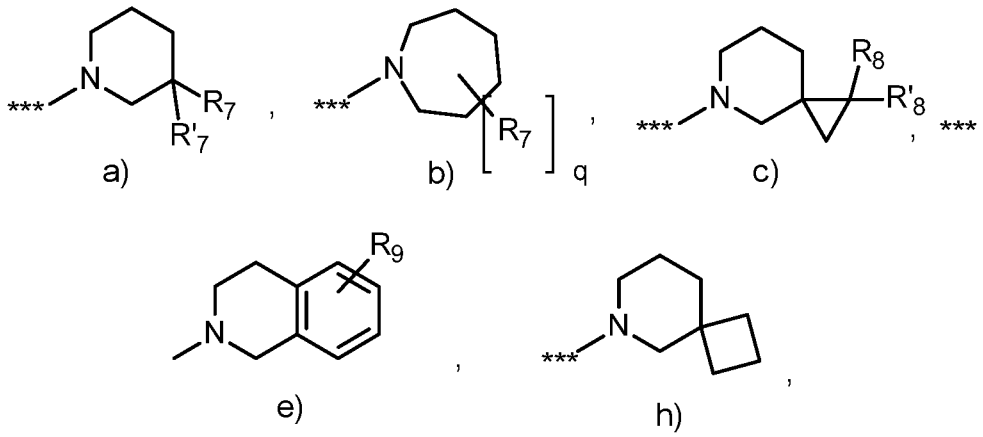
$R_3$ is hydrogen, ($C_1$-$C_2$)-alkyl;

$R_4$ is hydrogen, ($C_1$-$C_2$)-alkyl, ($C_3$-$C_4$)-cycloalkyl, trifluoromethyl, bromine, chlorine, phenyl;

where phenyl may be substituted by halogen,

$R_5$ is hydrogen, ($C_1$-$C_2$)-alkyl, methoxy, fluorine;

$R_6$ is one of the groups of the formulae a), b), c), e) or h),




in which *** marks the attachment to the adjacent piperidine ring,

in which $R_7$ or $R'_7$ is independently hydrogen, $(C_1\text{-}C_4)$-alkyl, $(C_3\text{-}C_4)$-cycloalkyl, $(C_1\text{-}C_2)$-alkoxy, $(C_3\text{-}C_4)$-cycloalkoxy, monofluoromethyl, difluoromethyl, trifluoromethyl, difluoromethoxy, phenyl,

where $(C_1\text{-}C_4)$-alkyl may be substituted by methoxy, n-butoxy, cyclopropyl, cyclobutoxy and up to disubstituted by fluorine,

where methoxy may be substituted by cyclopropyl, cyclobutyl, trifluoromethyl,

where cyclopropyl may be substituted by monofluoromethyl, difluoromethyl, trifluoromethyl,

where cyclopropyl may be up to disubstituted by fluorine,

where n-butoxy may be up to disubstituted by fluorine,

where $(C_1\text{-}C_2)$-alkoxy may be substituted by cyclopropyl, cyclobutyl, cyclobutoxy, trifluoromethyl and

where cyclopropyl and cyclobutyl may be up to disubstituted by fluorine,

where $(C_3\text{-}C_4)$-cycloalkoxy may be up to disubstituted by fluorine,

in which $R_8$ or $R'_8$ is independently hydrogen or fluorine,

in which $R_9$ is hydrogen, $(C_1\text{-}C_4)$-alkyl, $(C_1\text{-}C_2)$-alkoxy, methoxyethyl, fluorine, chlorine;

n represents 0 or 1 and

m represents 1 or 2,

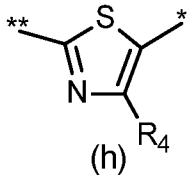
q represents 0 or 2,

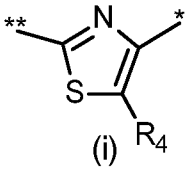
and the salts, solvates and solvates of the salts thereof.

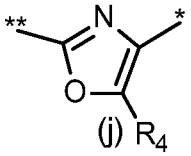
In the context of the present invention, preference is given to compounds of the formula (I)

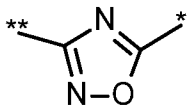
in which

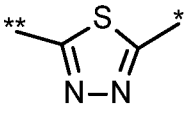
X, Y and Z are chosen such that the aromatic 5-membered ring has the structural formula h), i), j), k), r) or p),

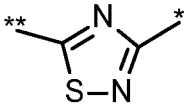

(h)


(i)


(j)


(k)


(r)


(p)

in which * marks the attachment to the carbonyl group and ** the attachment to the nitrogen atom of the adjacent amino group and

$R_1$ is pyridinyl, pyrazolyl, thiazolyl, thienyl, phenyl, tetrahydropyranyl or cyclohexyl,

in which pyridinyl may be substituted by 1 to 2 substituents selected independently from the group of ($C_1$-$C_2$)-alkyl, fluorine, chlorine, trifluoromethyl, trifluoromethoxy,

in which pyrazolyl may be substituted by 1 to 2 substituents selected independently from the group of ($C_1$-$C_2$)-alkyl, fluorine, chlorine, trifluoromethyl,

in which thiazolyl may be substituted by chlorine,

in which thienyl may be substituted by fluorine,

in which phenyl may be substituted by 1 to 2 substituents selected independently from the group of ($C_1$-$C_2$)-alkyl, ($C_3$-$C_4$)-cycloalkyl, methoxy, cyano, hydroxy, fluorine, chlorine, trifluoromethyl,

in which cyclohexyl and tetrahydropyranyl may be fused to pyridyl,

$R_2$ is hydrogen, methyl,

in which methyl may be substituted by cyano or methoxy,

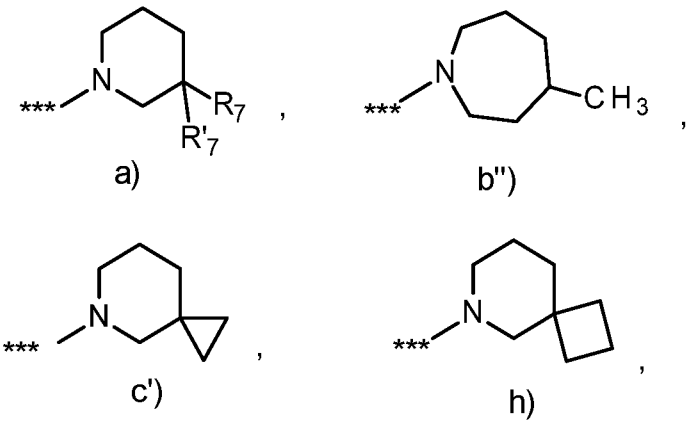
$R_3$ is hydrogen, ($C_1$-$C_2$)-alkyl;

$R_4$ is hydrogen, methyl, ethyl, cyclopropyl, trifluoromethyl, bromine, chlorine, phenyl;

where phenyl may be substituted by chlorine,

$R_5$ is hydrogen, fluorine;

$R_6$ is a group of the formula a), b''), c') or h),




in which *** marks the attachment to the adjacent piperidine ring,

in which $R_7$ or $R'_7$ is independently hydrogen, ($C_1$-$C_4$)-alkyl, ($C_3$-$C_4$)-cycloalkyl, ($C_1$-$C_2$)-alkoxy, ($C_3$-$C_4$)-cycloalkoxy, monofluoromethyl, difluoromethyl, trifluoromethyl, difluoromethoxy, phenyl,

where ($C_1$-$C_4$)-alkyl may be substituted by methoxy, n-butoxy, cyclopropyl, cyclobutoxy and up to disubstituted by fluorine,

where methoxy may be substituted by cyclopropyl, cyclobutyl, trifluoromethyl,

where cyclopropyl may be substituted by monofluoromethyl, difluoromethyl, trifluoromethyl,

where cyclopropyl may be up to disubstituted by fluorine,

where n-butoxy may be up to disubstituted by fluorine,

where ($C_1$-$C_2$)-alkoxy may be substituted by cyclopropyl, cyclobutyl, cyclobutoxy, trifluoromethyl and

where cyclopropyl and cyclobutyl may be up to disubstituted by fluorine,

where ($C_3$-$C_4$)-cycloalkoxy may be up to disubstituted by fluorine,

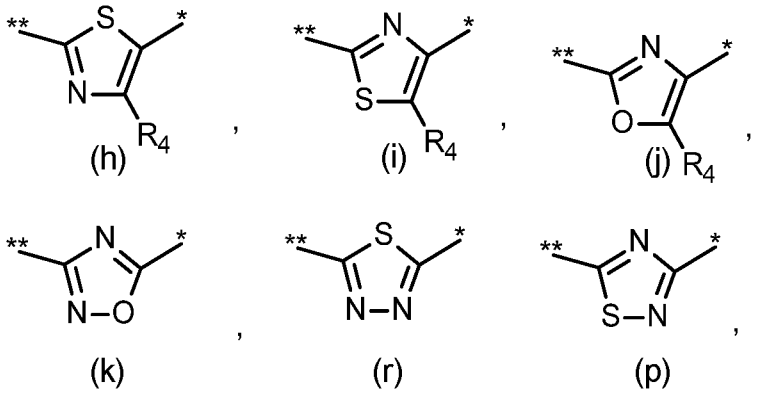
n represents 0 or 1 and

m represents 1 or 2,

and the salts, solvates and solvates of the salts thereof.

Preference is given in the context of the present invention to compounds of the formula (I) in which

X, Y and Z are chosen such that the aromatic 5-membered ring has the structural formula h), i), j), k), r) or p),




in which * marks the attachment to the carbonyl group and ** the attachment to the nitrogen atom of the adjacent amino group and

$R_1$ is pyridinyl, 2-ethylpyridinyl, 4,6-dimethylpyridinyl, 3,5-difluoropyridinyl, 3-fluoropyridinyl, 4-trifluoromethylpyridinyl, 6-trifluoromethylpyridinyl, 5-chloro-3-fluoropyridinyl, 3-chloro-5-fluoropyridinyl, 3-methylpyridinyl, 4-methylpyridinyl, 6-

methylpyridinyl, 3-chloropyridinyl, 5-chloropyridinyl, 6-trifluoromethoxypyridinyl, phenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 3-methoxyphenyl, 4-trifluoromethylphenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 3-hydroxyphenyl, 2,5-difluorophenyl, 5-chloro-2-hydroxyphenyl, 5-fluoro-2-methoxyphenyl, 5-chloro-2-fluorophenyl, 2-chloro-5-fluorophenyl, 2-chloro-4-fluorophenyl, 3-cyano-4-fluorophenyl, 2-cyclopropylphenyl, 4-chloro-1-methyl-1H-pyrazolyl, 5-chloro-1,3-thiazolyl, 5-fluoro-2-thienyl;

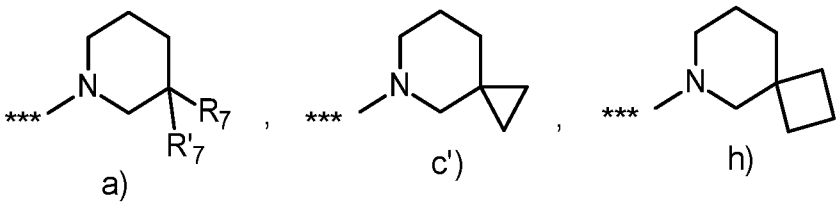
$R_2$ is hydrogen or methyl;

$R_3$ is hydrogen, methyl;

$R_4$ is hydrogen, ethyl or trifluoromethyl;

$R_5$ is hydrogen, methyl or fluorine;

$R_6$ is a group of the formula a), c') or h)




in which *** marks the attachment to the adjacent piperidine ring,

in which $R_7$ and $R'_7$ are independently hydrogen, methyl, ethyl, n-propyl, isopropyl, tert-butyl, 2-fluoroethyl, cyclopropyl, cyclobutyl, cyclopropylmethyl, methoxy, ethoxy, methoxymethyl, monofluoromethyl, difluoromethyl, trifluoromethyl, difluoromethoxy, 3,3-difluorocyclobutylmethoxy, cyclobutylmethoxy, cyclopropylmethoxy, cyclopropylmethoxymethyl, cyclobutyloxymethyl, 3-fluorobutyloxymethyl, 3,3-difluorocyclobutylmethoxymethyl, 2,2,2-trifluoroethoxy, 2,2,2-trifluoroethoxymethyl, 2,2-difluorocyclopropylmethoxy, cyclobutyloxy, 3,3-difluorocyclobutyloxy, fluoromethylcyclopropylmethoxy, difluoromethylcyclopropylmethoxy, trifluoromethylcyclopropylmethoxy, fluorine;

n represents 1 and

m represents 1,

and the salts, solvates and solvates of the salts thereof.

Preference is given in the context of the present invention to compounds of the formula (I) in which

X, Y and Z are 1,3-thiazolyl, 1,3-oxazolyl, 1,2,4-oxadiazolyl;

$R_1$ is pyridinyl, 2-ethylpyridinyl, 4,6-dimethylpyridinyl, 3,5-difluoropyridinyl, 3-fluoropyridinyl, 4-trifluoromethylpyridinyl, 6-trifluoromethylpyridinyl, 5-chloro-3-fluoropyridinyl, 3-chloro-5-fluoropyridinyl, 3-methylpyridinyl, 4-methylpyridinyl, 6-methylpyridinyl, 3-chloropyridinyl, 5-chloropyridinyl, 6-trifluoromethoxypyridinyl, phenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 3-methoxyphenyl, 4-trifluoromethylphenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 3-hydroxyphenyl, 2,5-difluorophenyl, 5-chloro-2-hydroxyphenyl, 5-fluoro-2-methoxyphenyl, 5-chloro-2-fluorophenyl, 2-chloro-5-fluorophenyl, 2-chloro-4-fluorophenyl, 3-cyano-4-fluorophenyl, 2-cyclopropylphenyl, 4-chloro-1-methyl-1H-pyrazolyl, 5-chloro-1,3-thiazolyl, 5-fluoro-2-thienyl;

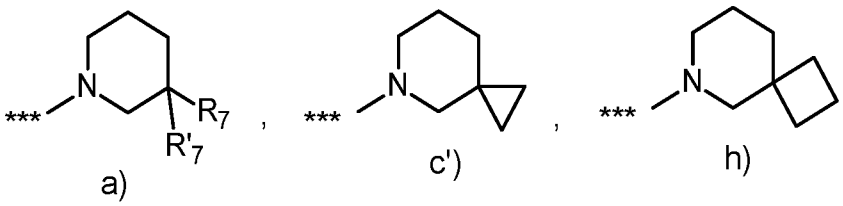
$R_2$ is hydrogen or methyl;

$R_3$ is hydrogen, methyl;

$R_4$ is hydrogen or methyl, ethyl, trifluoromethyl;

$R_5$ is hydrogen, methyl or fluorine;

$R_6$ is a group of the formula a), or c') or h)




in which *** marks the attachment to the adjacent piperidine ring,

in which $R_7$ and $R'_7$ are independently hydrogen, methyl, ethyl, n-propyl, isopropyl, tert-butyl, 2-fluoroethyl, cyclopropyl, cyclobutyl, cyclopropylmethyl, methoxy, ethoxy, methoxymethyl, monofluoromethyl, difluoromethyl, trifluoromethyl, difluoromethoxy, 3,3-difluorocyclobutylmethoxy, cyclobutylmethoxy, cyclopropylmethoxy, cyclopropylmethoxymethyl, cyclobutyloxymethyl, 3-fluorobutyloxymethyl, 3,3-

difluorocyclobutylmethoxymethyl, 2,2,2-trifluoroethoxy, 2,2,2-trifluoroethoxymethyl, 2,2-difluorocyclopropylmethoxy, cyclobutyloxy, 3,3-difluorocyclobutyloxy, fluoromethylcyclopropylmethoxy, difluoromethylcyclopropylmethoxy, trifluoromethylcyclopropylmethoxy, fluorine;

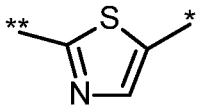
n represents 1 and

m represents 1,

and the salts, solvates and solvates of the salts thereof.

Preference is given in the context of the present invention to compounds of the formula (I) in which

X, Y and Z are chosen such that the aromatic 5-membered ring has the structural formula h'),




(h')

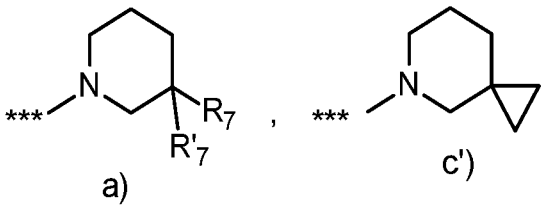
$R_1$ is pyridinyl, 2-ethylpyridinyl, 4,6-dimethylpyridinyl, 3,5-difluoropyridinyl, 3-fluoropyridinyl, 4-trifluoromethylpyridinyl, 6-trifluoromethylpyridinyl, 5-chloro-3-fluoropyridinyl, 3-chloro-5-fluoropyridinyl, 3-methylpyridinyl, 4-methylpyridinyl, 6-methylpyridinyl, 3-chloropyridinyl, 5-chloropyridinyl, 6-trifluoromethoxypyridinyl, phenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 3-methoxyphenyl, 4-trifluoromethylphenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 3-hydroxyphenyl, 2,5-difluorophenyl, 5-chloro-2-hydroxyphenyl, 5-fluoro-2-methoxyphenyl, 5-chloro-2-fluorophenyl, 2-chloro-5-fluorophenyl, 2-chloro-4-fluorophenyl, 3-cyano-4-fluorophenyl, 2-cyclopropylphenyl, 4-chloro-1-methyl-1H-pyrazolyl, 5-chloro-1,3-thiazolyl, 5-fluoro-2-thienyl;

$R_2$ is hydrogen or methyl;

$R_3$ is hydrogen or methyl;

$R_5$ is hydrogen, fluorine;

$R_6$ is a group of the formula a) or c')




in which *** marks the attachment to the adjacent piperidine ring,

in which $R_7$ and $R'_7$ are independently hydrogen, methyl, ethyl, n-propyl, isopropyl, tert-butyl, 2-fluoroethyl, cyclopropyl, cyclobutyl, cyclopropylmethyl, methoxy, ethoxy, methoxymethyl, monofluoromethyl, difluoromethyl, trifluoromethyl, difluoromethoxy, 3,3-difluorocyclobutylmethoxy, cyclobutylmethoxy, cyclopropylmethoxy, cyclopropylmethoxymethyl, cyclobutyloxymethyl, 3-fluorobutyloxymethyl, 3,3-difluorocyclobutylmethoxymethyl, 2,2,2-trifluoroethoxy, 2,2,2-trifluoroethoxymethyl, 2,2-difluorocyclopropylmethoxy, cyclobutyloxy, 3,3-difluorocyclobutyloxy, fluoromethylcyclopropylmethoxy, difluoromethylcyclopropylmethoxy, trifluoromethylcyclopropylmethoxy, fluorine;

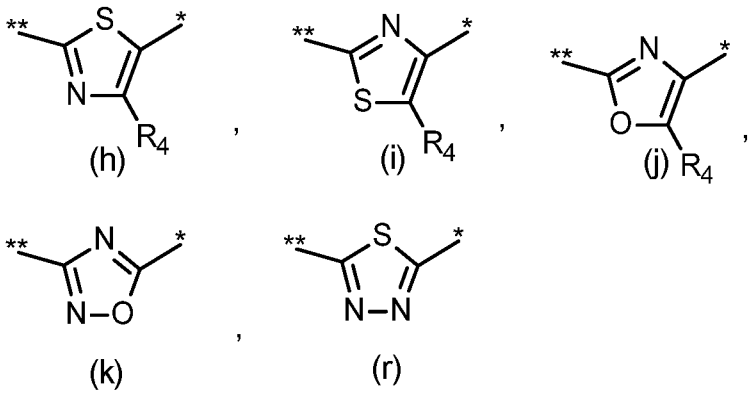
n represents 1 and

m represents 1,

and the salts, solvates and solvates of the salts thereof.

A particular embodiment of the present invention relates to compounds of the formula (I) in which

X, Y and Z are chosen such that the aromatic 5-membered ring has the structural formula h), i), j), k) or (r),




in which * marks the attachment to the carbonyl group and ** the attachment to the nitrogen atom of the adjacent amino group and

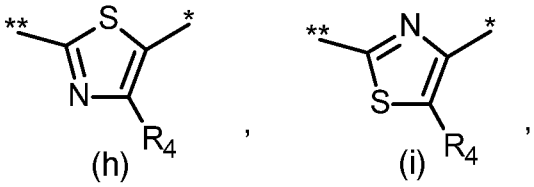
$R_4$ is hydrogen, methyl, ethyl, cyclopropyl, trifluoromethyl, bromine, chlorine, phenyl;

where phenyl may be substituted by chlorine,

and the salts, solvates and solvates of the salts thereof.

A particularly preferred embodiment of the present invention relates to compounds of the formula (I) in which

X, Y and Z are a group of the formula (h) or (i);




in which * marks the attachment to the carbonyl group and ** the attachment to the nitrogen atom of the adjacent amino group and

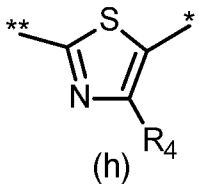
$R_4$ is hydrogen, methyl, ethyl, cyclopropyl, trifluoromethyl, bromine, chlorine, phenyl;

where phenyl may be substituted by chlorine,

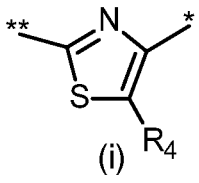
and the salts, solvates and solvates of the salts thereof.

A particularly preferred embodiment of the present invention relates to compounds of the formula (I) in which

X, Y and Z are chosen such that the aromatic 5-membered ring has the structural formula h) or i),



(h) ,



(i) ,

in which * marks the attachment to the carbonyl group and ** the attachment to the nitrogen atom of the adjacent amino group and

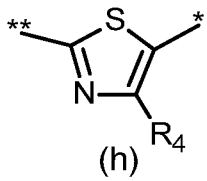
$R_4$ is hydrogen, methyl, ethyl, cyclopropyl, trifluoromethyl, bromine, chlorine, phenyl;

where phenyl may be substituted by chlorine,

and the salts, solvates and solvates of the salts thereof.

A very particularly preferred embodiment of the present invention relates to compounds of the formula (I) in which

X, Y and Z are a group of the formula (h);



(h) ,

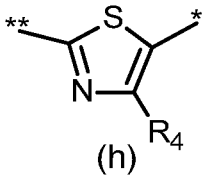
in which * marks the attachment to the carbonyl group and ** the attachment to the nitrogen atom of the adjacent amino group and

$R_4$ is hydrogen, methyl, ethyl, trifluoromethyl,

and the salts, solvates and solvates of the salts thereof.

A very particularly preferred embodiment of the present invention relates to compounds of the formula (I) in which

X, Y and Z are chosen such that the aromatic 5-membered ring has the structural formula h),



(h) ,

in which * marks the attachment to the carbonyl group and ** the attachment to the nitrogen atom of the adjacent amino group and

$R_4$ is hydrogen,

and the salts, solvates and solvates of the salts thereof.

A particular embodiment of the present invention relates to compounds of the formula (I) in which

$R_1$ is pyridinyl, pyrazolyl, thiazolyl, thienyl, phenyl;

in which pyridinyl may be substituted by 1 to 2 substituents selected independently from the group of ($C_1$-$C_2$)-alkyl, fluorine, chlorine, trifluoromethyl, trifluoromethoxy,

in which pyrazolyl may be substituted by 1 to 2 substituents selected independently from the group of methyl, chlorine,

in which thiazolyl may be substituted by chlorine,

in which thienyl may be substituted by fluorine,

in which phenyl may be substituted by 1 to 2 substituents selected independently from the group of ($C_1$-$C_2$)-alkyl, ($C_3$-$C_4$)-cycloalkyl, methoxy, cyano, hydroxy, fluorine, chlorine, trifluoromethyl;

and the salts, solvates and solvates of the salts thereof.

A particularly preferred embodiment of the present invention relates to compounds of the formula (I) in which

$R_1$ is pyridinyl, phenyl,

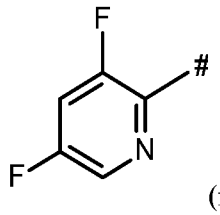
in which pyridinyl may be substituted by 1 to 2 substituents selected independently from the group of methyl, ethyl, fluorine, chlorine, trifluoromethyl, trifluoromethoxy,

in which phenyl may be substituted by 1 to 2 substituents selected independently from the group of methyl, cyclopropyl, methoxy, cyano, hydroxy, fluorine, chlorine, trifluoromethyl;

and the salts, solvates and solvates of the salts thereof.

A very particularly preferred embodiment of the present invention relates to compounds of the formula (I) in which

$R_1$ is a group of the formula (f);



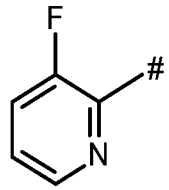
(f)

in which # marks the attachment to the adjacent -[$CHR_2$]$_n$$NR_3$- group,

and the salts, solvates and solvates of the salts thereof.

A very particularly preferred embodiment of the present invention relates to compounds of the formula (I) in which

$R_1$ is a group of the formula (f);



(f)

in which # marks the attachment to the adjacent -[$CHR_2$]$_n$$NR_3$- group,

and the salts, solvates and solvates of the salts thereof.

A particular embodiment of the present invention relates to compounds of the formula (I) in which

$R_2$ is hydrogen, ($C_1$-$C_4$)-alkyl;

in which ($C_1$-$C_4$)-alkyl may be up to trisubstituted by halogen,

or together with the carbon atom to which $R_2$ is bonded forms a ($C_3$-$C_4$)-cycloalkyl ring,

and the salts, solvates and solvates of the salts thereof.

A particularly preferred embodiment of the present invention relates to compounds of the formula (I) in which

$R_2$ is hydrogen, methyl, or together with the carbon atom to which $R_2$ is bonded forms a cyclopropyl ring;

and the salts, solvates and solvates of the salts thereof.

A very particularly preferred embodiment of the present invention relates to compounds of the formula (I) in which

$R_2$ is hydrogen;

and the salts, solvates and solvates of the salts thereof.

A very particularly preferred embodiment of the present invention relates to compounds of the formula (I) in which

$R_2$ is methyl;

and the salts, solvates and solvates of the salts thereof.

A particular embodiment of the present invention relates to compounds of the formula (I) in which

$R_3$ is hydrogen, $(C_1$-$C_4)$-alkyl,

in which $(C_1$-$C_4)$-alkyl may be up to trisubstituted by halogen,

and the salts, solvates and solvates of the salts thereof.

A particularly preferred embodiment of the present invention relates to compounds of the formula (I) in which

$R_3$ is hydrogen, methyl;

and the salts, solvates and solvates of the salts thereof.

A very particularly preferred embodiment of the present invention relates to compounds of the formula (I) in which

$R_3$ is hydrogen;

and the salts, solvates and solvates of the salts thereof.

A particular embodiment of the present invention relates to compounds of the formula (I) in which

$R_4$ is hydrogen, methyl, ethyl, cyclopropyl, trifluoromethyl, bromine, chlorine, phenyl;

where phenyl may be substituted by chlorine,

and the salts, solvates and solvates of the salts thereof.

A particularly preferred embodiment of the present invention relates to compounds of the formula (I) in which

$R_4$ is hydrogen, methyl, ethyl, trifluoromethyl,

and the salts, solvates and solvates of the salts thereof.

A very particularly preferred embodiment of the present invention relates to compounds of the formula (I) in which

$R_4$ is hydrogen,

and the salts, solvates and solvates of the salts thereof.

A particular embodiment of the present invention relates to compounds of the formula (I) in which

$R_5$ is hydrogen, ($C_1$-$C_4$)-alkyl, ($C_1$-$C_4$)-alkoxy, halogen,

and the salts, solvates and solvates of the salts thereof.

A particularly preferred embodiment of the present invention relates to compounds of the formula (I) in which

$R_5$ is hydrogen, fluorine,

and the salts, solvates and solvates of the salts thereof.

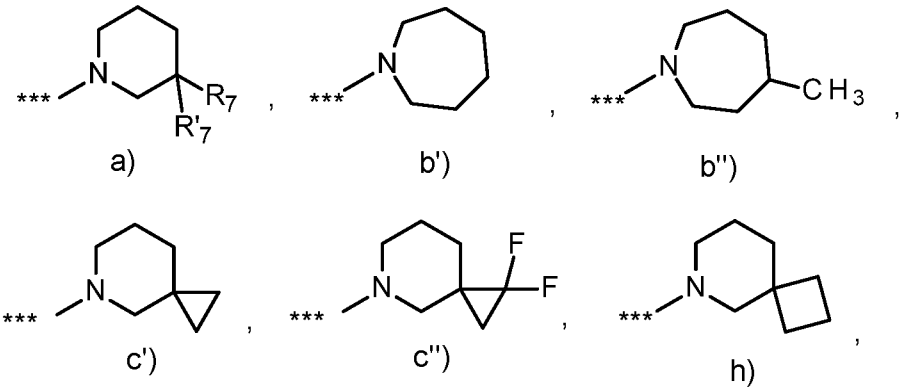
A very particularly preferred embodiment of the present invention relates to compounds of the formula (I) in which

$R_5$ is hydrogen,

and the salts, solvates and solvates of the salts thereof.

A particular embodiment of the present invention relates to compounds of the formula (I) in which

$R_6$ is a group of the formula a), b'), b'') or c'), c'') or h),




in which *** marks the attachment to the adjacent piperidine ring and

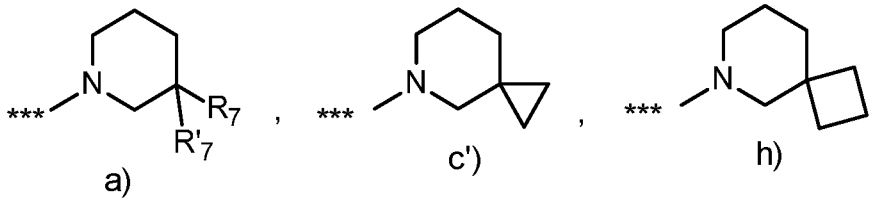
$R_7$ is hydrogen or methyl,

$R'_7$ is hydrogen, methyl, ethyl, n-propyl, isopropyl, tert-butyl, 2-fluoroethyl, cyclopropyl, cyclobutyl, cyclopropylmethyl, methoxy, ethoxy, methoxymethyl, monofluoromethyl, difluoromethyl, trifluoromethyl, difluoromethoxy, 3,3-difluorocyclobutylmethoxy, cyclobutylmethoxy, cyclopropylmethoxy, cyclopropylmethoxymethyl, cyclobutyloxymethyl, 3-fluorobutyloxymethyl, 3,3-difluorocyclobutylmethoxymethyl, 2,2,2-trifluoroethoxy, 2,2,2-trifluoroethoxymethyl, 2,2-difluorocyclopropylmethoxy, cyclobutyloxy, 3,3-difluorocyclobutyloxy, fluoromethylcyclopropylmethoxy, difluoromethylcyclopropylmethoxy, trifluoromethylcyclopropylmethoxy, fluorine,

and the salts, solvates and solvates of the salts thereof.

A particularly preferred embodiment of the present invention relates to compounds of the formula (I) in which

$R_6$ is a group of the formula a), c') or h),




in which *** marks the attachment to the adjacent piperidine ring and

$R_7$ is hydrogen,

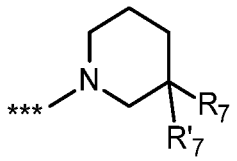
$R'_7$ is hydrogen, methyl, ethyl, n-propyl, isopropyl, tert-butyl, 2-fluoroethyl, cyclopropyl, cyclobutyl, cyclopropylmethyl, methoxy, ethoxy, methoxymethyl, monofluoromethyl,

difluoromethyl, trifluoromethyl, difluoromethoxy, 3,3-difluorocyclobutylmethoxy, cyclobutylmethoxy, cyclopropylmethoxy, cyclopropylmethoxymethyl, cyclobutyloxymethyl, 3-fluorobutyloxymethyl, 3,3-difluorocyclobutylmethoxymethyl, 2,2,2-trifluoroethoxy, 2,2,2-trifluoroethoxymethyl, 2,2-difluorocyclopropylmethoxy, cyclobutyloxy, 3,3-difluorocyclobutyloxy, fluoromethylcyclopropylmethoxy, difluoromethylcyclopropylmethoxy, trifluoromethylcyclopropylmethoxy, fluorine,

and the salts, solvates and solvates of the salts thereof.

A very particularly preferred embodiment of the present invention relates to compounds of the formula (I) in which

$R_6$ is a group of the formula a),



a)

in which *** marks the attachment to the adjacent piperidine ring and

$R_7$ is hydrogen,

$R'_7$ is methyl, ethyl, isopropyl, propyl, ethoxy, methoxymethyl, monofluoromethyl, difluoromethyl, trifluoromethyl, 3,3-difluorocyclobutylmethoxy, 2,2,2-trifluoroethoxymethyl, cyclopropylmethyl, 1-fluoromethylcyclopropylmethoxymethyl, 1-difluoromethylcyclopropylmethoxymethyl, 1-trifluoromethylcyclopropylmethoxymethyl, cyclobutylmethoxy, cyclopropylmethoxy, cyclobutyloxymethyl, cyclopropylmethoxymethyl, 3,3-difluorocyclobutylmethoxymethyl, 3-fluorobutyloxymethyl, 2,2-difluorocyclopropylmethoxy, cyclobutyloxy, 3,3-difluorocyclobutyloxy, 2-fluoroethyl, cyclopropyl, cyclobutyl, 2-methoxyethyl, tert-butyl,

and the salts, solvates and solvates of the salts thereof.

A particular embodiment of the present invention relates to compounds of the formula (I) in which

n represents 0 or 1,

and the salts, solvates and solvates of the salts thereof.

A particularly preferred embodiment of the present invention relates to compounds of the formula (I) in which

n represents 1,

and the salts, solvates and solvates of the salts thereof.

A particular embodiment of the present invention relates to compounds of the formula (I) in which

m represents 1 or 2,

and the salts, solvates and solvates of the salts thereof.

A particularly preferred embodiment of the present invention relates to compounds of the formula (I) in which

m represents 1,

and the salts, solvates and solvates of the salts thereof.

A particular embodiment of the present invention relates to compounds of the formula (I) in which

p represents 0, 1 or 2,

and the salts, solvates and solvates of the salts thereof.

A particularly preferred embodiment of the present invention relates to compounds of the formula (I) in which

p represents 1.

A particular embodiment of the present invention relates to compounds of the formula (I) in which

q represents 0 or 2,

and the salts, solvates and solvates of the salts thereof.

A particularly preferred embodiment of the present invention relates to compounds of the formula (I) in which

q represents 2,

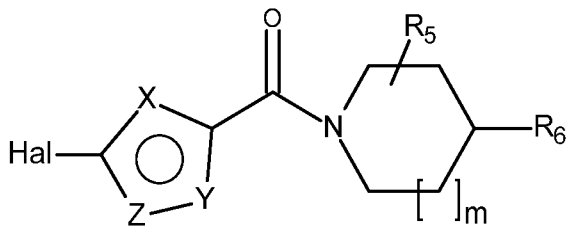
and the salts, solvates and solvates of the salts thereof.

The individual radical definitions specified in the respective combinations or preferred combinations of radicals are, independently of the respective combinations of the radicals specified, also replaced as desired by radical definitions of other combinations.

Very particular preference is given to combinations of two or more of the abovementioned preferred ranges.

The invention further provides a process for preparing the compounds of the formula (I), or the salts thereof, solvates thereof or the solvates of the salts thereof, wherein

[A] compounds of the formula (II)



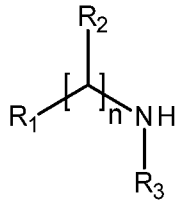

(II)

in which

X, Y, Z, $R_5$, $R_6$, and m have definitions given above,

Hal is a leaving group, preferably chlorine, bromine, iodine, or methylsulfonyl,

are reacted in the presence of a base with compounds of the formula (III)

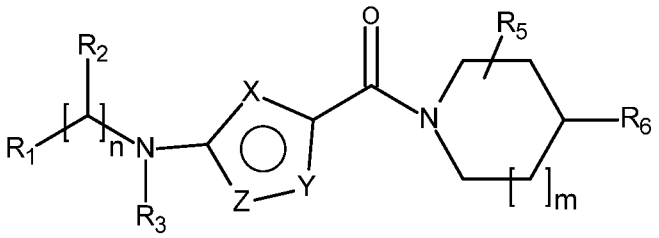



(III)

in which

$R_1$, $R_2$ and $R_3$ and n have the definitions given above,

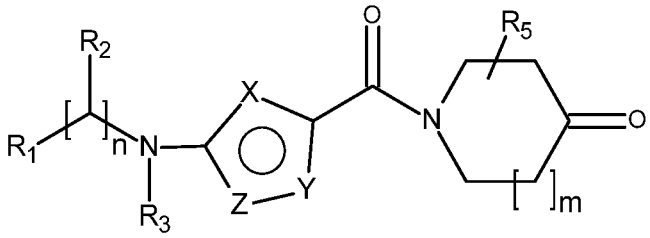
to give compounds of the formula (I-A)



(I-A)

or

[B] compounds of the formula (IV)

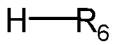


(IV)

in which

X, Y, Z, $R_1$, $R_2$, $R_3$, $R_4$ and $R_5$ and n and m have the definitions given above,

are reacted with compounds of the formula (V)

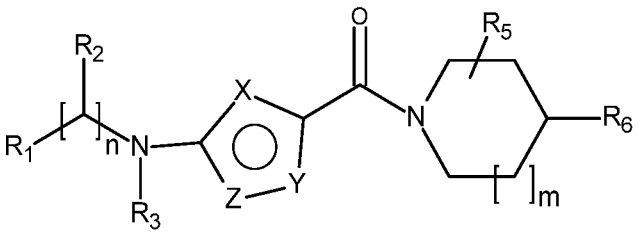


(V)

in which

$R_6$ has the definition given above,

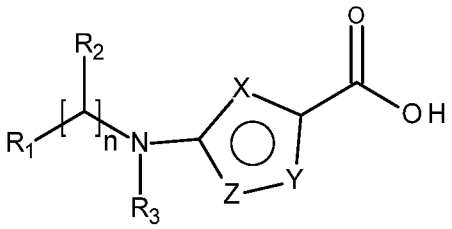
in the presence of a reducing agent and optionally an acid, preferably alkali metal borohydrides and acetic acid, to give compounds of the formula (I-B)



(I-B)

or

[C] compounds of the formula (VI)

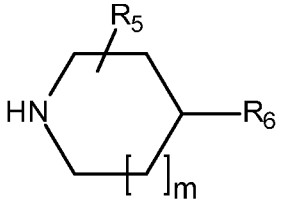


(VI)

in which

X, Y, Z, $R_1$, $R_2$ and $R_3$ and n have the definitions given above,

are reacted with compounds of the formula (VII)

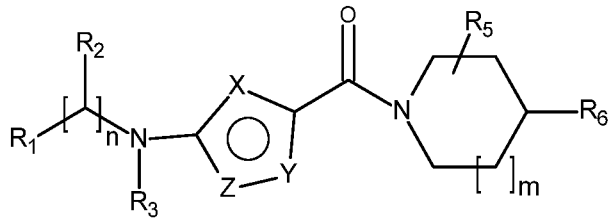


(VII)

in which

$R_5$ and $R_6$ and m have the definitions given above,

in the presence of a condensing or activating agent, preferably a phosphorus compound, to give compounds of the formula (I-C)



(I-C),

and the compounds of the formulae (I-A), (I-B), (I-C) thus obtained are optionally separated into their enantiomers and/or diastereomers and/or optionally converted with the appropriate (*i*) solvents and/or (*ii*) acids to the solvates, salts and/or solvates of the salts thereof.

The reaction of compound (II) with compound (III) in process step [A] to give compound (I-A) is a replacement of the Hal group in compound (II) by the nitrogen atom of the amine in compound (III), where the reaction, depending on the reactivities in the individual case, can be effected, for example, by heating in a solvent or dispersant.

Suitable bases for process step [A] are in particular alkali metal carbonates such as sodium carbonate, potassium carbonate or caesium carbonate, a tertiary amine base such as triethylamine, *N,N*-diisopropylethylamine, *N*-methylmorpholine (NMM), *N*-methylpiperidine (NMP), pyridine, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), 1,10-o-phenanthroline or 4-*N,N*-dimethylaminopyridin (DMAP). The base used is preferably sodium carbonate, potassium carbonate or caesium carbonate. The addition of an alkylation catalyst, for example lithium bromide, sodium iodide, potassium iodide, tetra-*n*-butylammonium bromide, copper(I) iodide or benzyltriethylammonium chloride, may be advantageous.

The base is preferably employed in an equimolar amount or in excess, usually in 1 to 5 times, preferably in 5 times, the molar amount.

Furthermore, the reaction can also proceed with palladium catalysis using $Pd_2(dba)_3$, caesium carbonate as auxiliary base and the following ligands: 1,1'- [1,1'-binaphthalene] -2,2'-diylbis [1,1-diphenylphosphine] or 1,1'-(9,9-dimethyl-9H-xanthene-4,5-diyl)bis[1,1-diphenylphosphine] (for literature see WO 2008052934 or WO 2015017305).

Suitable inert solvents for process step [A] are, for example, ethers such as diethyl ether, diisopropyl ether, methyl *tert*-butyl ether, tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane or bis(2-methoxyethyl) ether, hydrocarbons such as benzene, toluene, xylene, pentane, hexane, heptane,

cyclohexane or mineral oil fractions, or dipolar aprotic solvents such as acetone, methyl ethyl ketone, acetonitrile, *N,N*-dimethylformamide (DMF), *N,N*-dimethylacetamide (DMA), dimethyl sulfoxide (DMSO), *N,N'*-dimethylpropyleneurea (DMPU) or *N*-methylpyrrolidinone (NMP). It is also possible to use mixtures of such solvents. Preference is given to using acetonitrile or dimethylformamide.

The reaction (II) + (III) → (I-A) is generally carried out in a temperature range of from 0°C to +150°C, preferably at from +20°C to +140°C.

The reaction of the compound (IV) with (V) to give compound (I-B) in Process step [B] is a reductive amination. Suitable reducing agents for reductive aminations alkali metal borohydrides customary for such purposes such as sodium borohydride, sodium cyanoborohydride or sodium triacetoxyborohydride; preference is given to using sodium triacetoxyborohydride. The addition of an acid, such as acetic acid in particular, and/or of a dehydrating agent, for example molecular sieve or trimethyl orthoformate or triethyl orthoformate, may be advantageous in these reactions.

Suitable solvents for these reactions are especially alcohols such as methanol, ethanol, *n*-propanol or isopropanol, ethers such as diisopropyl ether, methyl *tert*-butyl ether, tetrahydrofuran, 1,4-dioxane or 1,2-dimethoxyethane, dichloromethane, polar aprotic solvents such as acetonitrile or *N,N*-dimethylformamide (DMF) or mixtures of such solvents; preference is given to using tetrahydrofuran. The reactions are generally effected within a temperature range of 0°C to +50°C.

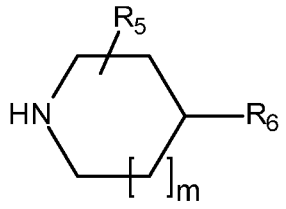
The protecting group PG used in compound (XI) or (XI') may be a standard amino protecting group, for example *tert*-butoxycarbonyl (Boc), benzyloxycarbonyl (Z) or (9*H*-fluoren-9-ylmethoxy)carbonyl (Fmoc); preference is given to using *tert*-butoxycarbonyl (Boc). The removal of the protecting group in process step takes place by known methods. Thus, the *tert*-butoxycarbonyl group is typically cleaved by treatment with a strong acid such as hydrogen chloride, hydrogen bromide or trifluoroacetic acid, in an inert solvent such as diethyl ether, 1,4-dioxane, dichloromethane or acetic acid. In the case of benzyloxycarbonyl as protecting group, this is preferably removed by hydrogenolysis in the presence of a suitable palladium catalyst such as palladium on activated carbon. The (9*H*-fluoren-9-ylmethoxy)carbonyl group is generally detached with the aid of a secondary amine base such as diethylamine or piperidine [see, for example, T.W. Greene and P.G.M. Wuts, *Protective Groups in Organic Synthesis*, Wiley, New York, 1999; P.J. Kocienski, *Protecting Groups*, 3rd edition, Thieme, 2005].

The process step [B] (VI) + (VII) → (I-C) [amide formation] is carried out by known methods with the aid of a condensing or activating agent. Suitable such agents are, for example, carbodiimides such as N,N'-diethyl-, N,N'-dipropyl-, N,N'-diisopropyl-, N,N'-dicyclohexylcarbodiimide (DCC) or N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (EDC), phosgene derivatives such as N,N'-carbonyldiimidazole (CDI) or isobutyl chloroformate, 1,2-oxazolium compounds such as 2-

ethyl-5-phenyl-1,2-oxazolium 3-sulfate or 2-tert-butyl-5-methylisoxazolium perchlorate, acylamino compounds such as 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline, α-chloroenamines such as 1-chloro-N,N,2-trimethylprop-1-ene-1-amine, 1,3,5-triazine derivatives such as 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride, phosphorus compounds such as n-propanephosphonic anhydride (PPA, T3P®), diethyl cyanophosphonate, diphenylphosphoryl azide (DPPA), bis(2-oxo-3-oxazolidinyl)phosphoryl chloride, benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate or benzotriazol-1-yloxytris(pyrrolidino)phosphonium hexafluorophosphate (PyBOP), or uronium compounds such as O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate (TBTU), O-(1H-1-chlorobenzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TCTU), O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HBTU), O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU) or 2-(2-oxo-1-(2H)-pyridyl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TPTU), optionally in combination with further auxiliaries such as 1-hydroxybenzotriazole (HOBt) or N-hydroxysuccinimide (HOSu), and suitable bases are alkali metal carbonates, for example sodium carbonate or potassium carbonate, or tertiary amine bases such as triethylamine, N-methylmorpholine (NMM), N-methylpiperidine (NMP), DIPEA, pyridine or 4-N,N-dimethylaminopyridine (DMAP). The condensing agent or activating agent used with preference is *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HATU) in combination with *N,N*-diisopropylethylamine as base.

Suitable inert solvents for these amide-forming reactions are, for example, ethers such as diethyl ether, diisopropyl ether, methyl *tert*-butyl ether, tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane or bis(2-methoxyethyl) ether, hydrocarbons such as benzene, toluene, xylene, pentane, hexane or cyclohexane, halohydrocarbons such as dichloromethane, trichloromethane, carbon tetrachloride, 1,2-dichloroethane, trichloroethylene or chlorobenzene, or polar aprotic solvents such as acetone, methyl ethyl ketone, ethyl acetate, acetonitrile, butyronitrile, pyridine, dimethyl sulfoxide (DMSO), *N,N*-dimethylformamide (DMF), *N,N'*-dimethylpropyleneurea (DMPU) or *N*-methylpyrrolidinone (NMP); it is also possible to use mixtures of such solvents. Preference is given to using dichloromethane, 1,2-dichloroethane, tetrahydrofuran, *N,N*-dimethylformamide or mixtures of these solvents. The reactions are generally conducted within a temperature range of from -20°C to +60°C, preferably at from 0°C to +40°C.

For their part, the compounds of the formula (II) can be prepared by processes known from the literature [amide formation] by reacting the amine (VII)

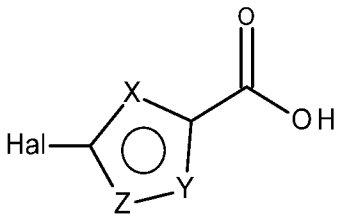


(VII)

in which

$R_5$ and $R_6$ and m have the definitions given above,

under the influence of a condensing or activating agent with a compound of the formula (X)

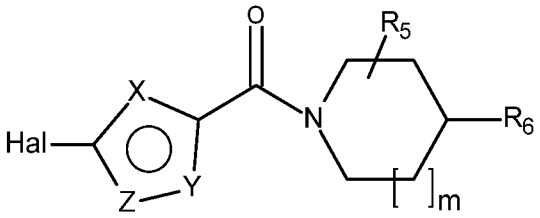


(X)

in which

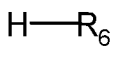
X, Y, Z, $R_4$ and Hal have the definitions given above,

to give a compound of the formula (II)



(II).

The compounds of the formula (VII) can be prepared by processes known from the literature [reductive amination] by reacting the amine (V)

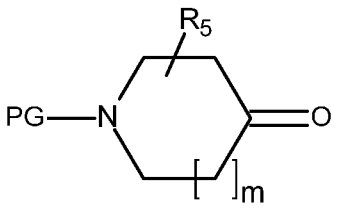


(V)

in which

$R_6$ has the definition given above,

with a protected piperidine derivative of the formula (XI)



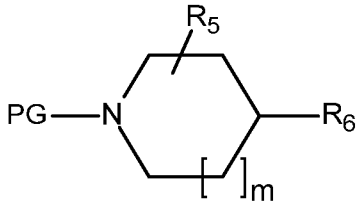

(XI)

in which

$R_5$ and m have the definitions given above and

PG is a suitable amino protecting group, preferably *tert*-butoxycarbonyl, benzyloxycarbonyl or (9*H*-fluoren-9-ylmethoxy)carbonyl,

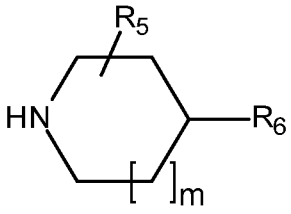
to give compounds of the formula (VII')




(VII')

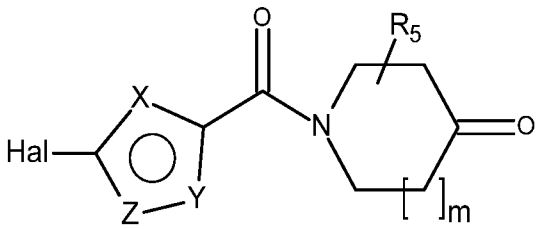
in which PG and $R_5$ and $R_6$ and m have the definitions given above,

followed by elimination of the protecting group PG to give the compound of the formula (VII)




(VII).

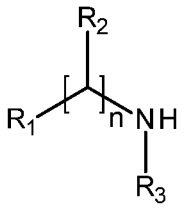
The compounds of the formula (IV) can be prepared by a process known from the literature [alkylation] by reacting compounds of the formula (II)



(II)

in which X, Y, Z, and $R_5$ and Hal and m have the definitions given above,

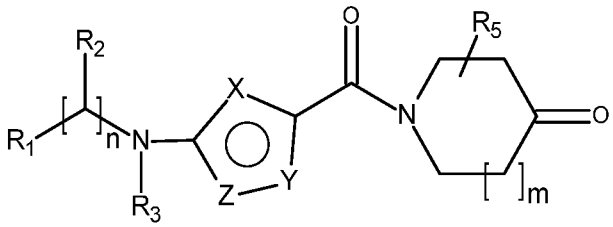
in the presence of a base with compounds of the formula (II)



(III)

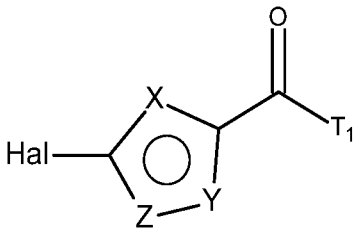
in which $R_1$, $R_2$, $R_3$ and n have the definitions given above,

to give compound (IV)



(IV).

The compounds of the formula (VI) can in turn be prepared by a process known from the literature [alkylation] by reacting compounds of the formula (XIII)

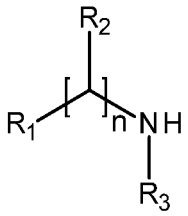


(XIII)

in which X, Y, Z, $R_4$ and Hal have the definitions given above and

$T_1$ is -O-($C_1$-$C_4$)-alkyl,

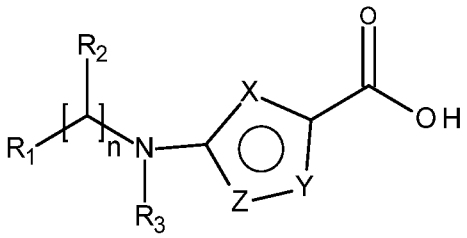
in the presence of a base with compounds of the formula (III)



(III)

in which $R_1$, $R_2$, $R_3$ and n have the definitions given above,

and hydrolysing under conditions known from the literature to give compounds of the formula (VI)



(VI).

The hydrolysis of the ester group $T_1$ is carried out by customary methods, by treating the esters in inert solvents with acids or bases, where in the latter variant the salts initially formed are converted into the free carboxylic acids by treatment with acid. In the case of the *tert*-butyl esters, the ester hydrolysis is preferably effected with acids.

Suitable inert solvents for these reactions are water or the organic solvents customary for ester cleavage. These preferably include alcohols such as methanol, ethanol, *n*-propanol, isopropanol, *n*-butanol or *tert*-butanol, ethers such as diethyl ether, tetrahydrofuran, 1,4-dioxane or 1,2-dimethoxyethane, or other solvents such as dichloromethane, acetone, methyl ethyl ketone, *N,N*-dimethylformamide or dimethyl sulfoxide. It is equally possible to use mixtures of these solvents. In the case of a basic ester hydrolysis, preference is given to using mixtures of water with dioxane, tetrahydrofuran, methanol, ethanol and/or dimethylformamide. In the case of the reaction with trifluoroacetic acid, preference is given to using dichloromethane, and in the case of the reaction with hydrogen chloride preference is given to using tetrahydrofuran, diethyl ether, dioxane or water.

Suitable bases are the customary inorganic bases. These especially include alkali metal or alkaline earth metal hydroxides, for example lithium hydroxide, sodium hydroxide, potassium hydroxide or barium hydroxide, or alkali metal or alkaline earth metal carbonates, such as sodium carbonate,

potassium carbonate or calcium carbonate. Preference is given to lithium hydroxide, sodium hydroxide or potassium hydroxide.

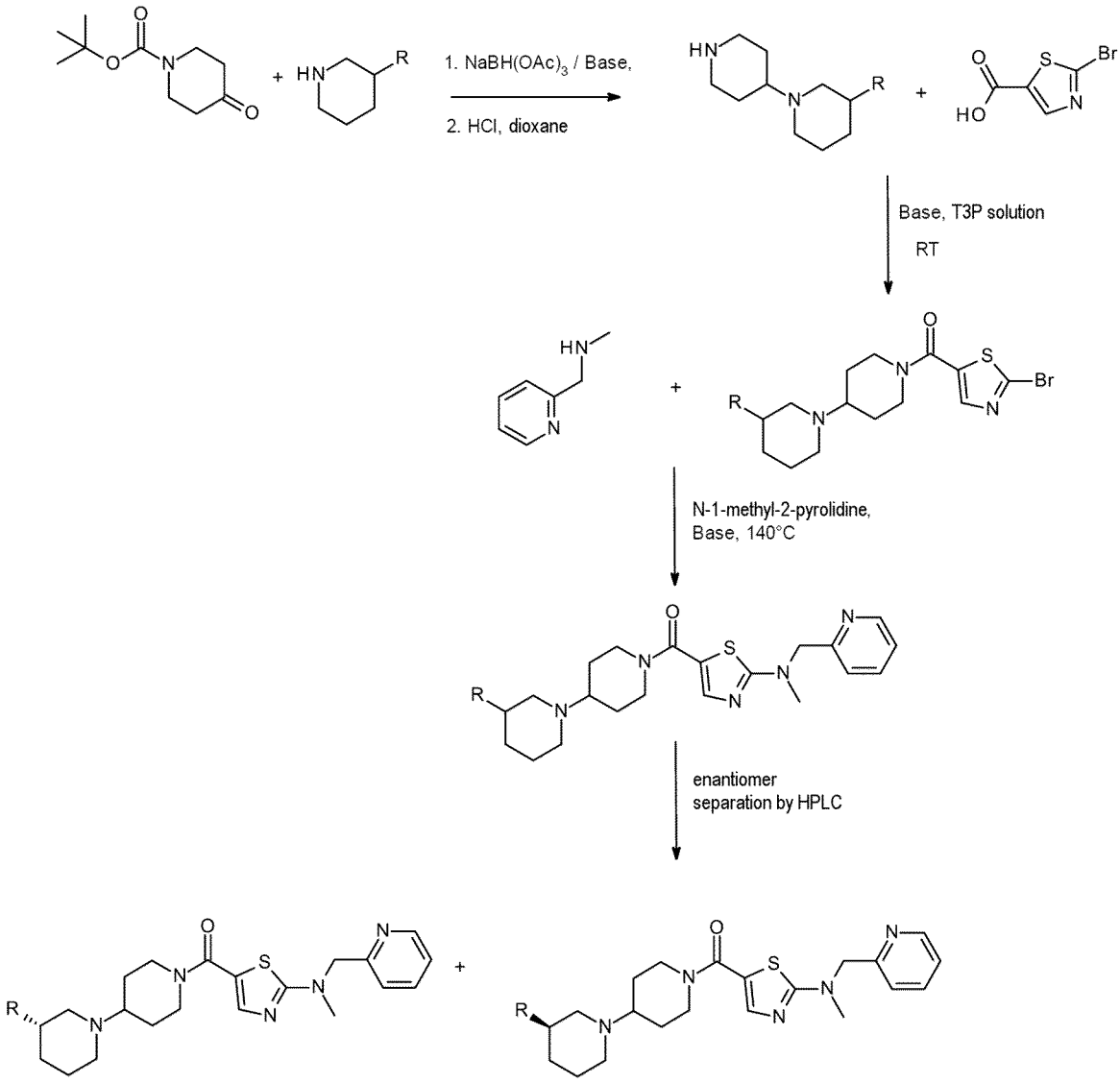
Suitable acids for the ester hydrolysis are generally sulfuric acid, hydrogen chloride/

hydrochloric acid, hydrogen bromide/hydrobromic acid, phosphoric acid, acetic acid, trifluoroacetic acid, toluenesulfonic acid, methanesulfonic acid or trifluoromethanesulfonic acid, or mixtures thereof, optionally with addition of water. Preference is given to hydrogen chloride or trifluoroacetic acid in the case of the *tert*-butyl esters and to hydrochloric acid in the case of the methyl esters.

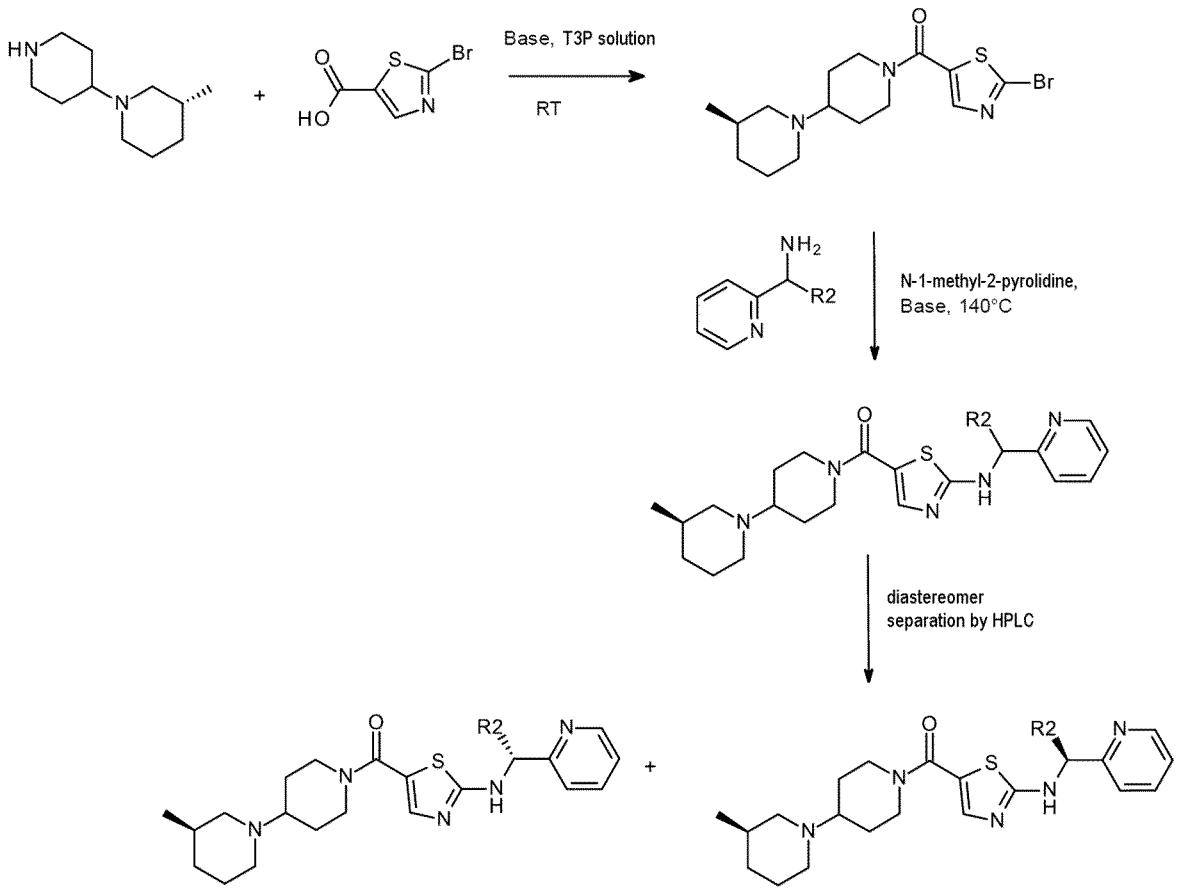
The ester hydrolysis is generally carried out within a temperature range from -20°C to +120°C, preferably at 0°C to +80°C.

The preparation of the compounds of the invention can be illustrated by way of example by the following reaction scheme:

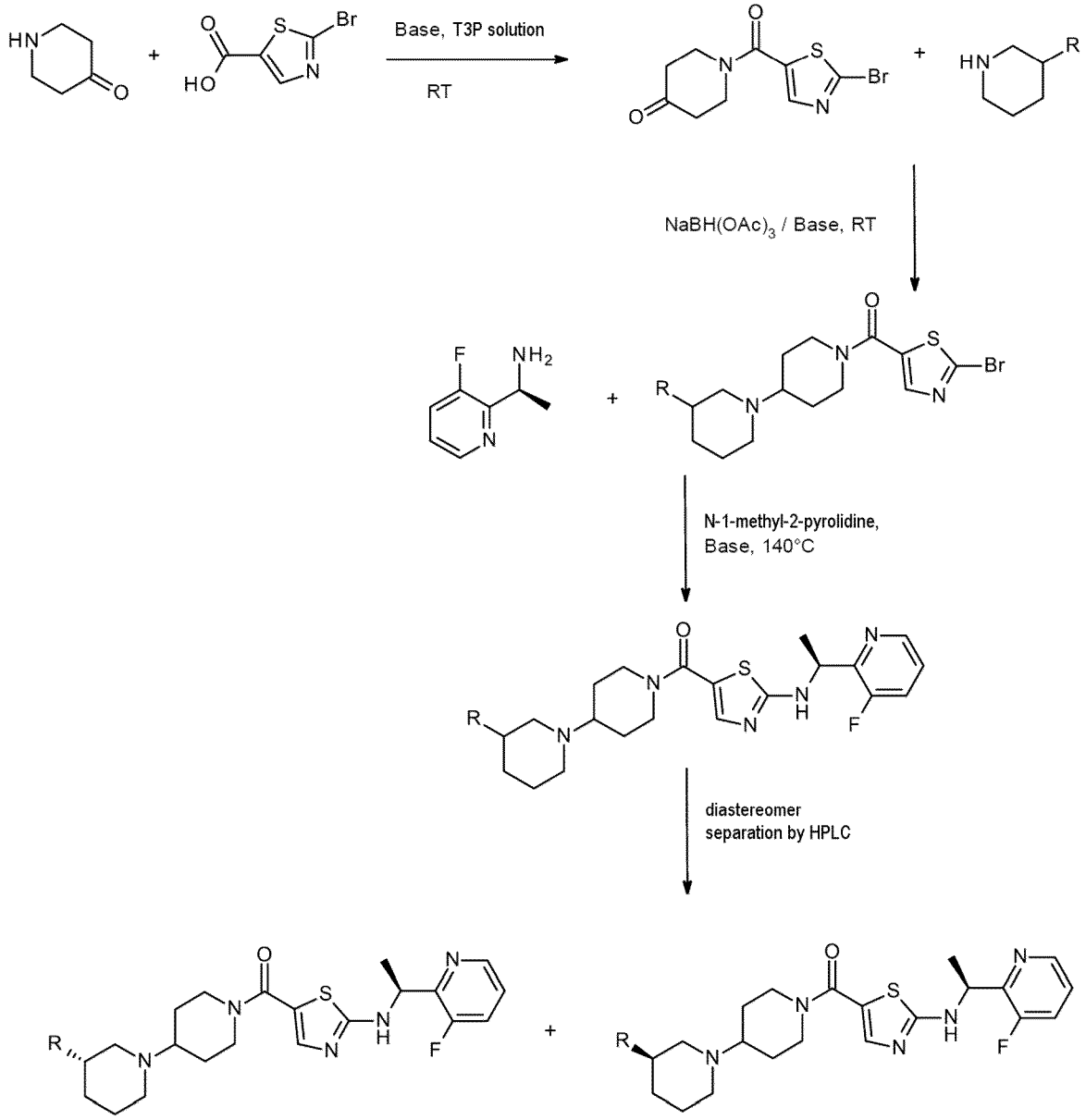
*Scheme 1*


1. NaBH(OAc)3 / Base,
2. HCl, dioxane
Base, T3P solution
RT
N-1-methyl-2-pyrolidine,
Base, 140°C
enantiomer
separation by HPLC

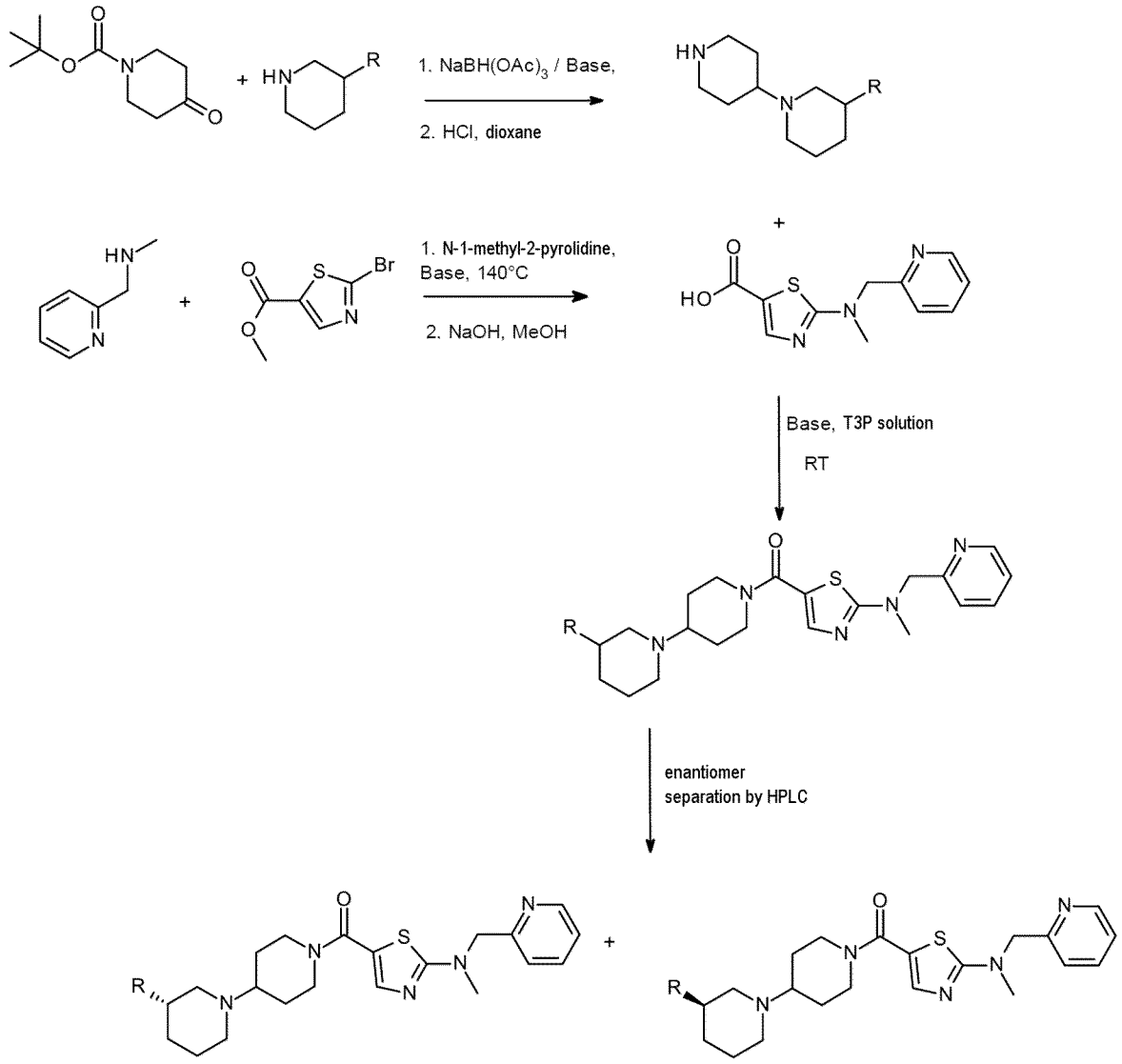
*Scheme 2*


Base, T3P solution
RT
N-1-methyl-2-pyrolidine,
Base, 140°C
diastereomer
separation by HPLC

*Scheme 3*


Base, T3P solution
RT
NaBH(OAc)3 / Base, RT
N-1-methyl-2-pyrolidine,
Base, 140°C
diastereomer
separation by HPLC

*Scheme 4*




The compounds of the invention have valuable pharmacological properties and can be used for prevention and treatment of diseases in humans and animals.

The compounds of the invention are potent and selective antagonists of the $\alpha_{2C}$-adrenergic receptor and are therefore suitable for treatment and/or prevention of disorders and pathological processes, in particular those caused by activation or by an activated $\alpha_{2C}$-adrenergic receptor, and of diseases secondary to $\alpha_{2C}$-adrenergic receptor-related damage.

The compounds of the invention are employed in a method for treatment and/or prevention of breathing difficulties, dysphagia, peripheral and cardiac vascular disorders and disorders of the peripheral and central nervous system.

The compounds of the invention are likewise employed in a method for treatment and/or prevention of breathing difficulties including sleep-induced breathing difficulties such as central and obstructive

sleep apnoea, snoring (primary and obstructive snoring), dysphagia, peripheral and cardiac vascular disorders including diabetic microangiopathies and disorders of the peripheral and central nervous system including neurodegenerative and neuroinflammatory disorders.

In the context of the present invention, these include in particular disorders such as breathing difficulties and sleep-induced breathing difficulties such as, *inter alia*, obstructive sleep apnoea (in adults and children), primary snoring, obstructive snoring (upper airway resistance syndrome, heavy snoring, hypopnoea syndrome), central sleep apnoea, Cheyne-Stokes respiration, primary sleep apnoea of infancy, apparent life-threatening event, central sleep apnoea as a result of the use of medicaments or the use of other substances, obesity hypoventilation syndrome, disrupted central respiratory drive, sudden infant death, primary alveolar hypoventilation syndrome, postoperative hypoxia and apnoea, muscular respiratory disorders, respiratory disorders following long-term ventilation, respiratory disorders during adaptation in high mountains, acute and chronic pulmonary diseases with hypoxia and hypercapnia, sleep-related non-obstructive alveolar hypoventilation and the congenital central alveolar hypoventilation syndrome, and dysphagia.

The compounds of the invention are preferably employed in a method for treatment and/or prevention of breathing difficulties including sleep-induced breathing difficulties including obstructive sleep apnoea (in adults and children), primary snoring, obstructive snoring (upper airway resistance syndrome, heavy snoring, hypopnoea syndrome), central sleep apnoea, Cheyne-Stokes respiration, primary sleep apnoea of infancy, apparent life-threatening event, central sleep apnoea as a result of the use of medicaments or the use of other substances, obesity hypoventilation syndrome, disrupted central respiratory drive, sudden infant death, primary alveolar hypoventilation syndrome, postoperative hypoxia and apnoea, muscular respiratory disorders, respiratory disorders following long-term ventilation, respiratory disorders during adaptation in high mountains, acute and chronic pulmonary diseases with hypoxia and hypercapnia, sleep-related non-obstructive alveolar hypoventilation and the congenital central alveolar hypoventilation syndrome, and dysphagia.

In the context of the present invention, peripheral and cardiac vascular disorders include diabetic microangiopathies, diabetic ulcers at the extremities, in particular for promoting wound healing of diabetic foot ulcers, diabetic heart failure, diabetic coronary microvascular cardiac disorders, thromboembolic disorders and ischaemias, peripheral circulatory disorders, Raynaud's phenomenon, systemic scleroderma, CREST syndrome, microcirculation disorders and intermittent claudication.

Likewise with preference, the compounds of the invention are employed in a method for treatment and/or prevention of peripheral and cardiac vascular disorders including diabetic microangiopathies, diabetic ulcers at the extremities, in particular for promoting wound healing of diabetic foot ulcers, diabetic heart failure, diabetic coronary microvascular cardiac disorders, thromboembolic disorders

and ischaemias, peripheral circulatory disorders, Raynaud's phenomenon, systemic scleroderma, CREST syndrome, microcirculation disorders and intermittent claudication.

In addition, the compounds of the invention can be employed in a method for treatment and/or prevention of disorders of the peripheral and central nervous system such as dementia, depression, schizophrenia, attention deficit disorder with or without hyperactivity (ADHS), Tourette's syndrome, post-traumatic stress disorder, obsessive-compulsive disorder, blepharospasm or other focal dystonias, drug-induced psychosis, temporal lobe epilepsy with psychosis, panic disorder, disorders caused by changes in sexual hormones, multiple sclerosis, Alzheimer's disease, Parkinson's disease and Huntington's disease, Pick's disease, Wilson's disease, progressive supranuclear paresis, corticobasal degeneration, tauopathy, frontotemporal dementia and parkinsonism linked to chromosome 17, multisystem atrophy, spinocerebellar ataxias, spinobulbar muscular atrophy of the Kennedy type, Friedreich's ataxia, dentatorubral-pallidoluysian atrophy, amyotrophic lateral sclerosis, primary lateral sclerosis, spinal muscular atrophy, Creutzfeldt-Jakob disease and variants of Creutzfeldt-Jakob disease, infantile neuroaxonal dystrophy, neurodegeneration with brain iron accumulation, frontotemporal lobar degeneration with ubiquitin proteasome system and familial encephalopathy with neuroserpin inclusions.

The compounds of the invention are preferably employed in a method for treatment and/or prevention of disorders of the peripheral and central nervous system, including dementia, depression, schizophrenia, attention deficit disorder with or without hyperactivity (ADHS), Tourette's syndrome, post-traumatic stress disorder, obsessive-compulsive disorder, blepharospasm or other focal dystonias, drug-induced psychosis, temporal lobe epilepsy with psychosis, panic disorder, disorders caused by changes in sexual hormones, multiple sclerosis, Alzheimer's disease, Parkinson's disease, Huntington's disease.

The compounds of the invention are also employed in a method for treatment and/or prevention of disorders of the peripheral and central nervous system such as dementia, depression, schizophrenia, attention deficit disorder with or without hyperactivity (ADHS), Tourette's syndrome, post-traumatic stress disorder, obsessive-compulsive disorder, blepharospasm or other focal dystonias, drug-induced psychosis, temporal lobe epilepsy with psychosis, panic disorder, disorders caused by changes in sexual hormones, multiple sclerosis, Alzheimer's disease, Parkinson's disease and Huntington's disease, Pick's disease, Wilson's disease, progressive supranuclear paresis, corticobasal degeneration, tauopathy, frontotemporal dementia and parkinsonism linked to chromosome 17, multisystem atrophy, spinocerebellar ataxias, spinobulbar muscular atrophy of the Kennedy type, Friedreich's ataxia, dentatorubral-pallidoluysian atrophy, amyotrophic lateral sclerosis, primary lateral sclerosis, spinal muscular atrophy, Creutzfeldt-Jakob disease and variants of Creutzfeldt-Jakob disease, infantile neuroaxonal dystrophy, neurodegeneration with brain iron

accumulation, frontotemporal lobar degeneration with ubiquitin proteasome system and familial encephalopathy with neuroserpin inclusions.

The compounds of the invention are moreover also suitable for treatment and/or prevention of cardiovascular disorders such as, for example, arrhythmias, atrial and ventricular arrhythmias and impaired conduction such as, for example, atrioventricular blocks degrees I-III, supraventricular tachyarrhythmia, atrial fibrillation, atrial flutter, ventricular fibrillation, ventricular flutter, ventricular tachyarrhythmia, Torsade de pointes tachycardia, atrial and ventricular extrasystoles, AV-junctional extrasystoles, sick sinus syndrome, syncopes, AV-nodal re-entry tachycardia, high blood pressure (hypertension), heart failure, coronary heart disease, stable and unstable angina pectoris, renal hypertension, peripheral and cardial vascular disorders, Wolff-Parkinson-White syndrome, acute coronary syndrome (ACS), autoimmune cardiac disorders (pericarditis, endocarditis, valvolitis, aortitis, cardiomyopathies), boxer cardiomyopathy, aneurysms, shock such as cardiogenic shock, septic shock and anaphylactic shock, furthermore for treatment and/or prevention of thromboembolic disorders and ischemias such as myocardial ischemia, myocardial infarction, stroke, cardiac hypertrophy, transient and ischemic attacks, preeclampsia, inflammatory cardiovascular disorders, spasms of the coronary arteries and peripheral arteries, edema formation such as, for example, pulmonary edema, cerebral edema, renal edema or edema caused by heart failure, peripheral circulatory disturbances, reperfusion damage, arterial and venous thromboses, microalbuminuria, myocardial insufficiency, endothelial dysfunction, micro- and macrovascular damage (vasculitis), and also to prevent restenoses, for example after thrombolysis therapies, percutaneous transluminal angioplasties (PTA), percutaneous transluminal coronary angioplasties (PTCA), heart transplants, bypass operations, pulmonary arterial hypertension (PAH) and other forms of pulmonary hypertension (PH).

In the context of the present invention, the term "heart failure" encompasses both acute and chronic forms of heart failure, and also specific or related disease types thereof, such as acute decompensated heart failure, right heart failure, left heart failure, global failure, ischaemic cardiomyopathy, dilatative cardiomyopathy, hypertrophic cardiomyopathy, idiopathic cardiomyopathy, congenital heart defects, heart valve defects, heart failure associated with heart valve defects, mitral valve stenosis, mitral valve insufficiency, aortic valve stenosis, aortic valve insufficiency, tricuspid valve stenosis, tricuspid valve insufficiency, pulmonary valve stenosis, pulmonary valve insufficiency, combined heart valve defects, myocardial inflammation (myocarditis), chronic myocarditis, acute myocarditis, viral myocarditis, diabetic heart failure, alcoholic cardiomyopathy, cardiac storage disorders and diastolic and systolic heart failure.

The compounds of the invention can also be used for treatment and/or prevention of asthmatic disorders of varying severity with intermittent or persistent characteristics (refractive asthma,

bronchial asthma, allergic asthma, intrinsic asthma, extrinsic asthma, medicament- or dust-induced asthma), of various forms of bronchitis (chronic bronchitis, infectious bronchitis, eosinophilic bronchitis), of bronchiectasis, pneumonia, farmer's lung and related disorders, coughs and colds (chronic inflammatory cough, iatrogenic cough), inflammation of the nasal mucosa (including medicament-related rhinitis, vasomotoric rhinitis and seasonal allergic rhinitis, for example hay fever) and of polyps.

In addition, the compounds of the invention are suitable for treatment and/or prevention of renal disorders, in particular renal insufficiency and kidney failure. In the context of the present invention, the terms "renal insufficiency" and "kidney failure" encompass both acute and chronic manifestations thereof and also underlying or related renal disorders such as renal hypoperfusion, intradialytic hypotension, obstructive uropathy, glomerulopathies, glomerulonephritis, acute glomerulonephritis, glomerulosclerosis, tubulointerstitial diseases, nephropathic disorders such as primary and congenital kidney disease, nephritis, immunological kidney disorders such as kidney transplant rejection and immunocomplex-induced kidney disorders, nephropathy induced by toxic substances, nephropathy induced by contrast agents, diabetic and non-diabetic nephropathy, pyelonephritis, renal cysts, nephrosclerosis, hypertensive nephrosclerosis and nephrotic syndrome which can be characterized diagnostically, for example by abnormally reduced creatinine and/or water excretion, abnormally elevated blood concentrations of urea, nitrogen, potassium and/or creatinine, altered activity of renal enzymes, for example glutamyl synthetase, altered urine osmolarity or urine volume, elevated microalbuminuria, macroalbuminuria, lesions on glomerulae and arterioles, tubular dilatation, hyperphosphatemia and/or need for dialysis. The present invention also encompasses the use of the compounds of the invention for treatment and/or prevention of sequelae of renal insufficiency, for example hypertension, pulmonary edema, heart failure, uremia, anemia, electrolyte disturbances (for example hyperkalemia, hyponatremia) and disturbances in bone and carbohydrate metabolism.

In addition, the compounds of the invention are suitable for treatment and/or prevention of disorders of the urogenital system, for example benign prostate syndrome (BPS), benign prostate hyperplasia (BPH), benign prostate enlargement (BPE), bladder outlet obstruction (BOO), lower urinary tract syndromes (LUTS), neurogenic overactive bladder (OAB), incontinence, for example mixed urinary incontinence, urge urinary incontinence, stress urinary incontinence or overflow urinary incontinence (MUI, UUI, SUI, OUI), pelvic pain, and also erectile dysfunction and female sexual dysfunction.

The compounds of the invention are further suitable for treatment and/or prevention of inflammatory disorders and autoimmune disorders such as, for example, rheumatoid disorders, inflammatory eye disorders, sepsis (SIRS), chronic obstructive pulmonary disease (COPD), acute respiratory distress syndrome (ARDS), acute lung injury (ALI), alpha-1-antitrypsin deficiency (AATD), pulmonary

emphysema (e.g. pulmonary emphysema induced by cigarette smoke), cystic fibrosis (CF), multiple organ failure (MODS, MOF), inflammatory disorders of the kidney, chronic intestinal inflammations (IBD, Crohn's disease, ulcerative colitis), pancreatitis, peritonitis, cystitis, urethritis, prostatitis, epidimytitis, oophoritis, salpingitis, vulvovaginitis, and also for treatment and/or prevention of fibrotic disorders of internal organs such as, for example, the lung, the heart, the kidney, the bone marrow and especially the liver, and also of dermatological fibroses and fibrotic disorders of the eye. In the context of the present invention, the term "fibrotic disorders" includes in particular disorders such as hepatic fibrosis, cirrhosis of the liver, pulmonary fibrosis, endomyocardial fibrosis, nephropathy, glomerulonephritis, interstitial renal fibrosis, fibrotic damage resulting from diabetes, bone marrow fibrosis, peritoneal fibrosis and similar fibrotic disorders, scleroderma, morphea, keloids, hypertrophic scarring, nevi, diabetic retinopathy, proliferative vitroretinopathy and disorders of the connective tissue (for example sarcoidosis). The compounds of the invention can likewise be used for promotion of wound healing, for controlling postoperative scarring, for example following glaucoma operations and cosmetically for aging or keratinized skin.

Moreover, the compounds of the invention are suitable for the treatment and/or prophylaxis of neoplastic disorders such as, for example, skin cancer, breast cancer, lung cancer, colon cancer and prostate cancer.

In addition, the compounds of the invention can be used for treatment and/or prevention of arteriosclerosis, impaired lipid metabolism and dyslipidaemias (hypolipoproteinaemia, hypertriglyceridaemias, hyperlipidaemia, combined hyperlipidaemias, hypercholesterolaemia, abetalipoproteinaemia, sitosterolaemia), xanthomatosis, Tangier disease, adiposity, obesity, metabolic disorders (metabolic syndrome, hyperglycaemia, insulin-dependent diabetes, non-insulin-dependent diabetes, gestation diabetes, hyperinsulinaemia, insulin resistence, glucose intolerance and diabetic sequelae, such as retinopathy, nephropathy and neuropathy), of anaemias such as haemolytic anaemias, haemoglobinopathies such as sickle cell anaemia and thalassaemias, megaloblastic anaemias, iron deficiency anaemias, anaemias owing to acute blood loss, displacement anaemias and aplastic anaemias, of disorders of the gastrointestinal tract and the abdomen (glossitis, gingivitis, periodontitis, esophagitis, eosinophilic gastroenteritis, mastocytosis, Crohn’s disease, colitis, proctitis, anus pruritis, diarrhea, celiac disease, hepatitis, hepatic fibrosis, cirrhosis of the liver, pancreatitis and cholecystitis), of disorders of the central nervous system and neurodegenerative disorders (stroke, epilepsy, depressions), immune disorders, thyroid disorders (hyperthyreosis), skin disorders (psoriasis, acne, eczema, neurodermitis, various forms of dermatitis, and also keratitis, bullosis, vasculitis, cellulitis, panniculitis, lupus erythematosus, erythema, lymphomas, skin cancer, Sweet syndrome, Weber-Christian syndrome, scar formation, wart formation, chilblains), of eye inflammation diseases (saccoidosis, blepharitis, conjunctivitis, iritis, uveitis, chorioiditis, ophthalmitis), viral diseases (caused by influenza, adeno and corona viruses,

such as, for example, HPV, HCMV, HIV, SARS), of disorders of the skeletal bone and the joints and also the skeletal muscle, of inflammatory changes of the arteries (multifarious forms of arteritis, such as, for example, endarteritis, mesarteritis, periarteritis, panarteritis, arteritis rheumatica, arteritis deformans, arteritis temporalis, arteritis cranialis, arteritis gigantocellularis and arteritis granulomatosa, and also Horton syndrome, Churg-Strauss syndrome and Takayasu arteritis), of Muckle-Well syndrome, of Kikuchi disease, of polychondritis, dermatosclerosis and also other disorders having an inflammatory or immunological component, such as, for example, cataract, cachexia, osteoporosis, gout, incontinence, lepra, Sezary syndrome and paraneoplastic syndrome, for rejection reactions after organ transplants and for wound healing and angiogenesis in particular in the case of chronic wounds.

By virtue of their property profile, the compounds of the invention are particularly suitable for treatment and/or prevention of breathing difficulties including sleep-induced breathing difficulties such as central and obstructive sleep apnoea, snoring (primary and obstructive snoring), dysphagia, peripheral and cardiac vascular disorders including diabetic microangiopathies and disorders of the peripheral and central nervous system including neurodegenerative and neuroinflammatory disorders.

The aforementioned well-characterized diseases in humans can also occur with comparable etiology in other mammals and can likewise be treated therein with the compounds of the present invention.

For the purposes of the present invention, the term “treatment” or “treating” includes inhibition, retardation, halting, alleviating, attenuating, restricting, reducing, suppressing, reversing or healing of a disease, a condition, a disorder, an injury or a health problem or of the development, course or progression of such states and/or symptoms of such states. The term “therapy” is understood here to be synonymous with the term “treatment”.

The terms “prevention” and “prophylaxis” are used synonymously in the context of the present invention and refer to the avoidance or reduction of the risk of contracting, experiencing, suffering from or having a disease, a condition, a disorder, an injury or a health problem or a development or progression of such states and/or the symptoms of such states.

The treatment or prevention of a disease, a condition, a disorder, an injury or a health problem may be partial or complete.

The present invention thus further provides for the use of the compounds of the invention for treatment and/or prevention of disorders, especially of the aforementioned disorders.

The present invention further provides for the use of the compounds of the invention for production of a medicament for treatment and/or prevention of disorders, especially of the aforementioned disorders.

The present invention further provides a medicament comprising at least one of the compounds of the invention for treatment and/or prevention of disorders, especially of the aforementioned disorders.

The present invention further provides for the use of the compounds of the invention in a method for treatment and/or prevention of disorders, especially of the aforementioned disorders.

The present invention further provides a method of treatment and/or prevention of disorders, especially of the aforementioned disorders, using an effective amount of at least one of the compounds of the invention.

The compounds of the invention can be used alone or, if required, in combination with one or more other pharmacologically active substances, provided that this combination does not lead to undesirable and unacceptable side effects. The present invention therefore further provides medicaments comprising at least one of the compounds of the invention and one or more further active ingredients, especially for treatment and/or prevention of the aforementioned disorders. Preferred examples of combination active ingredients suitable for this purpose include:

- TASK1 channel and TASK3 channel blockers, by way of example and with preference those disclosed in WO 2017/097792 A1, WO 2017/097671 A1, WO 2018/015196 A1, WO 2018/228907 A1, WO 2018/228909 A1,
- P2X3 receptor antagonists, by way of example and with preference gefapixant,
- respiratory stimulants, by way of example and with preference theophylline, doxapram, nikethamide, caffeine;
- psychostimulants, by way of example and with preference modafinil, armodafinil;
- amphetamines and amphetamine derivatives, by way of example and with preference amphetamine, metamphetamine, methylphenidate;
- serotonin reuptake inhibitors, by way of example and with preference fluoxetine, paroxetine, citalopram, escitalopram, sertraline, fluvoxamine, trazodone;
- serotonin precursors, by way of example and with preference L-tryptophan;

- selective serotonin noradrenaline reuptake inhibitors, by way of example and with preference venlafaxine, duloxetine;
- noradrenergic and specifically serotonergic antidepressants, by way of example and with preference mirtazapine;
- selective noradrenaline reuptake inhibitors, by way of example and with preference atomoxetine and reboxetine;
- muscarine receptor antagonists, by way of example and with preference oxybutynin;
- tricyclic antidepressants, by way of example and with preference amitriptyline, protriptyline, doxepine, trimipramine, imipramine, clomipramine, desipramine;
- GABA agonists, by way of example and with preference baclofen;
- alpha sympathomimetics, by way of example and with preference xylometazoline, oxymetazoline, phenylephrine, naphazoline, tetryzoline, tramazoline;
- glucocorticoids, by way of example and with preference fluticasone, budesonide, beclometasone, mometasone, tixocortol pivalate, triamcinolone acetonide;
- cannabinoid receptor agonists and antagonists;
- carboanhydrase inhibitors, by way of example and with preference acetazolamide, methazolamide and diclofenamide;
- opioid and benzodiazepine receptor antagonists, by way of example and with preference flumazenil, naloxone, naltrexone;
- cholinesterase inhibitors, by way of example and with preference neostigmine, pyridostigmine, physostigmine donepezil, galantamine, rivastigmine;
- N-methyl-D-aspartate and glutamate antagonists, by way of example and with preference amantadine, memantine, sabeluzole;
- nicotine receptor agonists;
- leukotriene receptor antagonists, by way of example and with preference montelukast, tripelukast;
- dopamine receptor antagonists, by way of example and with preference dromperidone, metoclopramide, benzamide, butyrophenone, phenothiazine;

- appetite suppressants, by way of example and with preference sibutramine, topiramate, lipase inhibitors, cannabinoid receptor antagonists, phentermine;

- proton pump inhibitors, by way of example and with preference pantoprazole, omeprazole, esomeprazole, lansoprazole, rabeprazole;

- hypotensive active ingredients, by way of example and with preference from the group of the calcium antagonists, angiotensin AII antagonists, ACE inhibitors, vasopeptidase inhibitors, endothelin antagonists, renin inhibitors, alpha receptor blockers, beta receptor blockers, mineralocorticoid receptor antagonists and also the diuretics;

- active ingredients that alter lipid metabolism, by way of example and with preference from the group of the thyroid receptor agonists, cholesterol synthesis inhibitors, by way of example and with preference HMG-CoA reductase inhibitors or squalene synthesis inhibitors, the 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 and lipoprotein(a) antagonists;

- inorganic nitrates and NO donors, for example sodium nitroprusside, nitroglycerin, isosorbide mononitrate, isosorbide dinitrate, molsidomine or SIN-1, and inhaled NO;

- compounds which inhibit the degradation of cyclic guanosine monophosphate (cGMP) and/or cyclic adenosine monophosphate (cAMP), for example inhibitors of phosphodiesterases (PDE) 1, 2, 3, 4 and/or 5, especially PDE 5 inhibitors such as sildenafil, vardenafil, tadalafil, udenafil, dasantafil, avanafil, mirodenafil or lodenafil;

- NO- and heme-independent activators of soluble guanylate cyclase (sGC), such as in particular the compounds described in WO 01/19355, WO 01/19776, WO 01/19778, WO 01/19780, WO 02/070462 and WO 02/070510;

- NO-independent but heme-dependent stimulators of soluble guanylate cyclase (sGC), such as in particular riociguat and the compounds described in WO 00/06568, WO 00/06569, WO 02/42301, WO 03/095451, WO 2011/147809, WO 2012/004258, WO 2012/028647 and WO 2012/059549;

- compounds which influence the energy metabolism of the heart, by way of example and with preference etomoxir, dichloroacetate, ranolazine or trimetazidine;

- antithrombotic agents, by way of example and with preference from the group of platelet aggregation inhibitors, the anticoagulants and the profibrinolytic substances;

- anti-obstructive agents as used, for example, for treatment of chronic obstructive pulmonary disease (COPD) or bronchial asthma, by way of example and with preference from the group of the inhalatively or systemically administered agonists of the beta-adrenergic receptor (beta-mimetics) and the inhalatively administered anti-muscarinergic substances;

- antiinflammatory, immunomodulating, immunosuppressive and/or cytotoxic agents, by way of example and with preference from the group of the systemically or inhalatively administered corticosteroids and also dimethyl fumarate, fingolimod, glatiramer acetate, beta-interferons, natalizumab, teriflunomide, mitoxantrone, immunoglobulins, acetylcysteine, montelukast, tipelukast, azathioprine, cyclophosphamide, hydroxycarbamide, azithromycin, IFN-γ, pirfenidone or etanercept;

- compounds which inhibit the signal transduction cascade, by way of example and with preference from the group of the kinase inhibitors, in particular from the group of the tyrosine kinase and/or serine/threonine kinase inhibitors, by way of example and with preference nintedanib, dasatinib, nilotinib, bosutinib, regorafenib, sorafenib, sunitinib, cediranib, axitinib, telatinib, imatinib, brivanib, pazopanib, vatalanib, gefitinib, erlotinib, lapatinib, canertinib, lestaurtinib, pelitinib, semaxanib or tandutinib;

- prostacyclin analogs and IP receptor agonists, by way of example and with preference iloprost, beraprost, treprostinil, epoprostenol or selexipag;

- endothelin receptor antagonists, by way of example and with preference bosentan, darusentan, ambrisentan or sitaxsentan;

- compounds which inhibit human neutrophile elastase (HNE), by way of example and with preference sivelestat or DX-890 (reltran);

- compounds which inhibit the degradation and alteration of the extracellular matrix, by way of example and with preference inhibitors of the matrix metalloproteases (MMPs), especially inhibitors of stromelysin, collagenases, gelatinases and aggrecanases (in this context particularly of MMP-1, MMP-3, MMP-8, MMP-9, MMP-10, MMP-11 and MMP-13) and of metalloelastase (MMP-12);

- compounds which block the binding of serotonin to its receptors, by way of example and with preference antagonists of the 5-$HT_{2B}$ receptor such as PRX-08066;

- antagonists of growth factors, cytokines and chemokines, by way of example and with preference antagonists of TGF-β, CTGF, IL-1, IL-4, IL-5, IL-6, IL-8, IL-13 and integrins;

- rho kinase-inhibiting compounds, by way of example and with preference fasudil, Y-27632, SLx-2119, BF-66851, BF-66852, BF-66853, KI-23095 or BA-1049; and/or

- antifibrotic agents, by way of example and with preference pirfenidone, lysophosphatidic acid receptor 1 (LPA-1) antagonists, CTGF inhibitors, IL-4 antagonists, IL-13 antagonists, TGF-β antagonists.

In a particularly preferred embodiments of the invention, the compounds of the invention are administered in combination with one or more further active compounds selected from the group consisting of respiratory stimulants, psychostimulants, serotonin reuptake inhibitors, noradrenergic, serotonergic and tricyclic antidepressants, P2X3 antagonists, sGC stimulators, mineralocorticoid receptor antagonists, antiinflammatory drugs, immunomodulators, immunosuppressives and cytotoxic drugs.

In a preferred embodiment of the invention, the compounds of the invention are administered in combination with a beta-adrenergic receptor agonist, by way of example and with preference albuterol, isoproterenol, metaproterenol, terbutalin, fenoterol, formoterol, reproterol, salbutamol or salmeterol.

In a preferred embodiment of the invention, the compounds of the invention are administered in combination with an antimuscarinergic substance, by way of example and with preference ipratropium bromide, tiotropium bromide or oxitropium bromide.

In a preferred embodiment of the invention, the compounds of the invention are administered in combination with a corticosteroid, by way of example and with preference prednisone, prednisolone, methylprednisolone, triamcinolone, dexamethasone, beclomethasone, betamethasone, flunisolide, budesonide or fluticasone.

Antithrombotic agents are preferably understood to mean compounds from the group of the platelet aggregation inhibitors, the anticoagulants and the profibrinolytic substances.

In a preferred embodiment of the invention, the compounds of the invention are administered in combination with a platelet aggregation inhibitor, by way of example and with preference aspirin, clopidogrel, ticlopidine or dipyridamole.

In a preferred embodiment of the invention, the compounds of the invention are administered in combination with a thrombin inhibitor, by way of example and with preference ximelagatran, melagatran, dabigatran, bivalirudin or clexane.

In a preferred embodiment of the invention, the compounds of the invention are administered in combination with a GPIIb/IIIa antagonist, by way of example and with preference tirofiban or abciximab.

In a preferred embodiment of the invention, the compounds of the invention are administered in combination with a factor Xa inhibitor, by way of example and with preference rivaroxaban, apixaban, 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 the invention are administered in combination with heparin or with a low molecular weight (LMW) heparin derivative.

In a preferred embodiment of the invention, the compounds of the invention are administered in combination with a vitamin K antagonist, by way of example and with preference coumarin.

Antihypertensives are preferably understood to mean compounds from the group of calcium antagonists, angiotensin AII antagonists, ACE inhibitors, endothelin antagonists, renin inhibitors, alpha-receptor blockers, beta-receptor blockers, mineralocorticoid receptor antagonists, and diuretics.

In a preferred embodiment of the invention, the compounds of the invention are administered in combination with a calcium antagonist, by way of example and with preference nifedipine, amlodipine, verapamil or diltiazem.

In a preferred embodiment of the invention, the compounds of the invention are administered in combination with an alpha-1 receptor blocker, by way of example and with preference prazosin.

In a preferred embodiment of the invention, the compounds of the invention are administered in combination with a beta receptor blocker, by way of example and with preference propranolol, atenolol, timolol, pindolol, alprenolol, oxprenolol, penbutolol, bupranolol, metipranolol, nadolol, mepindolol, carazalol, 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 the invention are administered in combination with an angiotensin AII antagonist, by way of example and with preference losartan, candesartan, valsartan, telmisartan or embursatan.

In a preferred embodiment of the invention, the compounds of the invention are administered in combination with an ACE inhibitor, by way of example and with preference enalapril, captopril, lisinopril, ramipril, delapril, fosinopril, quinopril, perindopril or trandopril.

In a preferred embodiment of the invention, the compounds of the invention are administered in combination with an endothelin antagonist, by way of example and with preference bosentan, darusentan, ambrisentan or sitaxsentan.

In a preferred embodiment of the invention, the compounds of the invention are administered in combination with a renin inhibitor, by way of example and with preference aliskiren, SPP-600 or SPP-800.

In a preferred embodiment of the invention, the compounds of the invention are administered in combination with a mineralocorticoid receptor antagonist, by way of example and with preference spironolactone, eplerenone or finerenone.

In a preferred embodiment of the invention, the compounds of the invention are administered in combination with a diuretic, by way of example and with preference furosemide, bumetanide, torsemide, bendroflumethiazide, chlorothiazide, hydrochlorothiazide, hydroflumethiazide, methyclothiazide, polythiazide, trichlormethiazide, chlorthalidone, indapamide, metolazone, quinethazone, acetazolamide, dichlorphenamide, methazolamide, glycerol, isosorbide, mannitol, amiloride or triamterene.

Modifiers of lipid metabolism are preferably understood to mean compounds from the group of CETP inhibitors, thyroid receptor agonists, cholesterol synthesis inhibitors such as HMG-CoA reductase inhibitors 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 the invention are administered in combination with a CETP inhibitor, by way of example and with preference torcetrapib (CP-529 414), JJT-705 or CETP vaccine (Avant).

In a preferred embodiment of the invention, the compounds of the invention are administered in combination with a thyroid receptor agonist, by way of example and with preference D-thyroxine, 3,5,3'-triiodothyronine (T3), CGS 23425 or axitirome (CGS 26214).

In a preferred embodiment of the invention, the compounds of the invention are administered in combination with an HMG-CoA reductase inhibitor from the class of statins, by way of example and with preference lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin, rosuvastatin or pitavastatin.

In a preferred embodiment of the invention, the compounds of the invention are administered in combination with a squalene synthesis inhibitor, by way of example and with preference BMS-188494 or TAK-475.

In a preferred embodiment of the invention, the compounds of the invention are administered in combination with an ACAT inhibitor, by way of example and with preference avasimibe, melinamide, pactimibe, eflucimibe or SMP-797.

In a preferred embodiment of the invention, the compounds of the invention are administered in combination with an MTP inhibitor, by way of example and with preference implitapide, BMS-201038, R-103757 or JTT-130.

In a preferred embodiment of the invention, the compounds of the invention are administered in combination with a PPAR-gamma agonist, by way of example and with preference pioglitazone or rosiglitazone.

In a preferred embodiment of the invention, the compounds of the invention are administered in combination with a PPAR-delta agonist, by way of example and with preference GW 501516 or BAY 68-5042.

In a preferred embodiment of the invention, the compounds of the invention are administered in combination with a cholesterol absorption inhibitor, by way of example and with preference ezetimibe, tiqueside or pamaqueside.

In a preferred embodiment of the invention, the compounds of the invention are administered in combination with a lipase inhibitor, by way of example and with preference orlistat.

In a preferred embodiment of the invention, the compounds of the invention are administered in combination with a polymeric bile acid adsorber, by way of example and with preference cholestyramine, colestipol, colesolvam, CholestaGel or colestimide.

In a preferred embodiment of the invention, the compounds of the invention are administered in combination with a bile acid reabsorption inhibitor, by way of example and with preference ASBT (= IBAT) inhibitors, for example AZD-7806, S-8921, AK-105, BARI-1741, SC-435 or SC-635.

In a preferred embodiment of the invention, the compounds of the invention are administered in combination with a lipoprotein(a) antagonist, by way of example and with preference gemcabene calcium (CI-1027) or nicotinic acid.

Particular preference is given to combinations of the compounds of the invention with one or more further active compounds selected from the group of respiratory stimulants, psychostimulants,

serotonin reuptake inhibitors, noradrenergic, serotonergic and tricyclic antidepressants, sGC stimulators, mineralocorticoid receptor antagonists, and/or antiinflammatory drugs, immunomodulators, immunosuppressives and/or cytotoxic drugs.

If required, the compounds of the invention can also be used in combination with one or more other medical means, provided that this combination does not lead to undesirable and unacceptable side effects. Preferred examples of medical means suitable for this purpose include:

- devices for positive airway pressure ventilation, by way of example and with preference CPAP (continuous positive airway pressure) devices, BiPAP (bilevel positive airway pressure) devices and IPPV (intermittent positive pressure ventilation) devices
- neurostimulators of the *Nervus hypoglossus*
- intraoral means, by way of example and with preference protrusion braces
- nasal disposable valves
- nasal stents

The present invention further provides medicaments which comprise at least one compound of the invention, typically together with one or more inert, non-toxic, pharmaceutically suitable excipients, and for the use thereof for the aforementioned purposes.

The compounds of the invention can act systemically and/or locally. For this purpose, they can be administered in a suitable manner, for example by the oral, parenteral, pulmonal, nasal, pharyngeal, sublingual, lingual, buccal, rectal, dermal, transdermal, conjunctival or otic route, or as an implant or stent.

The compounds of the invention can be administered in administration forms suitable for these administration routes.

Suitable administration forms for oral administration are those which work according to the prior art and release the compounds of the invention rapidly and/or in a modified manner and which contain the compounds of the invention in crystalline and/or amorphized and/or dissolved form, for example tablets (uncoated or coated tablets, for example with gastric juice-resistant or retarded-dissolution or insoluble coatings which control the release of the compound of the invention), tablets or films/oblates which disintegrate rapidly in the oral cavity, films/lyophilizates, capsules (for example hard or soft gelatin capsules), sugar-coated tablets, granules, pellets, powders, emulsions, suspensions, aerosols or solutions.

Parenteral administration can bypass an absorption step (e.g. take place intravenously, intraarterially, intracardially, intraspinally or intralumbally) or include an absorption (e.g. take place inhalatively, intramuscularly, subcutaneously, intracutaneously, percutaneously or intraperitoneally). Administration forms suitable for parenteral administration include inter alia preparations for injection and infusion in the form of solutions, suspensions, emulsions, lyophilizates or sterile powders.

For the other administration routes, suitable examples are inhalable medicament forms (including powder inhalers, nebulizers, metered aerosols), nasal drops, solutions or sprays, throat sprays, tablets, films/oblates or capsules for lingual, sublingual or buccal administration, suppositories, ear or eye preparations, vaginal capsules, aqueous suspensions (lotions, shaking mixtures), lipophilic suspensions, ointments, creams, transdermal therapeutic systems (e.g. patches), milk, pastes, foams, sprinkling powders, implants or stents.

Oral, parenteral and local administration are preferred, in particular oral, intravenous, intranasal and pharyngeal administration.

The compounds of the invention can be converted to the administration forms mentioned. This can be accomplished in a manner known per se by mixing with inert, non-toxic, pharmaceutically suitable excipients. These excipients include *inter alia* carriers (for example microcrystalline cellulose, lactose, mannitol), solvents (e.g. liquid polyethylene glycols), emulsifiers and dispersing or wetting agents (for example sodium dodecylsulfate, polyoxysorbitan oleate), binders (for example polyvinylpyrrolidone), synthetic and natural polymers (for example albumin), stabilizers (e.g. antioxidants, for example ascorbic acid), colourants (e.g. inorganic pigments, for example iron oxides) and flavour and/or odour correctors.

In general, it has been found to be advantageous in the case of parenteral administration to administer amounts of about 0.001 to 1 mg/kg, preferably about 0.01 to 0.5 mg/kg body weight to achieve effective results. In the case of oral administration the dosage is about 0.01 to 100 mg/kg, preferably about 0.01 to 20 mg/kg and most preferably 0.1 to 10 mg/kg body weight. In the case of intrapulmonary administration, the amount is generally about 0.1 to 50 mg per inhalation.

It may nevertheless be necessary in some cases to depart from the stated amounts, specifically as a function of body weight, route of administration, individual response to the active ingredient, nature of the formulation and time at which or interval over which administration takes place. For instance, in some cases, less than the abovementioned minimum amount may be sufficient, whereas in other cases it is necessary to exceed the cited upper limit. In the case of administration of larger amounts, it may be advisable to divide them into several individual doses over the day.

The working examples which follow illustrate the invention. The invention is not restricted to the examples.

## A. Examples

**Abbreviations and acronyms:**

| | |
|---|---|
| abs. | absolute |
| Ac | acetyl |
| aq. | aqueous, aqueous solution |
| Boc | *tert*-butoxycarbonyl |
| br. | broad (in NMR signal) |
| Ex. | Example |
| Bu | butyl |
| c | Concentration |
| ca. | *circa*, about |
| cat. | catalytic |
| CI | chemical ionization (in MS) |
| d | doublet (in NMR) |
| d | day(s) |
| DCI | direct chemical ionization (in MS) |
| dd | doublet of doublets (in NMR) |
| diamix | diastereomer mixture |
| DMF | *N,N*-dimethylformamide |
| DMSO | dimethyl sulfoxide |
| dq | doublet of quartets (in NMR) |
| dt | doublet of triplet (in NMR) |
| o. t. | of theory (in chemical yield) |
| EI | electron impact ionization (in MS) |
| eq. | equivalent(s) |
| ESI | electrospray ionization (in MS) |
| Et | ethyl |
| h | hour(s) |
| HATU | *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate |
| HOBt | 1-hydroxy-1*H*-benzotriazole hydrate |
| HPLC | high-pressure, high-performance liquid chromatography |
| iPr | isopropyl |
| concentrated | concentrated (in the case of a solution) |
| LC | liquid chromatography |
| LC-MS | liquid chromatography-coupled mass spectrometry |

| | |
|---|---|
| Lit. | literature (reference) |
| m | multiplet (in NMR) |
| Me | methyl |
| min | minute(s) |
| MS | mass spectrometry |
| MTBE | methyl tert-butyl ether |
| NMR | nuclear magnetic resonance spectrometry |
| Ph | phenyl |
| Pr | propyl |
| q | quartet (in NMR) |
| quant. | quantitative (in chemical yield) |
| RP | reverse phase (in HPLC) |
| RT | Room temperature/Retention time |
| $R_t$ | retention time (in HPLC, LC-MS) |
| s | singlet (in NMR) |
| t | triplet (in NMR) |
| tBu | *tert*-butyl |
| TFA | trifluoroacetic acid |
| THF | tetrahydrofuran |
| UV | ultraviolet spectrometry |
| v/v | volume to volume ratio (of a solution) |
| tog. | together |

**LC-MS, GC-MS and HPLC methods**

Method 1 (LC-MS):

MS instrument type: Thermo Scientific FT-MS; UHPLC+ instrument type: Thermo Scientific UltiMate 3000; column: Waters, HSST3, 2.1 x 75 mm, C18 1.8 µm; eluent A: 1 l water + 0.01% formic acid; eluent B: 1 l acetonitrile + 0.01% formic acid; gradient: 0.0 min 10% B → 2.5 min 95% B → 3.5 min 95% B; oven: 50°C; flow rate: 0.90 ml/min; UV detection: 210 nm/optimum integration path 210-300 nm.

Method 2 (LC-MS):

Instrument: Waters ACQUITY SQD UPLC System; column: Waters Acquity UPLC HSS T3 1.8 µm 50 x 1 mm; eluent A: 1 l water + 0.25 ml 99% formic acid, eluent B: 1 l acetonitrile + 0.25 ml 99%

formic acid; gradient: 0.0 min 90% A → 1.2 min 5% A → 2.0 min 5% A; oven: 50°C; flow rate: 0.40 ml/min; UV detection: 210 nm.

Method 3 (LC-MS):

MS instrument type: Thermo Scientific FT-MS; UHPLC+ instrument type: Thermo Scientific UltiMate 3000; column: Waters, BEH C18 1.7 µ, 2.1 x 50 mm; eluent A: 1 l water + 1.0 ml (25% ammonia); eluent B: 1 l acetonitrile; gradient: 0.0 min 5% B → 2.5 min 95% B → 3.5 min 95% B; oven: 50°C; flow rate: 0.90 ml/min; UV detection: 210 nm/optimum integration path 210-300 nm.

Method 4 (LC-MS):

MS instrument type Thermo Scientific FT-MS; UHPLC+ instrument type: Thermo Scientific Vanquish; column Waters, HSST3, 2.1 x 75 mm, C18 1.8 µm; eluent A 1 l of water + 0.01% formic acid; eluent B 1 l of acetonitrile + 0.01% formic acid; gradient 0.0 min 10% B → 2.5 min 95% B → 3.5 min 95% B; oven 50°C; flow rate 0.90 ml/min; UV detection 210 nm.

Method 5 (LC-MS):

Instrument: Waters Single Quad MS System; Instrument: Waters UPLC Acquity; column: Waters BEH C18 1.7 µ 50 x 2.1 mm; eluent A: 1 l water + 1.0 ml (25% ammonia)/l, eluent B: 1 l acetonitrile; gradient: 0.0 min 92% A → 0.1 min 92% A → 1.8 min 5% A → 3.5 min 5% A; oven: 50°C; flow rate: 0.45 ml/min; UV detection: 210 nm.

Method 6 (LC-MS)

Instrument MS: Waters SQD2; Instrument HPLC: Waters UPLC; column: Zorbax SB-Aq (Agilent), 50 mm x 2.1 mm, 1.8 µm; eluent A: water + 0.025% formic acid, eluent B: acetonitrile (ULC) + 0.025% formic acid; gradient: 0.0 min 98%A - 0.9 min 25%A – 1.0 min 5%A - 1.4 min 5%A – 1.41 min 98%A – 1.5 min 98%A; oven: 40°C; flow rate: 0.600 ml/min; UV detection: DAD; 210 nm.

Further details:

The descriptions of the coupling patterns of $^1$H NMR signals which follow are guided by the visual appearance of the signals in question and do not necessarily correspond to a strict, physically correct interpretation. In general, the stated chemical shift refers to the center of the signal in question; in the case of broad multiplets, an interval is generally given.

In all $^1$H NMR spectra data, the chemical shifts δ[ppm] = are stated in ppm.

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

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

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

Melting points and melting ranges, if stated, are uncorrected.

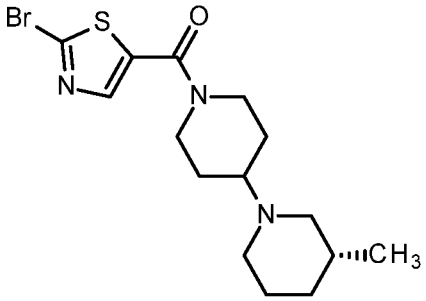
In cases where the reaction products were obtained by trituration, stirring or recrystallization, it was frequently possible to isolate further amounts of product from the respective mother liquor by chromatography. However, a description of this chromatography is dispensed with hereinbelow unless a large part of the total yield could only be isolated in this step.

All reactants or reagents whose preparation is not described explicitly hereinafter were purchased commercially from generally accessible sources. For all other reactants or reagents whose preparation is likewise not described hereinafter and which were not commercially obtainable or were obtained from sources which are not generally accessible, a reference is given to the published literature in which their preparation is described.

**Starting compounds and intermediates:**

**Example 1A**

(5-Bromo-1,3-thiazol-2-yl)[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone



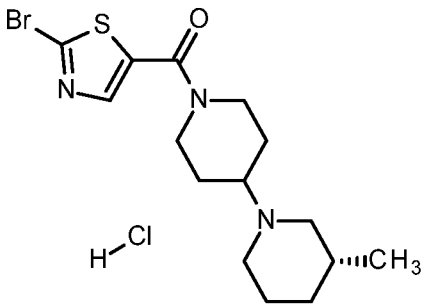

To a solution of 7.8 g (37.49 mmol) of 2-bromo-1,3-thiazole-5-carboxylic acid and 9.57 g (37.49 mmol) of (3*R*)-3-methyl-1,4'-bipiperidine hydrochloride (1:1) (WO2015091420 Example 1A; CAS Registry Number 1799475-27-6) in 312 ml of acetonitrile was added 19.59 ml (112.48 mmol) of *N*,*N*-diisopropylethylamine, followed by dropwise addition to the reaction solution, at room temperature, of 29 ml (48.74 mmol) of a 50% T3P solution in ethyl acetate (2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphorinane 2,4,6-trioxide). After the addition had ended, the reaction solution was stirred at room temperature overnight. Subsequently, the solution was concentrated to dryness under reduced pressure and taken up in about 250 ml of dichloromethane. The organic solution obtained was washed with saturated sodium hydrogencarbonate solution, then the organic phase was separated off and filtered through a hydrophobic filter (pleated filter, MN 616 WA 1/4, D = 12.5 cm), dried and concentrated to dryness under reduced pressure. The residue obtained was purified further by column chromatography on silica gel (Isolera Biotage SNAP-Ultra 100 g column, eluent: dichloromethane → gradient over 15 CV (CV = column volumes) → dichloromethane/methanol 85:15). This gave 9.5 g (25 mmol, 67% of theory) of the target compound as a yellow oil.

$^1$H-NMR (600 MHz, DMSO-$d_6$, δ/ppm): 0.74-0.89 (m, 4H, therein at 0.83 (d, 3H)), 1.31-1.68 (m, 6H), 1.70-1.82 (m, 3H), 2.05 (td, 1H), 2.44-2.57 (m, 4H, partly hidden by DMSO), 2.69-2.85 (m, 3H), 7.97 (s, 1H).

LC-MS (Method 1): $R_t$ = 0.69 min; m/z = 372/374 $(M+H)^+$.

**Example 2A**

(2-Bromo-1,3-thiazol-5-yl)[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone hydrochloride (1:1)



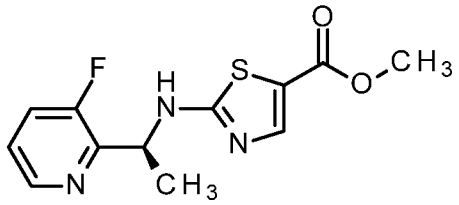

To a solution of 4 g (19.23 mmol) of 2-bromo-1,3-thiazole-5-carboxylic acid and 4.46 g (17.48 mmol) of (3*R*)-3-methyl-1,4'-bipiperidine hydrochloride (1:1) (WO2015091420 Example 1A; CAS Registry Number 1799475-27-6) in 60 ml of acetonitrile was added 15.22 ml (87.40 mmol) of *N*,*N*-diisopropylethylamine, followed by dropwise addition to the reaction solution, at room temperature, of 6.12 ml (20.98 mmol) of 2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphorinane 2,4,6-trioxide. After the addition had ended, the reaction solution was stirred at room temperature overnight. Subsequently, the solution was concentrated under reduced pressure, and 30 ml of saturated sodium hydrogencarbonate solution was added. The mixture obtained was repeatedly extracted with dichloromethane, then the organic phase was removed and dried over magnesium sulfate, filtered and concentrated to dryness under reduced pressure. The residue obtained was purified further by column chromatography on silica gel (Isolera Biotage SNAP-Ultra 340 g column, eluent: dichloromethane → gradient over 15 CV (CV = column volumes) → dichloromethane/methanol 85:15). The product-containing fractions were combined and concentrated. The residue obtained was converted to the hydrochloride salt, filtered off with suction and dried under reduced pressure. This gave 3.80 g (9.30 mmol, 100% purity, 53% of theory) of the target product in solid form.

$^1$H-NMR (400 MHz, DMSO-$d_6$, δ/ppm): 0.90 (d, 3H), 1.01-1.17 (m, 1H), 1.56-1.91 (m, 6H), 1.92-2.06 (m, 1H), 2.07-2.21 (, 2H), 2.42-2.63 (m, 2H, partly hidden by DMSO), 2.74-2.94 (m, 2H), 3.22-3.55 (m, 2H, partly hidden by $H_2O$), 4.00-4.71 (m, 2H), 7.97-8.06 (m, 1H), 10.13 (br. s, 1H).

LC-MS (Method 2): $R_t$ = 0.53 min; m/z = 372/374 $(M+H)^+$.

**Example 3A**

Methyl 2-{[(1*S*)-1-(3-fluoropyridin-2-yl)ethyl]amino}-1,3-thiazole-5-carboxylate



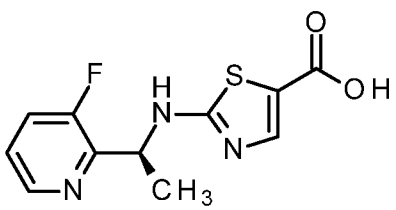
Methyl 2-bromo-1,3-thiazole-5-carboxylate (1.30 g, 5.87 mmol), (1*S*)-1-(3-fluoropyridin-2-yl)ethanamine dihydrochloride (1.50 g, 7.04 mmol) and N,N-diisopropylethylamine (6.0 ml, 34 mmol) were introduced into a microwave vessel, the vessel was closed, and the mixture was stirred at 110°C. After 1 h, the reaction mixture was taken up in water and extracted with ethyl acetate. The organic phase was washed with water and saturated sodium chloride solution, and dried over sodium sulfate. The desiccant was filtered off and the filtrate was concentrated. The residue was applied to Isolute® and purified using a Biotage cartridge (50 g Sfähr HC; Cy/EA gradient: 12-100% EA; flow rate: 120 ml/min). The product-containing fractions were combined and concentrated and the residue was dried under high vacuum. This gave 497 mg (100% purity, 30% of theory) of the target compound.

LC-MS (Method 1): $R_t$ = 1.43 min; MS (ESIpos): m/z = 282 $[M+H]^+$

$^1$H-NMR (500 MHz, DMSO-d6) δ [ppm]: 1.476 (5.96), 1.490 (6.01), 3.706 (16.00), 5.323 (0.45), 5.337 (0.66), 5.351 (0.45), 7.394 (0.66), 7.403 (1.17), 7.412 (1.32), 7.420 (1.34), 7.429 (0.79), 7.691 (0.86), 7.693 (0.87), 7.710 (6.66), 7.714 (1.10), 7.728 (0.79), 7.731 (0.75), 8.404 (0.90), 8.407 (1.47), 8.410 (0.95), 8.414 (0.99), 8.416 (1.46), 8.419 (0.86), 9.042 (1.19), 9.057 (1.17).

**Example 4A**

2-{[(1*S*)-1-(3-Fluoropyridin-2-yl)ethyl]amino}-1,3-thiazole-5-carboxylic acid

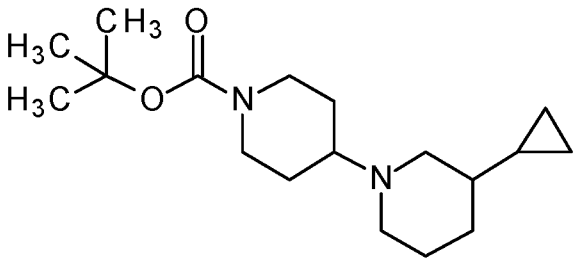


To an initial charge of methyl 2-{[(1S)-1-(3-fluoropyridin-2-yl)ethyl]amino}-1,3-thiazole-5-carboxylate (497 mg, 1.77 mmol) in 18 ml of THF was added lithium hydroxide solution (7.1 ml, 1.0 M, 7.1 mmol), and the mixture was stirred at 60°C. After 3 h, the reaction mixture was acidified with formic acid and purified by preparative HPLC (column: Chromatorex C18 10 µm, 250 x 30 mm, eluent A=water, B=acetonitrile; gradient: 0.0 min 15% B; 4.5 min 30% B; 11.5 min 50% B; 12 min 100% B; 18 min 100% B; flow rate: 50 ml/min; 0.1% formic acid). The product-containing fractions were combined and lyophilized. This gave 347 mg (100% purity, 73% of theory) of the target compound.

LC-MS (Method 1): $R_t$ = 0.96 min; MS (ESIpos): m/z = 268 $[M+H]^+$.

**Example 5A (MBM12257-1)**

*rac-tert*-Butyl 3-cyclopropyl[1,4'-bipiperidine]-1'-carboxylate



tert-Butyl 4-oxopiperidine-1-carboxylate (548 mg, 2.75 mmol), *rac*-3-cyclopropylpiperidine hydrochloride (890 mg, 5.50 mmol) and N,N-diisopropylethylamine (960 µl, 5.5 mmol) formed an initial charge in 30 ml of dichloromethane. Subsequently, concentrated acetic acid (240 µl, 4.1 mmol) was added and the mixture was stirred at room temperature overnight. Sodium triacetoxyborohydride (700 mg, 3.30 mmol) was added, and stirring of the mixture was continued at room temperature overnight. More sodium triacetoxyborohydride (700 mg, 3.30 mmol) was added, and the mixture was stirred at room temperature for a further 48 h. Water was added to the reaction mixture, which was extracted with dichloromethane. The organic phase was washed with saturated sodium hydrogencarbonate solution and dried over sodium sulfate. The desiccant was filtered off and the filtrate was concentrated. The residue was purified by preparative HPLC (instrument: Waters Prep LC/MS system, column: XBridge C18 5 µm 100 x 30 mm. Eluent A: water, eluent B: acetonitrile, eluent C: 2% ammonia in water, eluent D: acetonitrile/water (80% by vol. / 20% by vol.), total flow rate: 80 ml/min, room temperature, wavelength: 200-400 nm, at-column injection (complete injection); gradient profile: eluent A 0 to 2 min 23 ml, eluent B 0 to 2 min 47 ml, eluent

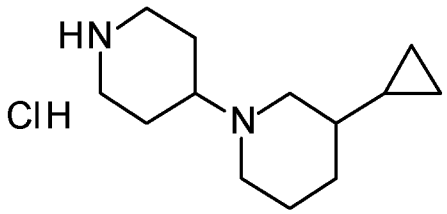
A 2 to 10 min from 23 ml to 0 ml and eluent B from 47 ml to 70 ml, 10 to 12 min 0 ml eluent A and 70 ml eluent B. Constant flow rate of eluent C and eluent D of 5 ml/min each over the entire run time). The product-containing fractions were combined and lyophilized. This gave 370 mg (100% purity, 44% of theory) of the target compound.

LC-MS (Method 1): $R_t$ = 1.07 min; MS (ESIpos): m/z = 309 $[M+H]^+$.

$^1$H-NMR (400 MHz, DMSO-d6) δ [ppm]: 0.040 (0.69), 0.045 (0.55), 0.315 (0.46), 0.326 (0.55), 0.331 (0.40), 0.335 (0.49), 0.344 (0.43), 1.380 (16.00), 1.675 (0.45), 1.966 (0.48).

**Example 6A**

*rac*-3-Cyclopropyl-1,4'-bipiperidine hydrochloride

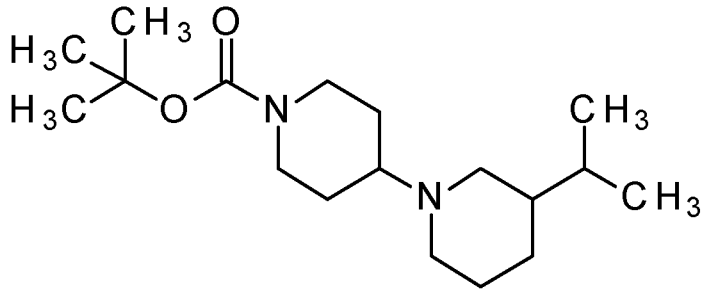



To a solution of *rac-tert*-butyl 3-cyclopropyl[1,4'-bipiperidine]-1'-carboxylate (370 mg, 1.20 mmol) in 12 ml of dichloromethane was added hydrochloric acid in 1,4-dioxane (1.5 ml, 4.0 M, 6.0 mmol), and the mixture was stirred at room temperature overnight. The reaction mixture was concentrated and the residue was stirred with MTBE. The solids were filtered off with suction, washed with MTBE and dried under high vacuum. This gave 269 mg (92% of theory) of the target compound.

$^1$H-NMR (400 MHz, DMSO-d6) δ [ppm]: -0.007 (7.11), 0.107 (2.05), 0.129 (8.51), 0.140 (13.48), 0.152 (8.25), 0.160 (4.71), 0.173 (2.21), 0.369 (1.04), 0.382 (1.68), 0.401 (15.88), 0.421 (16.00), 0.441 (2.10), 0.492 (1.16), 0.504 (2.34), 0.512 (2.98), 0.524 (4.52), 0.533 (3.66), 0.544 (3.85), 0.555 (2.17), 1.197 (0.84), 1.208 (0.81), 1.227 (2.58), 1.238 (2.52), 1.257 (4.02), 1.268 (4.70), 1.285 (4.79), 1.296 (5.00), 1.324 (2.69), 1.394 (0.52), 1.773 (4.45), 1.801 (6.64), 1.829 (7.94), 1.880 (2.30), 1.932 (1.86), 1.954 (4.46), 1.964 (4.20), 1.985 (6.58), 2.007 (4.29), 2.017 (4.74), 2.038 (1.68), 2.261 (4.98), 2.288 (7.77), 2.317 (3.98), 2.365 (0.52), 2.523 (0.96), 2.669 (0.45), 2.709 (0.53), 2.764 (1.68), 2.791 (4.85), 2.815 (6.49), 2.843 (6.08), 2.888 (6.34), 2.991 (0.41), 3.241 (5.33), 3.271 (5.29), 3.292 (5.19), 3.325 (5.22), 3.407 (10.60), 3.449 (4.30), 3.476 (2.20), 9.112 (1.96), 9.283 (2.33), 10.954 (2.68).

**Example 7A**

*rac-tert*-Butyl 3-isopropyl[1,4'-bipiperidine]-1'-carboxylate



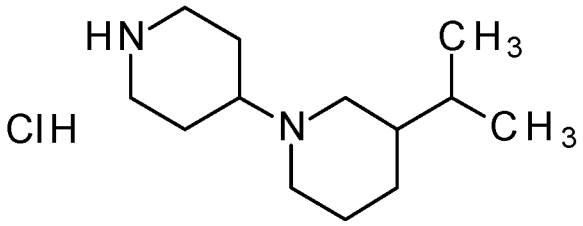
*tert*-Butyl 4-oxopiperidine-1-carboxylate (940 mg, 4.72 mmol) and *rac*-3-isopropylpiperidine (1.20 g, 9.43 mmol) formed an initial charge in 50 ml of dichloromethane. Subsequently, concentrated acetic acid (400 µl, 7.1 mmol) was added and the mixture was stirred at room temperature overnight. Sodium triacetoxyborohydride (1.20 g, 5.66 mmol) was added, and stirring of the mixture was continued at room temperature overnight. More sodium triacetoxyborohydride (1.20 g, 5.66 mmol) was added, and the mixture was stirred at room temperature for a further 48 h. Water was added to the reaction mixture, which was extracted with dichloromethane. The organic phase was washed with saturated sodium hydrogencarbonate solution and dried over sodium sulfate. The desiccant was filtered off and the filtrate was concentrated. The residue was purified by preparative HPLC (instrument: Waters Prep LC/MS system, column: XBridge C18 5 µm 100 x 30 mm. Eluent A: water, eluent B: acetonitrile, eluent C: 2% ammonia in water, eluent D: acetonitrile/water (80% by vol. / 20% by vol.), total flow rate: 80 ml/min, room temperature, wavelength: 200-400 nm, complete injection; gradient profile: eluent A 0 to 2 min 39 ml, eluent B 0 to 2 min 31 ml, eluent A 2 to 10 min from 39 ml to 15 ml and eluent B from 31 ml to 55 ml, 10 to 12 min 0 ml eluent A and 70 ml eluent B. Constant flow rate of eluent C and eluent D of 5 ml/min each over the entire run time). The product-containing fractions were combined and lyophilized. This gave 269 mg (100% purity, 18% of theory) of the target compound.

LC-MS (Method 1): $R_t$ = 1.14 min; MS (ESIpos): m/z = 311 $[M+H]^+$.

$^1$H-NMR (400 MHz, DMSO-d6) δ [ppm]: 0.826 (2.33), 0.831 (2.37), 0.843 (2.52), 0.848 (2.58), 1.363 (0.49), 1.379 (16.00), 1.396 (0.42), 1.640 (0.47), 1.672 (0.42), 1.854 (0.44).

**Example 8A**

*rac*-3-Isopropyl-1,4'-bipiperidine hydrochloride

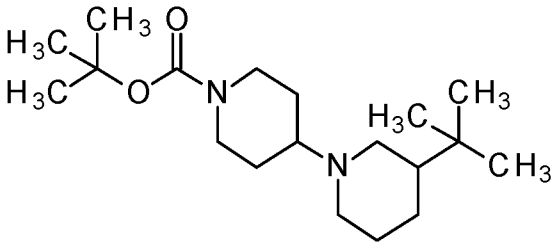


To a solution of *rac-tert*-butyl 3-cyclopropyl[1,4'-bipiperidine]-1'-carboxylate (269 mg, 866 µmol) in 10 ml of dichloromethane was added hydrochloric acid in 1,4-dioxane (1.1 ml, 4.0 M, 4.3 mmol), and the mixture was stirred at room temperature overnight. The reaction mixture was concentrated and the residue was stirred with MTBE. The solids were filtered off with suction, washed with MTBE and dried under high vacuum. This gave 219 mg (102% of theory) of the target compound.

$^1$H-NMR (400 MHz, DMSO-d6) δ [ppm]: 0.851 (10.57), 0.870 (16.00), 0.888 (11.48), 1.101 (0.55), 1.127 (0.62), 1.140 (0.61), 1.155 (0.68), 1.170 (0.71), 1.498 (0.84), 1.514 (1.24), 1.530 (1.22), 1.547 (0.77), 1.711 (1.13), 1.741 (0.99), 1.839 (2.12), 1.861 (2.62), 1.916 (0.50), 1.938 (1.06), 1.946 (1.09), 1.968 (1.54), 1.977 (1.55), 2.000 (1.14), 2.008 (1.10), 2.029 (0.41), 2.261 (1.10), 2.300 (1.48), 2.340 (0.92), 2.641 (0.43), 2.669 (1.15), 2.694 (0.99), 2.724 (0.46), 2.793 (0.64), 2.815 (0.80), 2.841 (0.94), 2.876 (1.42), 2.900 (1.37), 3.248 (1.20), 3.276 (1.19), 3.295 (0.46), 3.329 (1.88), 3.415 (3.01), 3.563 (0.51), 8.988 (0.51), 9.174 (0.61), 10.825 (0.69).

**Example 9A**

*rac-tert*-Butyl 3-tert-butyl[1,4'-bipiperidine]-1'-carboxylate



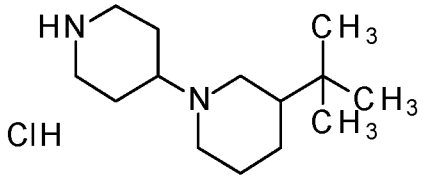
tert-Butyl 4-oxopiperidine-1-carboxylate (505 mg, 2.53 mmol), *rac*-3-*tert*-butylpiperidine hydrochloride (900 mg, 5.06 mmol) and N,N-diisopropylethylamine (880 µl, 5.1 mmol) formed an initial charge in 25 ml of dichloromethane. Subsequently, concentrated acetic acid (220 µl, 3.8 mmol) was added and the mixture was stirred at room temperature overnight. Sodium triacetoxyborohydride (644 mg, 3.04 mmol) was added, and the mixture was stirred at room temperature overnight. More sodium triacetoxyborohydride (644 mg, 3.04 mmol) was added, and the mixture was stirred at room temperature for a further 48 h. Water was added to the reaction mixture, which was extracted with dichloromethane. The organic phase was washed with saturated sodium hydrogencarbonate solution and dried over sodium sulfate. The desiccant was filtered off and the filtrate was concentrated. The residue was purified by preparative HPLC (instrument: Waters Prep LC/MS system, column: XBridge C18 5 µm 100 x 30 mm. Eluent A: water, eluent B: acetonitrile, eluent C: 2% ammonia in water, eluent D: acetonitrile/water (80% by vol. / 20% by vol.), total flow rate: 80 ml/min, room temperature, wavelength: 200-400 nm, at-column injection (complete injection); gradient profile: eluent A 0 to 2 min 23 ml, eluent B 0 to 2 min 47 ml, eluent A 2 to 10 min from 23 ml to 0 ml and eluent B from 47 ml to 70 ml, 10 to 12 min 0 ml eluent A and 70 ml eluent B. Constant flow rate of eluent C and eluent D of 5 ml/min each over the entire run time). The product-containing fractions were combined and lyophilized. This gave 318 mg (100% purity, 39% of theory) of the target compound.

LC-MS (Method 1): $R_t$ = 1.20 min; MS (ESIpos): m/z = 325 $[M+H]^+$.

$^1$H-NMR (400 MHz, DMSO-d6) δ [ppm]: 0.828 (12.43), 1.379 (16.00), 1.643 (0.52), 1.674 (0.48), 1.838 (0.48), 3.325 (0.48), 3.394 (0.47).

**Example 10A**

*rac*-3-*tert*-Butyl-1,4'-bipiperidine hydrochloride



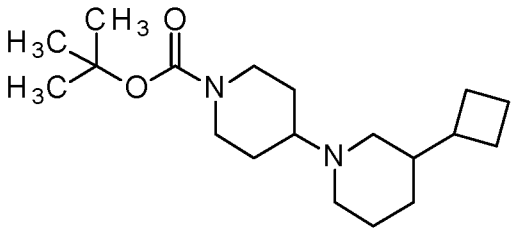

To a solution of *rac*-*tert*-butyl 3-*tert*-butyl[1,4'-bipiperidine]-1'-carboxylate (318 mg, 980 µmol) in 10 ml of dichloromethane was added hydrochloric acid in 1,4-dioxane (1.2 ml, 4.0 M, 4.9 mmol), and the mixture was stirred at room temperature overnight. The reaction mixture was concentrated

and the residue was stirred with MTBE. The solids were filtered off with suction, washed with MTBE and dried under high vacuum. This gave 262 mg (102% of theory) of the target compound.

$^1$H-NMR (400 MHz, DMSO-d6) δ [ppm]: 0.867 (16.00), 1.855 (0.79), 1.863 (0.79), 3.280 (0.47), 3.298 (0.49), 3.403 (0.64).

**Example 11A**

*rac-tert*-Butyl 3-cyclobutyl[1,4'-bipiperidine]-1'-carboxylate



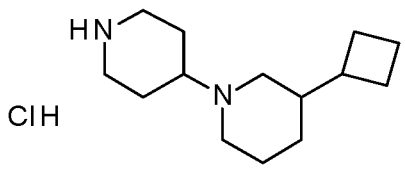
*tert*-Butyl 4-oxopiperidine-1-carboxylate (622 mg, 3.12 mmol) and *rac*-3-isopropylpiperidine (870 mg, 6.25 mmol) formed an initial charge in 30 ml of dichloromethane. Subsequently, concentrated acetic acid (270 µl, 4.7 mmol) was added and the mixture was stirred at room temperature overnight. Sodium triacetoxyborohydride (795 mg, 3.75 mmol) was added, and stirring of the mixture was continued at room temperature overnight. More sodium triacetoxyborohydride (795 mg, 3.75 mmol) was added, and the mixture was stirred at room temperature for a further 48 h. Water was added to the reaction mixture, which was extracted with dichloromethane. The organic phase was washed with saturated sodium hydrogencarbonate solution and dried over sodium sulfate. The desiccant was filtered off and the filtrate was concentrated. The residue was purified by preparative HPLC (instrument: Waters Prep LC/MS system, column: XBridge C18 5 µm 100 x 30 mm. Eluent A: water, eluent B: acetonitrile, eluent C: 2% ammonia in water, eluent D: acetonitrile/water (80% by vol. / 20% by vol.), total flow rate: 80 ml/min, room temperature, wavelength: 200-400 nm, at-column injection (complete injection); gradient profile: eluent A 0 to 2 min 23 ml, eluent B 0 to 2 min 47 ml, eluent A 2 to 10 min from 23 ml to 0 ml and eluent B from 47 ml to 70 ml, 10 to 12 min 0 ml eluent A and 70 ml eluent B. Constant flow rate of eluent C and eluent D of 5 ml/min each over the entire run time). The product-containing fractions were combined and lyophilized. This gave 285 mg (100% purity, 28% of theory) of the target compound.

LC-MS (Method 1): $R_t$ = 1.21 min; MS (ESIpos): m/z = 323 $[M+H]^+$.

$^1$H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.376 (16.00), 1.588 (0.43), 1.615 (0.69), 1.631 (0.54), 1.638 (0.62), 1.657 (0.54), 1.669 (0.44), 1.695 (0.51), 2.664 (0.40).

**Example 12A**

*rac*-3-Cyclobutyl-1,4'-bipiperidine hydrochloride

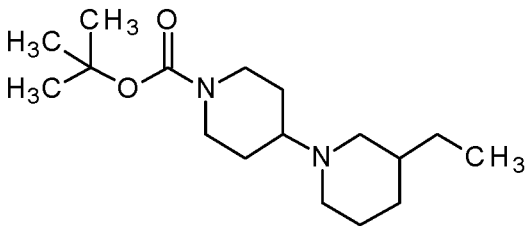



To a solution of *rac-tert*-butyl 3-cyclobutyl[1,4'-bipiperidine]-1'-carboxylate (285 mg, 884 µmol) in 10 ml of dichloromethane was added hydrochloric acid in 1,4-dioxane (1.1 ml, 4.0 M, 4.4 mmol), and the mixture was stirred at room temperature overnight. The reaction mixture was concentrated and the residue was stirred with MTBE. The solids were filtered off with suction, washed with MTBE and dried under high vacuum. This gave 239 mg (104% of theory) of the target compound.

$^1$H-NMR (400 MHz, DMSO-d6) δ [ppm]: -0.007 (6.02), 0.870 (0.97), 0.924 (1.22), 0.945 (3.13), 0.955 (3.18), 0.975 (3.52), 0.985 (3.20), 1.006 (1.58), 1.016 (1.21), 1.100 (0.44), 1.622 (1.41), 1.644 (3.83), 1.664 (6.30), 1.684 (11.25), 1.711 (15.25), 1.723 (13.76), 1.745 (6.18), 1.765 (2.62), 1.798 (5.25), 1.835 (12.60), 1.857 (6.07), 1.865 (5.13), 1.909 (6.81), 1.940 (14.55), 1.961 (16.00), 1.992 (11.77), 2.018 (7.93), 2.037 (4.66), 2.058 (1.74), 2.237 (5.21), 2.280 (5.86), 2.321 (4.20), 2.366 (0.71), 2.579 (2.03), 2.669 (0.44), 2.710 (0.71), 2.760 (1.61), 2.783 (3.71), 2.813 (3.96), 2.835 (4.04), 2.862 (6.36), 2.890 (6.50), 3.052 (0.80), 3.102 (5.60), 3.129 (4.84), 3.204 (0.58), 3.234 (0.65), 3.308 (6.16), 3.400 (12.79), 3.433 (4.77), 3.462 (2.40), 3.562 (13.01), 5.751 (5.23), 9.063 (2.45), 9.270 (3.09), 10.963 (3.35).

**Example 13A**

*rac-tert*-Butyl 3-ethyl[1,4'-bipiperidine]-1'-carboxylate



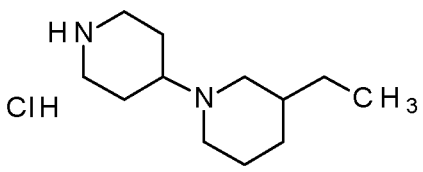
*tert*-Butyl 4-oxopiperidine-1-carboxylate (880 mg, 4.42 mmol) and *rac*-3-ethylpiperidine (1.00 g, 8.83 mmol) formed an initial charge in 45 ml of dichloromethane. Subsequently, concentrated acetic acid (380 µl, 6.6 mmol) was added and the mixture was stirred at room temperature overnight. Sodium triacetoxyborohydride (1.12 g, 5.30 mmol) was added, and stirring of the mixture was continued at room temperature overnight. More sodium triacetoxyborohydride (1.12 g, 5.30 mmol) was added, and the mixture was stirred at room temperature for a further 24 h. Water was added to the reaction mixture, which was extracted with dichloromethane. The organic phase was washed with saturated sodium hydrogencarbonate solution and dried over sodium sulfate. The desiccant was filtered off and the filtrate was concentrated. The residue was purified by preparative HPLC (instrument: Waters Prep LC/MS system, column: XBridge C18 5 µm 100 x 30 mm. Eluent A: water, eluent B: acetonitrile, eluent C: 2% ammonia in water, eluent D: acetonitrile/water (80% by vol. / 20% by vol.), total flow rate: 80 ml/min, room temperature, wavelength: 200-400 nm, complete injection; gradient profile: eluent A 0 to 2 min 39 ml, eluent B 0 to 2 min 31 ml, eluent A 2 to 10 min from 39 ml to 15 ml and eluent B from 31 ml to 55 ml, 10 to 12 min 0 ml eluent A and 70 ml eluent B. Constant flow rate of eluent C and eluent D of 5 ml/min each over the entire run time). The product-containing fractions were combined and lyophilized. This gave 413 mg (100% purity, 32% of theory) of the target compound.

LC-MS (Method 1): $R_t$ = 1.02 min; MS (ESIpos): m/z = 297 $[M+H]^+$.

$^1$H-NMR (400 MHz, DMSO-d6) δ [ppm]: 0.824 (1.01), 0.842 (2.62), 0.861 (1.26), 1.147 (0.42), 1.165 (0.44), 1.274 (0.47), 1.382 (16.00), 1.642 (0.43), 1.670 (0.54), 1.771 (0.44), 2.731 (0.48).

**Example 14A**

*rac*-3-Ethyl-1,4'-bipiperidine hydrochloride



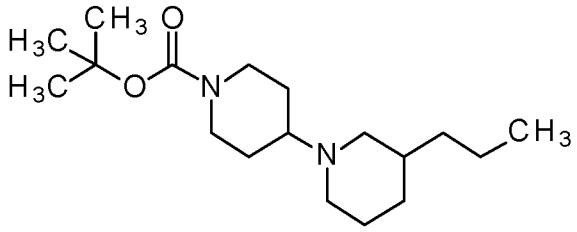

To a solution of *rac-tert*-butyl 3-ethyl[1,4'-bipiperidine]-1'-carboxylate (413 mg, 1.39 mmol) in 15 ml of dichloromethane was added hydrochloric acid in 1,4-dioxane (1.7 ml, 4.0 M, 7.0 mmol), and the mixture was stirred at room temperature overnight. The reaction mixture was concentrated

and the residue was stirred with MTBE. The solids were filtered off with suction, washed with MTBE and dried under high vacuum. This gave 329 mg (101% of theory) of the target compound.

$^1$H-NMR (400 MHz, DMSO-d6) δ [ppm]: -0.013 (0.73), 0.859 (6.26), 0.877 (16.00), 0.896 (7.64), 1.033 (0.99), 1.045 (0.92), 1.064 (1.06), 1.076 (0.99), 1.094 (0.47), 1.162 (0.68), 1.180 (1.11), 1.196 (1.51), 1.214 (1.77), 1.233 (1.16), 1.250 (0.66), 1.267 (1.17), 1.283 (1.51), 1.301 (1.62), 1.320 (0.90), 1.335 (0.57), 1.778 (1.45), 1.846 (2.85), 1.896 (1.77), 1.931 (2.06), 1.963 (1.96), 2.247 (1.45), 2.279 (2.41), 2.311 (1.15), 2.366 (0.42), 2.579 (1.36), 2.604 (1.18), 2.632 (0.52), 2.669 (0.41), 2.709 (0.40), 2.793 (0.93), 2.818 (0.98), 2.902 (1.75), 3.266 (1.53), 3.289 (1.51), 3.299 (1.34), 3.389 (5.67), 3.421 (3.80), 3.464 (0.57), 8.902 (0.64), 9.081 (0.73), 10.735 (0.76).

**Example 15A**

*rac-tert*-Butyl 3-propyl[1,4'-bipiperidine]-1'-carboxylate



tert-Butyl 4-oxopiperidine-1-carboxylate (426 mg, 2.14 mmol), *rac*-3-propylpiperidine hydrochloride (700 mg, 4.28 mmol) and N,N-diisopropylethylamine (740 µl, 4.3 mmol) formed an initial charge in 25 ml of dichloromethane. Subsequently, concentrated acetic acid (180 µl, 3.2 mmol) was added and the mixture was stirred at room temperature overnight. Sodium triacetoxyborohydride (544 mg, 2.57 mmol) was added, and stirring of the mixture was continued at room temperature overnight. More sodium triacetoxyborohydride (544 mg, 2.57 mmol) was added, and the mixture was stirred at room temperature for a further 24 h. Water was added to the reaction mixture, which was extracted with dichloromethane. The organic phase was washed with saturated sodium hydrogencarbonate solution and dried over sodium sulfate. The desiccant was filtered off and the filtrate was concentrated. The residue was purified by preparative HPLC (instrument: Waters Prep LC/MS system, column: XBridge C18 5 µm 100 x 30 mm. Eluent A: water, eluent B: acetonitrile, eluent C: 2% ammonia in water, eluent D: acetonitrile/water (80% by vol. / 20% by vol.), total flow rate: 80 ml/min, room temperature, wavelength: 200-400 nm, at-column injection (complete injection); gradient profile: eluent A 0 to 2 min 23 ml, eluent B 0 to 2 min 47 ml, eluent A 2 to 10 min from 23 ml to 0 ml and eluent B from 47 ml to 70 ml, 10 to 12 min 0 ml eluent A and

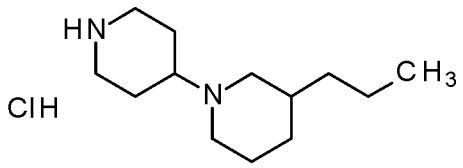
70 ml eluent B; constant flow rate of eluent C and eluent D of 5 ml/min each over the entire run time). The product-containing fractions were combined and lyophilized. This gave 262 mg (100% purity, 39% of theory) of the target compound.

LC-MS (Method 1): $R_t$ = 1.16 min; MS (ESIpos): m/z = 311 $[M+H]^+$.

$^1$H-NMR (400 MHz, DMSO-d6) δ [ppm]: -0.008 (2.34), 0.820 (1.16), 0.838 (2.67), 0.856 (1.34), 1.241 (0.67), 1.260 (0.99), 1.279 (0.61), 1.375 (16.00), 1.633 (0.59), 1.665 (0.51), 1.764 (0.42), 2.704 (0.46).

**Example 16A**

*rac*-3-Propyl-1,4'-bipiperidine hydrochloride

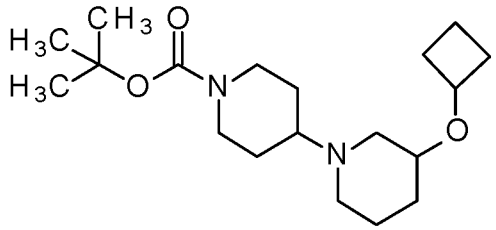



To a solution of *rac-tert*-butyl 3-propyl[1,4'-bipiperidine]-1'-carboxylate (262 mg, 844 µmol) in 9 ml of dichloromethane was added hydrochloric acid in 1,4-dioxane (1.1 ml, 4.0 M, 4.2 mmol), and the mixture was stirred at room temperature overnight. The reaction mixture was concentrated and the residue was stirred with MTBE. The solids were filtered off with suction, washed with MTBE and dried under high vacuum. This gave 209 mg (100% of theory) of the target compound.

$^1$H-NMR (400 MHz, DMSO-d6) δ [ppm]: 0.871 (16.00), 1.070 (2.56), 1.203 (4.53), 1.313 (5.20), 1.757 (3.92), 1.844 (7.04), 1.956 (7.10), 2.272 (6.15), 2.903 (5.47), 8.881 (2.30), 9.035 (2.55), 10.678 (2.54).

**Example 17A**

*rac-tert*-Butyl 3-(cyclobutyloxy)[1,4'-bipiperidine]-1'-carboxylate



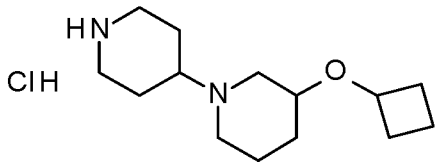
tert-Butyl 4-oxopiperidine-1-carboxylate (520 mg, 2.61 mmol), *rac*-3-(cyclobutyloxy)piperidine hydrochloride (1.00 g, 5.22 mmol) and N,N-diisopropylethylamine (910 µl, 5.2 mmol) formed an initial charge in 30 ml of dichloromethane. Subsequently, concentrated acetic acid (220 µl, 3.9 mmol) was added and the mixture was stirred at room temperature overnight. Sodium triacetoxyborohydride (663 mg, 3.13 mmol) was added, and the mixture was stirred at room temperature overnight. More sodium triacetoxyborohydride (663 mg, 3.13 mmol) was added, and the mixture was stirred at room temperature for a further 24 h. Water was added to the reaction mixture, which was extracted with dichloromethane. The organic phase was washed with saturated sodium hydrogencarbonate solution and dried over sodium sulfate. The desiccant was filtered off and the filtrate was concentrated. The residue was purified by preparative HPLC (instrument: Waters Prep LC/MS system, column: XBridge C18 5 µm 100 x 30 mm. Eluent A: water, eluent B: acetonitrile, eluent C: 2% ammonia in water, eluent D: acetonitrile/water (80% by vol. / 20% by vol.), total flow rate: 80 ml/min, room temperature, wavelength: 200-400 nm, complete injection; gradient profile: eluent A 0 to 2 min 39 ml, eluent B 0 to 2 min 31 ml, eluent A 2 to 10 min from 39 ml to 15 ml and eluent B from 31 ml to 55 ml, 10 to 12 min 0 ml eluent A and 70 ml eluent B. Constant flow rate of eluent C and eluent D of 5 ml/min each over the entire run time). The product-containing fractions were combined and lyophilized. This gave 563 mg (100% purity, 64% of theory) of the target compound.

LC-MS (Method 1): $R_t$ = 1.07 min; MS (ESIpos): m/z = 339 $[M+H]^+$.

$^1$H-NMR (400 MHz, DMSO-d6) δ [ppm]: 1.380 (16.00), 1.393 (0.57), 1.419 (0.43), 1.582 (0.52), 1.624 (0.57), 1.657 (0.42), 1.788 (0.46), 1.811 (0.50), 1.922 (0.43), 2.104 (0.42), 2.639 (0.40), 3.966 (0.53), 3.984 (0.48).

**Example 18A**

*rac*-3-(Cyclobutyloxy)-1,4'-bipiperidine hydrochloride

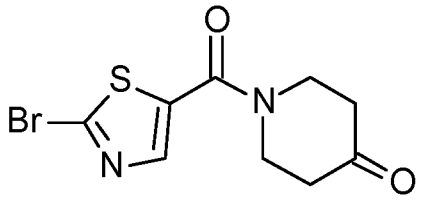



To a solution of *rac-tert*-butyl 3-(cyclobutyloxy)[1,4'-bipiperidine]-1'-carboxylate (563 mg, 1.66 mmol) in 9 ml of dichloromethane was added hydrochloric acid in 1,4-dioxane (2.1 ml, 4.0 M, 8.3 mmol), and the mixture was stirred at room temperature overnight. The reaction mixture was concentrated and the residue was stirred with MTBE. The solids were filtered off with suction, washed with MTBE and dried under high vacuum. This gave 560 mg (123% of theory) of the target compound.

$^1$H-NMR (400 MHz, DMSO-d6) δ [ppm]: -0.014 (1.61), 0.477 (0.73), 1.101 (1.06), 1.295 (2.84), 1.318 (3.53), 1.341 (2.98), 1.370 (1.34), 1.380 (1.14), 1.407 (3.70), 1.426 (7.05), 1.432 (6.36), 1.452 (9.04), 1.473 (4.46), 1.478 (4.82), 1.498 (1.74), 1.596 (6.92), 1.621 (7.91), 1.716 (2.44), 1.752 (2.59), 1.801 (7.88), 1.827 (13.14), 1.851 (16.00), 1.918 (8.14), 1.952 (10.89), 1.983 (12.81), 2.141 (11.90), 2.156 (13.86), 2.249 (6.47), 2.277 (7.78), 2.684 (4.33), 2.709 (4.65), 2.734 (1.86), 2.862 (9.48), 2.892 (9.28), 3.008 (2.10), 3.038 (2.19), 3.077 (1.92), 3.108 (3.04), 3.134 (2.28), 3.226 (3.32), 3.281 (8.20), 3.311 (12.64), 3.400 (14.00), 3.410 (15.15), 3.470 (4.85), 3.827 (8.21), 4.041 (6.97), 4.059 (9.25), 4.078 (6.14), 4.095 (1.76), 9.028 (2.52), 9.176 (3.33), 9.256 (2.35), 9.325 (2.19), 11.297 (3.16).

**Example 19A**

1-[(2-Bromo-1,3-thiazol-5-yl)carbonyl]piperidin-4-one



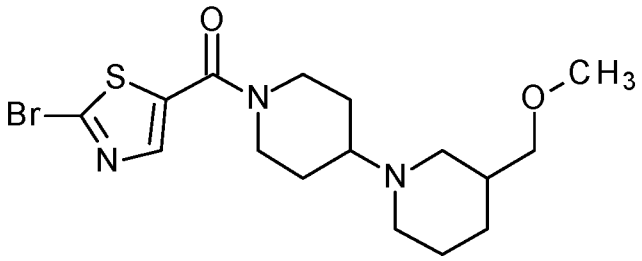

To a solution of 5 g (24.04 mmol) of 2-bromo-1,3-thiazole-5-carboxylic acid and 3.26 g (24.04 mmol) of piperidin-4-one hydrochloride (1:1) in 250 ml of acetonitrile was added 16.75 ml (96.14 mmol) of *N,N*-diisopropylethylamine, followed by dropwise addition to the reaction solution, at room temperature, of 18.6 ml (19.88 mmol) of a 50% T3P solution in ethyl acetate (2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphorinane 2,4,6-trioxide). After the addition had ended, the reaction solution was stirred at room temperature overnight. Subsequently, the solution was concentrated to dryness

under reduced pressure and taken up in about 250 ml of ethyl acetate. The organic solution obtained was washed with saturated sodium hydrogencarbonate solution, then the organic phase was separated off and filtered through a hydrophobic filter (pleated filter, MN 616 WA 1/4, D = 12.5 cm), dried and concentrated to dryness under reduced pressure. The residue was applied to Isolute® and purified using a Biotage cartridge (50 g Sfähr HC; cyclohexane/ethyl acetate gradient: 12-100% ethyl acetate; flow rate: 120 ml/min). This gave 4.89 g (16.91 mmol, 70% of theory) of the target compound as a white solid.

LC-MS (Method 1): $R_t$ = 0.96 min; m/z = 288/290 $(M+H)^+$.

**Example 20A**

(2-Bromo-1,3-thiazol-5-yl)[3-(methoxymethyl)[1,4'-bipiperidine]-1'-yl]methanone (racemic)



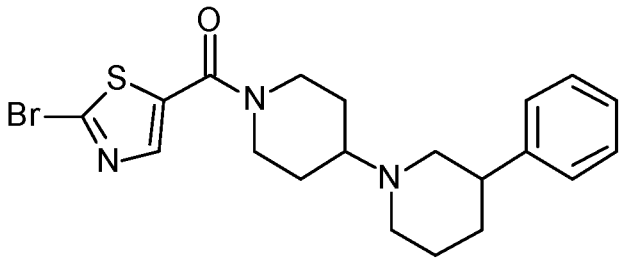

1-[(2-Bromo-1,3-thiazol-5-yl)carbonyl]piperidin-4-one (100 mg, 346 µmol) and 89 mg (692 µmol) of 3-(methoxymethyl)piperidine (racemic) were dissolved in 3.5 ml of dichloromethane, and acetic acid (0.03 ml, 519 µmol) was added. Subsequently, sodium triacetoxyborohydride (88 mg, 415 µmol) was added to the reaction, and the mixture was stirred at 37°C for 2.5 h. Thereafter, another 50 mg of sodium triacetoxyborohydride was added to the reaction mixture, which was stirred at that temperature for 2 days. After a further 50 mg of sodium triacetoxyborohydride had been added, the reaction mixture was heated to 50°C and stirred at that temperature for 1 h. The reaction mixture was diluted with dichloromethane and washed successively with saturated sodium hydrogencarbonate solution and water. The organic phase was subsequently separated off and filtered through a hydrophobic filter (pleated filter, MN 616 WA 1/4, D = 12.5 cm), dried and concentrated to dryness under reduced pressure. The residue was purified by preparative HPLC (column: Chromatorex C18 10 µm, 125 x 40 mm; eluent A = water, B = acetonitrile; gradient: 0.0 min 10% B; 20 min 95% B; flow rate: 100 ml/min; 0.05% formic acid, UV detection: DAD; 210 nm). Removal of the solvent gave 51 mg (37% of theory) of the title compound.

LC-MS (Method 1): $R_t$ = 0.70 min; m/z = 402/404 $(M+H)^+$.

$^1$H-NMR (400 MHz, DMSO-d6) δ [ppm]: 0.85-1.00 (m, 1H), 1.32-1.52 (m, 3H), 1.54-1.64 (m, 2H), 1.65-1.81 (m, 3H), 1.90 (t, 1H), 2.12 (t, 1H), 2.44-2.59 (m, 3H, hidden by DMSO), 2.73 (br. d, 1H), 2.83 (br. d, 1H), 3.12-3.19 (m, 2H), 3.21 (s, 3H), 3.87-4.53 (m, 2H), 7.97 (s, 1H).

**Example 21A**

(2-Bromo-1,3-thiazol-5-yl)[3-phenyl[1,4'-bipiperidine]-1'-yl]methanone (racemic)

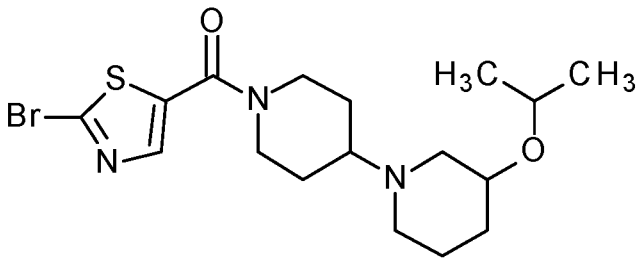



1-[(2-Bromo-1,3-thiazol-5-yl)carbonyl]piperidin-4-one (500 mg, 1.73 mmol) and 558 mg (3.46 mmol) of 3-phenylpiperidine (racemic) were dissolved in 17.5 ml of dichloromethane, and acetic acid (0.15 ml, 2.59 mmol) and 4 Å molecular sieve were added. Subsequently, sodium triacetoxyborohydride (440 mg, 2.08 mmol) was added to the reaction, and the mixture was stirred at room temperature overnight. After the molecular sieve had been removed by filtration, saturated sodium hydrogencarbonate solution was added to the reaction mixture (caution: vigorous evolution of gas). Subsequently, the organic phase was separated off, and the aqueous phase was extracted three times with dichloromethane. The combined organic phases were washed with oversaturated sodium chloride solution and filtered through a hydrophobic filter (pleated filter, MN 616 WA 1/4, D = 12.5 cm), dried and concentrated to dryness under reduced pressure. The residue was purified by preparative HPLC (column: Chromatorex C18 10 µm, 125 x 40 mm; eluent A = water, B = acetonitrile; gradient: 0.0 min 10% B; 20 min 95% B; flow rate: 100 ml/min; 0.05% formic acid, UV detection: DAD; 210 nm). Removal of the solvent gave 188 mg (25% of theory) of the title compound.

LC-MS (Method 1): $R_t$ = 1.04 min; m/z = 434/436 $(M+H)^+$.

**Example 22A**

(2-Bromo-1,3-thiazol-5-yl)[3-isopropoxy[1,4'-bipiperidine]-1'-yl]methanone (racemic)

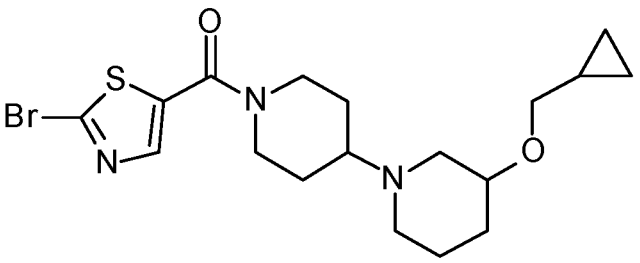


1-[(2-Bromo-1,3-thiazol-5-yl)carbonyl]piperidin-4-one (500 mg, 1.73 mmol) and 495 mg (3.46 mmol) of 3-isopropoxypiperidine (racemic) were dissolved in 17.5 ml of dichloromethane, and acetic acid (0.15 ml, 2.59 mmol) and 4 Å molecular sieve were added. Subsequently, sodium triacetoxyborohydride (440 mg, 2.08 mmol) was added to the reaction, and the mixture was stirred at room temperature for 1 h. Thereafter, a further 400 mg of sodium triacetoxyborohydride was added to the reaction mixture, and the reaction mixture was stirred at room temperature overnight. After the molecular sieve had been removed by filtration, saturated sodium hydrogencarbonate solution was added to the reaction mixture (caution: vigorous evolution of gas). Subsequently, the organic phase was separated off, and the aqueous phase was extracted three times with dichloromethane. The combined organic phases were washed with oversaturated sodium chloride solution and filtered through a hydrophobic filter (pleated filter, MN 616 WA 1/4, D = 12.5 cm), dried and concentrated to dryness under reduced pressure. The residue was purified by preparative HPLC (column: Chromatorex C18 10 µm, 125 x 40 mm; eluent A = water, B = acetonitrile; gradient: 0.0 min 10% B; 20 min 95% B; flow rate: 100 ml/min; 0.05% formic acid, UV detection: DAD; 210 nm). Removal of the solvent gave 149 mg (21% of theory) of the title compound.

LC-MS (Method 1): $R_t$ = 0.81 min; m/z = 416/418 $(M+H)^+$.

**Example 23A**

(2-Bromo-1,3-thiazol-5-yl)[3-(cyclopropylmethoxy)[1,4'-bipiperidine]-1'-yl]methanone (racemic)

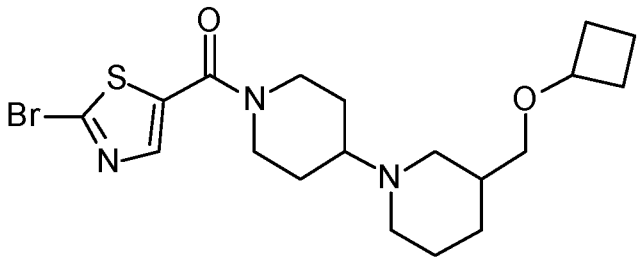


1-[(2-Bromo-1,3-thiazol-5-yl)carbonyl]piperidin-4-one (447 mg, 1.55 mmol) and 296 mg (1.55 mmol) of 3-(cyclopropylmethoxy)piperidine hydrochloride (1:1) (racemic) were dissolved in 17.5 ml of dichloromethane, and triethylamine (0.32 ml, 2.31 mmol) and 4 Å molecular sieve were added. Subsequently, sodium triacetoxyborohydride (393 mg, 1.85 mmol) was added to the reaction, and the mixture was stirred at 45°C overnight. After the molecular sieve had been removed by filtration, saturated sodium hydrogencarbonate solution was added to the reaction mixture (caution: vigorous evolution of gas). Subsequently, the organic phase was separated off, and the aqueous phase was extracted three times with dichloromethane. The combined organic phases were washed with oversaturated sodium chloride solution and filtered through a hydrophobic filter (pleated filter, MN 616 WA 1/4, D = 12.5 cm), dried and concentrated to dryness under reduced pressure. The residue was purified by preparative HPLC (column: Chromatorex C18 10 µm, 125 x 40 mm; eluent A = water, B = acetonitrile; gradient: 0.0 min 10% B; 20 min 95% B; flow rate: 100 ml/min; 0.05% formic acid, UV detection: DAD; 210 nm). Removal of the solvent gave 63 mg (9.5% of theory) of the title compound.

LC-MS (Method 1): $R_t$ = 0.85 min; m/z = 428/430 $(M+H)^+$.

**Example 24A**

(2-Bromo-1,3-thiazol-5-yl){3-[(cyclobutyloxy)methyl][1,4'-bipiperidine]-1'-yl}methanone (racemic)



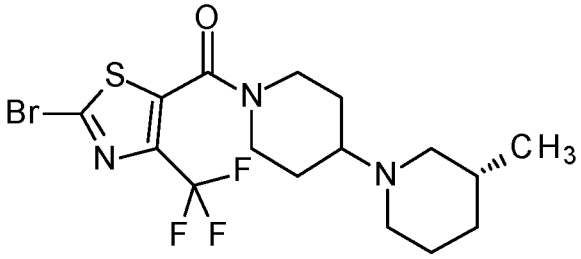

1-[(2-Bromo-1,3-thiazol-5-yl)carbonyl]piperidin-4-one (300 mg, 1.04 mmol) and 213 mg (1.04 mmol) of 3-[(cyclobutyloxy)methyl]piperidine hydrochloride (1:1) (racemic) were dissolved in 3.5 ml of dichloromethane, and triethylamine (0.22 ml, 1.56 mmol) and 4 Å molecular sieve were added. Subsequently, sodium triacetoxyborohydride (264 mg, 1.25 mmol) was added to the reaction, and the mixture was stirred at 45°C overnight. After the molecular sieve had been removed by filtration, saturated sodium hydrogencarbonate solution was added to the reaction mixture (caution: vigorous evolution of gas). Subsequently, the organic phase was separated off, and the aqueous phase

was extracted three times with dichloromethane. The combined organic phases were washed with oversaturated sodium chloride solution and filtered through a hydrophobic filter (pleated filter, MN 616 WA 1/4, D = 12.5 cm), dried and concentrated to dryness under reduced pressure. The residue was purified by preparative HPLC (column: Chromatorex C18 10 µm, 125 x 40 mm; eluent A = water, B = acetonitrile; gradient: 0.0 min 10% B; 20 min 95% B; flow rate: 100 ml/min; 0.05% formic acid, UV detection: DAD; 210 nm). Removal of the solvent gave 57 mg (12.5% of theory) of the title compound.

LC-MS (Method 1): $R_t$ = 1.01 min; m/z = 442/444 $(M+H)^+$.

**Example 25A**

[2-Bromo-4-(trifluoromethyl)-1,3-thiazol-5-yl][(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone



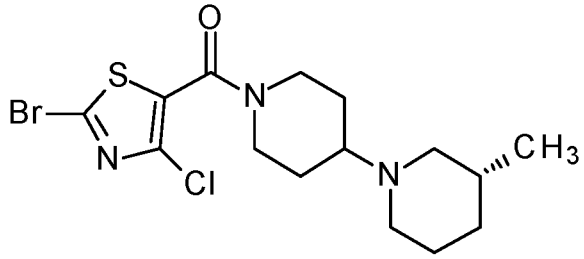

To a solution of 0.5 g (1.81 mmol) of 2-bromo-4-(trifluoromethyl)-1,3-thiazole-5-carboxylic acid and 0.46 g (1.81 mmol) of (3*R*)-3-methyl-1,4'-bipiperidine hydrochloride (1:1) (WO2015091420 Example 1A; CAS Registry Number 1799475-27-6) in 15 ml of acetonitrile was added 0.95 ml (5.43 mmol) of *N*,*N*-diisopropylethylamine, followed by dropwise addition to the reaction solution, at room temperature, of 1.4 ml (2.36 mmol) of a 50% T3P solution in ethyl acetate (2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphorinane 2,4,6-trioxide). After the addition had ended, the reaction solution was stirred at room temperature overnight. Subsequently, the solution was concentrated to dryness under reduced pressure and taken up in about 50 ml of dichloromethane. The organic solution obtained was washed with saturated sodium hydrogencarbonate solution, then the organic phase was separated off and filtered through a hydrophobic filter (pleated filter, MN 616 WA 1/4, D = 12.5 cm), dried and concentrated to dryness under reduced pressure. The residue obtained was purified further by column chromatography on silica gel (Isolera Biotage SNAP-Ultra 25 g column, eluent: dichloromethane → gradient over 15 CV (CV = column volumes) → dichloromethane/methanol 85:15). This gave 270 mg (0.57 mmol, 32% of theory) of the target compound.

$^1$H-NMR (400 MHz, DMSO-$d_6$, δ/ppm): 0.74-0.89 (m, 4H, therein at 0.82 (d, 3H)), 1.27-1.46 (m, 3H), 1.46-1.70 (m, 4H), 1.71-1.84 (m, 2H), 2.05 (br. t, 1H), 2.44-2.57 (m, 1H, partly hidden by DMSO), 2.68-2.85 (m, 3H), 3.04 (br. t, 1H), 3.53 (br. d, 1H), 4.41 (br. d, 1H).

LC-MS (Method 1): $R_t$ = 0.98 min; m/z = 440/442 $(M+H)^+$.

**Example 26A**

(2-Bromo-4-chloro-1,3-thiazol-5-yl)[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone

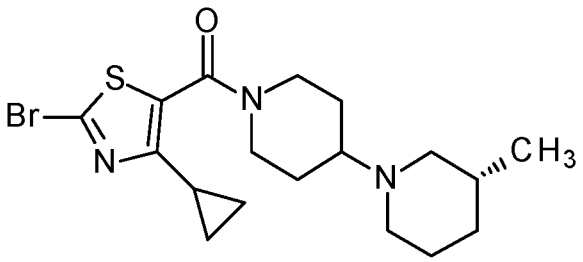



To a solution of 0.5 g (2.06 mmol) of 2-bromo-4-chloro-1,3-thiazole-5-carboxylic acid and 0.53 g (2.06 mmol) of (3*R*)-3-methyl-1,4'-bipiperidine hydrochloride (1:1) (WO2015091420 Example 1A; CAS Registry Number 1799475-27-6) in 17 ml of acetonitrile was added 1.1 ml (6.19 mmol) of *N*,*N*-diisopropylethylamine, followed by dropwise addition to the reaction solution, at room temperature, of 1.6 ml (2.68 mmol) of a 50% T3P solution in ethyl acetate (2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphorinane 2,4,6-trioxide). After the addition had ended, the reaction solution was stirred at room temperature overnight. Subsequently, the solution was concentrated to dryness under reduced pressure and taken up in about 50 ml of dichloromethane. The organic solution obtained was washed with saturated sodium hydrogencarbonate solution, then the organic phase was separated off and filtered through a hydrophobic filter (pleated filter, MN 616 WA 1/4, D = 12.5 cm), dried and concentrated to dryness under reduced pressure. This gave 410 mg (1.01 mmol, 49% of theory) of the target compound.

LC-MS (Method 1): $R_t$ = 0.84 min; m/z = 406/408 $(M+H)^+$.

**Example 27A**

(2-Bromo-4-cyclopropyl-1,3-thiazol-5-yl)[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone



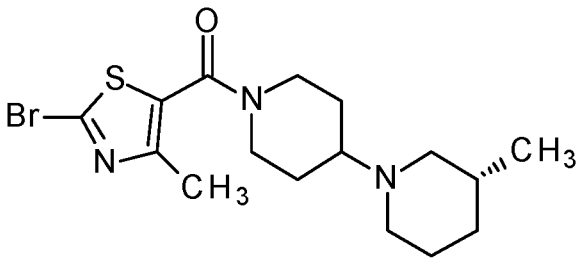
To a solution of 5 g (20.15 mmol) of 2-bromo-4-cyclopropyl-1,3-thiazole-5-carboxylic acid and 5.14 g (20.16 mmol) of (3*R*)-3-methyl-1,4'-bipiperidine hydrochloride (1:1) (WO2015091420 Example 1A; CAS Registry Number 1799475-27-6) in 167 ml of acetonitrile was added 10.5 ml (60.46 mmol) of *N*,*N*-diisopropylethylamine, followed by dropwise addition to the reaction solution, at room temperature, of 15.6 ml (26.20 mmol) of a 50% T3P solution in ethyl acetate (2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphorinane 2,4,6-trioxide). After the addition had ended, the reaction solution was stirred at room temperature overnight. Subsequently, the solution was concentrated to dryness under reduced pressure and taken up in about 50 ml of dichloromethane. The organic solution obtained was washed with saturated sodium hydrogencarbonate solution, then the organic phase was separated off and filtered through a hydrophobic filter (pleated filter, MN 616 WA 1/4, D = 12.5 cm), dried and concentrated to dryness under reduced pressure. The residue obtained was purified further by column chromatography on silica gel (Isolera Biotage Sfähr 25 g column, eluent: dichloromethane → gradient over 15 CV (CV = column volumes) → dichloromethane/methanol 85:15). This gave 6.51 g (15.79 mmol, 78% of theory) of the target compound.

$^1$H-NMR (400 MHz, DMSO-$d_6$, δ/ppm): 0.74-0.84 (m, 4H, therein at 0.82 (d, 3H)), 0.84-0.91 (m, 2H), 0.95-1.04 (m, 2H), 1.31-1.46 (m, 3H), 1.46-1.67 (m, 3H), 1.69-1.82 (m, 3H), 1.90-1.98 (m, 1H), 2.03 (br. t, 1H), 2.43-2.53 (m, 1H, partly hidden by DMSO), 2.69-2.80 (m, 2H), 2.86-3.07 (m, 2H), 3.82-4.33 (m, 2H).

LC-MS (Method 1): $R_t$ = 0.94 min; m/z = 412/414 $(M+H)^+$.

**Example 28A**

(2-Bromo-4-methyl-1,3-thiazol-5-yl)[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone



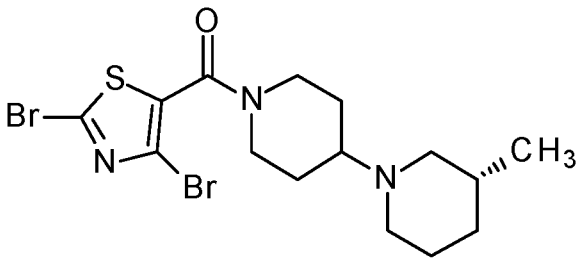
To a solution of 4.7 g (21.17 mmol) of 2-bromo-4-methyl-1,3-thiazole-5-carboxylic acid and 5.4 g (21.17 mmol) of (3*R*)-3-methyl-1,4'-bipiperidine hydrochloride (1:1) (WO2015091420 Example 1A; CAS Registry Number 1799475-27-6) in 176 ml of acetonitrile was added 11.1 ml (63.50 mmol) of *N*,*N*-diisopropylethylamine, followed by dropwise addition to the reaction solution, at room temperature, of 16.4 ml (27.52 mmol) of a 50% T3P solution in ethyl acetate (2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphorinane 2,4,6-trioxide). After the addition had ended, the reaction solution was stirred at room temperature overnight. Subsequently, the solution was concentrated to dryness under reduced pressure and taken up in about 50 ml of dichloromethane. The organic solution obtained was washed with saturated sodium hydrogencarbonate solution, then the organic phase was separated off and filtered through a hydrophobic filter (pleated filter, MN 616 WA 1/4, D = 12.5 cm), dried and concentrated to dryness under reduced pressure. The residue obtained was purified further by column chromatography on silica gel (Isolera Biotage Sfähr 25 g column, eluent: dichloromethane → gradient over 15 CV (CV = column volumes) → dichloromethane/methanol 85:15). This gave 6.48 g (16.77 mmol, 79% of theory) of the target compound.

$^1$H-NMR (400 MHz, DMSO-$d_6$, δ/ppm): 0.74-0.88 (m, 4H, therein at 0.82 (d, 3H)), 1.28-1.46 (m, 3H), 1.46-1.67 (m, 3H), 1.67-1.82 (m, 3H), 1.97-2.07 (m, 1H), 2.31 (s, 3H), 2.42-2.53 (m, 1H, partly hidden by DMSO), 2.68-2.79 (m, 2H), 2.82-3.08 (m, 2H), 3.65-4.51 (m, 2H).

LC-MS (Method 1): $R_t$ = 0.74 min; m/z = 386/388 $(M+H)^+$.

**Example 29A**

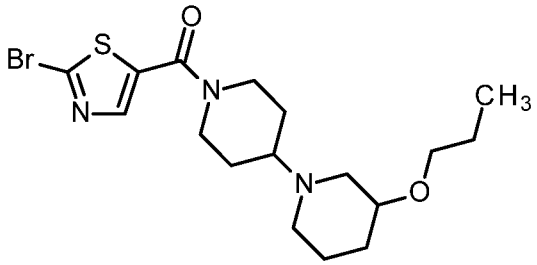
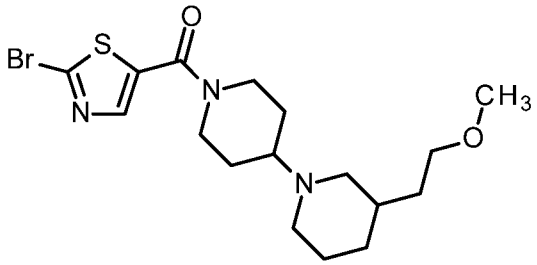
(2,4-Bromo-1,3-thiazol-5-yl)[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone

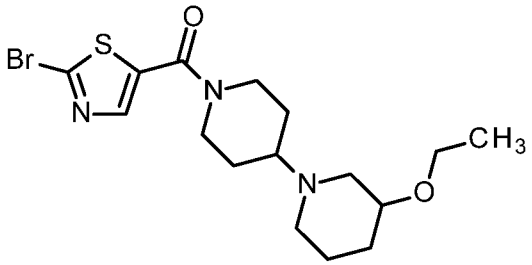
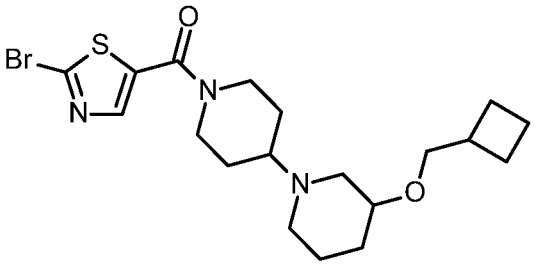


To a solution of 0.5 g (1.74 mmol) of 2,4-dibromo-1,3-thiazole-5-carboxylic acid and 0.45 g (1.74 mmol) of (3*R*)-3-methyl-1,4'-bipiperidine hydrochloride (1:1) (WO2015091420 Example 1A; CAS Registry Number 1799475-27-6) in 14 ml of acetonitrile was added 0.91 ml (5.23 mmol) of *N*,*N*-diisopropylethylamine, followed by dropwise addition to the reaction solution, at room temperature, of 1.35 ml (2.27 mmol) of a 50% T3P solution in ethyl acetate (2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphorinane 2,4,6-trioxide). After the addition had ended, the reaction solution was stirred at room temperature overnight. Subsequently, the solution was concentrated to dryness under reduced pressure and taken up in about 50 ml of dichloromethane. The organic solution obtained was washed with saturated sodium hydrogencarbonate solution, then the organic phase was separated off and filtered through a hydrophobic filter (pleated filter, MN 616 WA 1/4, D = 12.5 cm), dried and concentrated to dryness under reduced pressure. This gave 0.52 g (1.12 mmol, 65% of theory) of the target compound.

LC-MS (Method 1): $R_t$ = 0.87 min; m/z = 449 $(M+H)^+$.

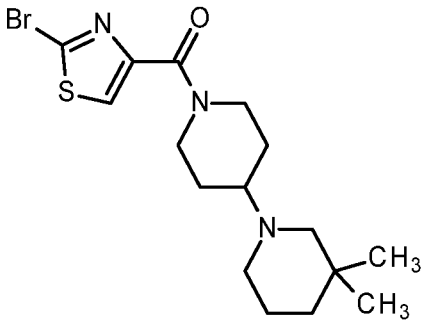
**Analogously to Examples 20A to 24A, the following compounds of Examples 30A to 33A were prepared from the respectively specified starting materials:**

| Example | Name / Structure / Starting material | Analytical data |
|---|---|---|
| **30A** | (2-Bromo-1,3-thiazol-5-yl)[3-propoxy[1,4'-bipiperidine]-1'-yl]methanone (*racemic*)<br>  <br>from 1-[(2-bromo-1,3-thiazol-5-yl)carbonyl]piperidin-4-one and 3-propoxypiperidine (*racemic*) | LC-MS (Method 1):<br>$R_t$ = 0.90 min; m/z = 416/418 $(M+H)^+$. |
| **31A** | (2-Bromo-1,3-thiazol-5-yl)-3-(2-methoxyethyl)[1,4'-bipiperidine]-1'-yl]methanone (*racemic*)<br>  <br>from 1-[(2-bromo-1,3-thiazol-5-yl)carbonyl]piperidin-4-one and 3-(2-methoxyethyl)piperidine hydrochloride (1:1) (*racemic*) | LC-MS (Method 1):<br>$R_t$ = 0.79 min; m/z = 416/418 $(M+H)^+$. |

| Example | Name / Structure / Starting material | Analytical data |
|---|---|---|
| **32A** | (2-Bromo-1,3-thiazol-5-yl)[3-ethoxy[1,4'-bipiperidine]-1'-yl]methanone (*racemic*)<br>  <br>from 1-[(2-bromo-1,3-thiazol-5-yl)carbonyl]piperidin-4-one and 3-ethoxypiperidine (*racemic*) | LC-MS (Method 1):<br>$R_t$ = 0.75 min; m/z = 402/404 $(M+H)^+$. |
| **33A** | (2-Bromo-1,3-thiazol-5-yl)[3-(cyclobutylmethoxy)[1,4'-bipiperidine]-1'-yl]methanone (*racemic*)<br>  <br>from 1-[(2-bromo-1,3-thiazol-5-yl)carbonyl]piperidin-4-one and 3-(cyclobutylmethoxy)piperidine hydrochloride (1:1) (*racemic*) | LC-MS (Method 1):<br>$R_t$ = 1.08 min; m/z = 442/444 $(M+H)^+$. |

**Example 34A**

(2-Bromo-1,3-thiazol-4-yl)(3,3-dimethyl[1,4'-bipiperidine]-1'-yl)methanone



To a solution of 116 mg (0.56 mmol) of 2-bromo-1,3-thiazole-4-carboxylic acid and 150 mg (0.56 mmol) of 3,3-dimethyl-1,4'-bipiperidine dihydrochloride (WO2021089683 Example 48A; CAS Registry Number 2642237-13-4) in 5 ml of acetonitrile was added 0.29 ml (1.67 mmol) of *N,N*-diisopropylethylamine, followed by dropwise addition to the reaction solution, at room temperature, of 0.43 ml (0.72 mmol) of a 50% T3P solution in ethyl acetate (2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphorinane 2,4,6-trioxide). After the addition had ended, the reaction solution was stirred at room temperature overnight. Subsequently, water was added to the solution, which was extracted with ethyl acetate. After the organic phase had been separated off, the organic solution obtained was washed with saturated sodium chloride solution, the organic phase was then separated off and filtered through a hydrophobic filter (pleated filter, MN 616 WA 1/4, D = 12.5 cm), dried and concentrated to dryness under reduced pressure.

The resultant residue was purified by preparative HPLC.

**Method:**

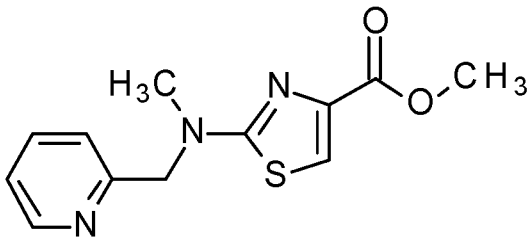
Instrument: Waters Prep LC/MS system, column: XBridge C18 5 µm 100 x 30 mm. Eluent A: water, eluent B: acetonitrile, eluent C: 2% ammonia in water, eluent D: acetonitrile/water (80% by vol. / 20% by vol.), total flow rate: 80 ml/min, room temperature, wavelength: 200-400 nm, at-column injection (complete injection); gradient profile: eluent A 0 to 2 min 39 ml, eluent B 0 to 2 min 31 ml, eluent A 2 to 10 min from 39 ml to 15 ml and eluent B from 31 ml to 55 ml, 10 to 12 min 0 ml eluent A and 70 ml eluent B. Constant flow rate of eluent C and eluent D of 5 ml/min each over the entire run time.

In this way, 73 mg (34% of theory, 0.19 mmol, 100% purity) of the title compound was obtained.

LC-MS (Method 1): $R_t$ = 0.79 min; m/z = 386/388 $(M+H)^+$.

**Example 35A**

Methyl 2-[methyl(pyridin-2-ylmethyl)amino]-1,3-thiazole-4-carboxylate



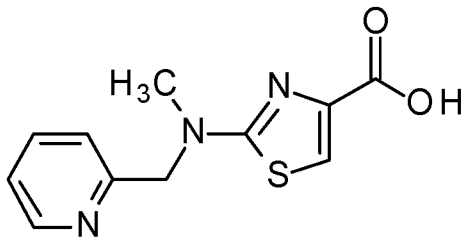
Methyl 2-bromo-1,3-thiazole-4-carboxylate (182 mg, 0.82 mmol) and *N*-methyl-1-(pyridin-2-yl)methanamine (100 mg, 0.82 mmol) were dissolved in 2 ml of 1-methyl-2-pyrrolidone, and 0.42 ml of N,N-diisopropylethylamine was added. Thereafter, the reaction mixture (closed vessel) was stirred at 140°C overnight. After cooling to room temperature, the reaction mixture was taken up in ethyl acetate, and washed with water and saturated sodium chloride solution. The organic phase was subsequently separated off and filtered through a hydrophobic filter (pleated filter, MN 616 WA 1/4, D = 12.5 cm) and concentrated to dryness under reduced pressure. The resulting residue was purified by preparative HPLC (column: Chromatorex C18 10 µm, 125 x 40 mm; wavelength 210 nm; eluent A = water, B = acetonitrile; gradient: 5 min 10% B; 20 min 95% B; flow rate: 100 ml/min; 0.05% formic acid). The product-containing fractions were combined and concentrated and the residue was dried under high vacuum. This gave 109 mg (50% of theory, 0.41 mmol) of the target compound.

LC-MS (Method 1): $R_t$ = 1.05 min; MS (ESIpos): m/z = 264 $[M+H]^+$

$^1$H-NMR (400 MHz, DMSO-d6) δ [ppm]: 3.14 (s, 3H), 3.75 (s, 3H), 4.79 (s, 2H), 7.24-7.33 (m, 2H), 7.64 (s, 1H), 7.77 (td, 1H), 8.51-8.56 (m, 1H).

**Example 36A (HAHN 10982-2-1)**

2-[Methyl(pyridin-2-ylmethyl)amino]-1,3-thiazole-4-carboxylic acid

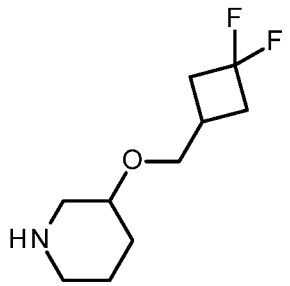


Methyl 2-[methyl(pyridin-2-ylmethyl)amino]-1,3-thiazole-4-carboxylate (340 mg, 1.29 mmol) was dissolved in 12 ml of methanol, 6.5 ml of a 1*N* sodium hydroxide solution (1.0 M, 6.5 mmol) was added, and the mixture was stirred at room temperature overnight. Thereafter, the reaction mixture was concentrated to dryness, dissolved completely in water and adjusted to pH 3-4 with a 1*N* hydrochloric acid solution. The resulting solution was concentrated, stirred with methanol and filtered, and the filtrate was concentrated to dryness under reduced pressure. This gave 134 mg (100% purity, 0.54 mmol, 42% of theory) of the target compound.

LC-MS (Method 1): $R_t$ = 0.71 min; MS (ESIpos): m/z = 250 $[M+H]^+$.

**Example 37A**

3-[(3,3-Difluorocyclobutyl)methoxy]piperidine (racemate)



2.19 g (9.29 mmol) of 3-[(3,3-difluorocyclobutyl)methoxy]pyridine (WO2021089683 Example 11A) was dissolved in 50 ml of ethanol, 0.5 ml (9.28 mmol) of sulfuric acid and 211 mg (0.93 mmol) of platinum(IV) oxide were added, and hydrogenation was effected under standard hydrogen pressure overnight. On completion of conversion, the reaction mixture was filtered through Celite, and the filtrate was then concentrated to dryness. The resulting residue was purified by preparative HPLC.

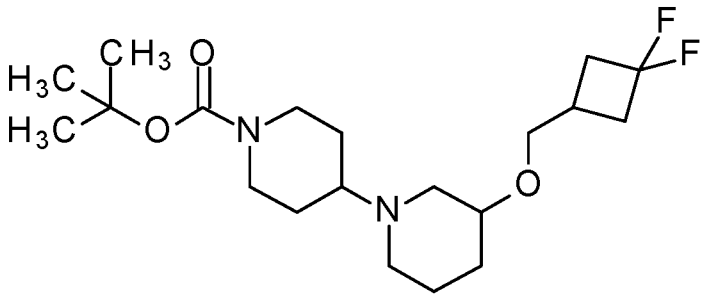
Method:

Instrument: Waters Prep LC/MS system, column: XBridge C18 5 µm 100 x 30 mm. Eluent A: water, eluent B: acetonitrile, eluent C: 2% ammonia in water, eluent D: acetonitrile/water (80% by vol./20% by vol.), total flow rate: 80 ml/min, room temperature, wavelength: 200-400 nm, at-column injection (complete injection); gradient profile: eluent A 0 to 2 min 70 ml, eluent B 0 to 2 min 0 ml, eluent A 2 to 10 min from 70 ml to 0 ml and eluent B from 0 ml to 70 ml, 10 to 12 min 0 ml eluent A and 70 ml eluent B. Constant flow rate of eluent C and eluent D of 5 ml/min each over the entire run time.

The product-containing fractions were combined and lyophilized. 388 mg of the target compound was obtained. The target compound was converted further without analysis.

**Example 38A**

*tert*-Butyl 3-[(3,3-difluorocyclobutyl)methoxy][1,4'-bipiperidine]-1'-carboxylate (*racemic*)



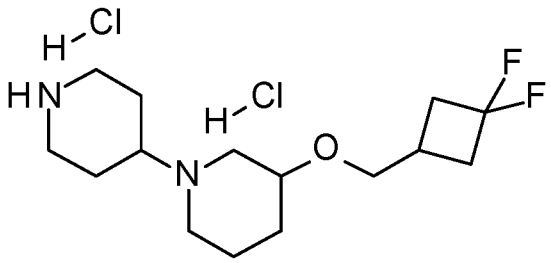
*tert*-Butyl 4-oxopiperidine-1-carboxylate (340 mg, 1.71 mmol) and 3-[(3,3-difluorocyclobutyl)methoxy]piperidine (*racemic*) (350 mg, 1.71 mmol) formed an initial charge in 10 ml of dichloromethane. Subsequently, concentrated acetic acid (146 µl, 2.56 mmol) was added and the mixture was stirred at room temperature for 1 h. Sodium triacetoxyborohydride (434 mg, 2.05 mmol) was added, and the mixture was stirred at room temperature overnight. Water was added to the reaction mixture, which was extracted with dichloromethane. The organic phase was subsequently separated off and filtered through a hydrophobic filter (pleated filter, MN 616 WA 1/4, D = 12.5 cm) and concentrated to dryness under reduced pressure. The residue was purified by preparative HPLC (instrument: Waters Prep LC/MS system, column: XBridge C18 5 µm 100 x 30 mm. Eluent A: water, eluent B: acetonitrile, eluent C: 2% ammonia in water, eluent D: acetonitrile/water (80% by vol. / 20% by vol.), total flow rate: 80 ml/min, room temperature, wavelength: 200-400 nm, at-column injection (complete injection); gradient profile: eluent A 0 to 2 min 39 ml, eluent B 0 to 2 min 31 ml, eluent A 2 to 10 min from 39 ml to 15 ml and eluent B from 31 ml to 55 ml, 10 to 12 min 0 ml eluent A and 70 ml eluent B. Constant flow rate of eluent C and

eluent D of 5 ml/min each over the entire run time). The product-containing fractions were combined and lyophilized. This gave 67 mg (0.17 mmol, 10% of theory) of the target compound.

$^1$H-NMR (400 MHz, DMSO-d6) δ [ppm]: 0.99-1.14 (m, 1H), 1.19-1.45 (m, 13H, therein at 1.38 (s, 9H), 1.58-1.69 (m, 3H), 1.84-1.93 (m, 1H), 1.96 (t, 1H), 2.08 (t, 1H), 2.22-3.37 (m, 3H), 2.37-2.47 (m, 1H), 2-48-2.71 (m, 4H, partly hidden by DMSO), 2.92 (br. d, 1H), 3.21-3.36 (m, 1H, partly hidden by $H_2O$), 3.39-3.51 (m, 2H), 3.95 (br. d, 2H).

**Example 39A**

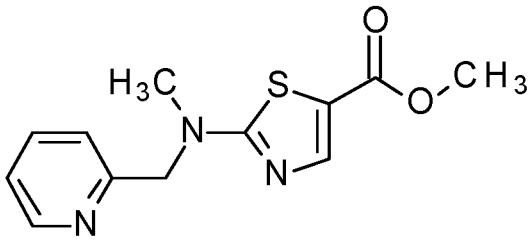
3-[(3,3-Difluorocyclobutyl)methoxy]-1,4'-bipiperidine dihydrochloride (*racemic*)



To a solution of *tert*-butyl 3-[(3,3-difluorocyclobutyl)methoxy][1,4'-bipiperidine]-1'-carboxylate *(racemic)* (65 mg, 0.17 mmol) in 5 ml of dichloromethane was added hydrochloric acid in 1,4-dioxane (0.2 ml, 4.0 M, 0.84 mmol), and the mixture was stirred at room temperature overnight. The reaction mixture was concentrated to dryness under reduced pressure. 60 mg of the target compound was obtained. The target compound was converted further without purification and without analysis.

**Example 40A**

Methyl 2-[methyl(pyridin-2-ylmethyl)amino]-1,3-thiazole-5-carboxylate



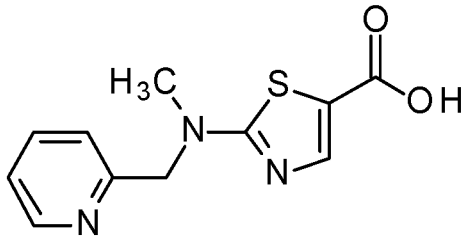
Methyl 2-bromothiazole-5-carboxylate (1.82 g, 8.19 mmol) and *N*-methyl-1-(pyridin-2-yl)methanamine (1 g, 8.19 mmol) were dissolved in 50 ml of 1-methyl-2-pyrrolidone, and 3 ml of *N*,*N*-diisopropylethylamine was added. Thereafter, the reaction mixture (closed vessel) was stirred at 140°C overnight. After cooling to room temperature, the reaction mixture was taken up in ethyl acetate, and washed with water and saturated sodium chloride solution. The organic phase was subsequently separated off and filtered through a hydrophobic filter (pleated filter, MN 616 WA 1/4, D = 12.5 cm) and concentrated to dryness under reduced pressure. The resulting residue was purified by preparative HPLC (column: Chromatorex C18 10 µm, 125 x 40 mm; wavelength 210 nm; eluent A = water, B = acetonitrile; gradient: 5 min 10% B; 20 min 95% B; flow rate: 100 ml/min; 0.05% formic acid). The product-containing fractions were combined and concentrated and the residue was dried under high vacuum. This gave 879 mg (41% of theory, 0.33 mmol) of the target compound.

LC-MS (Method 1): $R_t$ = 1.22 min; MS (ESIpos): m/z = 264 $[M+H]^+$.

$^1$H-NMR (400 MHz, DMSO-d6) δ [ppm]: 3.21 (s, 3H), 3.73 (s, 3H), 4.85 (s, 2H), 7.26-7.34 (m, 2H), 7.78 (td, 1H), 7.85 (s, 1H), 8.53 (d, 1H).

**Example 41A**

2-[Methyl(pyridin-2-ylmethyl)amino]-1,3-thiazole-4-carboxylic acid



Methyl 2-[methyl(pyridin-2-ylmethyl)amino]-1,3-thiazole-5-carboxylate (870 mg, 3.30 mmol) was dissolved in 32 ml of methanol, 16.5 ml of a 1*N* sodium hydroxide solution (1.0 M, 6.5 mmol) was added, and the mixture was stirred at room temperature overnight. Thereafter, the reaction mixture was concentrated to dryness, dissolved completely in water and adjusted to pH 3-4 with a 1*N* hydrochloric acid solution. The resulting solution was concentrated to dryness under reduced pressure. The residue was purified by preparative HPLC.

Method:

Instrument: Waters Prep LC/MS system, column: Phenomenex Kinetex C18 5µm 100 x 30 mm. Eluent A: water, eluent B: acetonitrile, eluent C: 2% formic acid in water, eluent D: acetonitrile/water (80% by vol./20% by vol.), total flow rate: 80 ml/min, room temperature, wavelength: 200-400 nm, at-column injection (complete injection); gradient profile: eluent A 0 to 2 min 70 ml, eluent B 0 to 2 min 0 ml, eluent A 2 to 10 min from 70 ml to 55 ml and eluent B from 0 ml to 15 ml, 10 to 12 min 0 ml eluent A and 70 ml eluent B. Constant flow rate of eluent C and eluent D of 5 ml/min each over the entire run time.

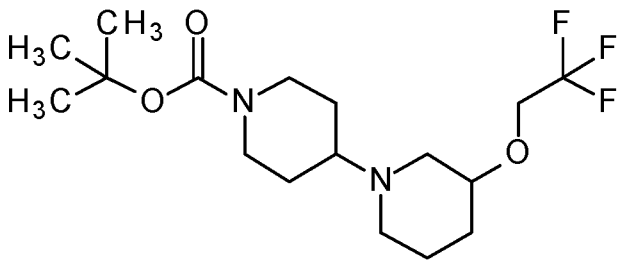
The product-containing fractions were combined and lyophilized. This gave 550 mg (2.21 mmol, 67% of theory) of the target compound.

LC-MS (Method 1): $R_t$ = 0.74 min; MS (ESIpos): m/z = 250 $[M+H]^+$.

$^1$H-NMR (400 MHz, DMSO-d6) δ [ppm]: 3.20 (s, 3H), 4.84 (s, 2H), 7.25-7.34 (m, 2H), 7.73-7.82 (m, 2H), 8.53 (d, 1H).

**Example 42A**

*tert*-Butyl 3-(2,2,2-trifluoroethoxy)[1,4'-bipiperidine]-1'-carboxylate (*racemic*)

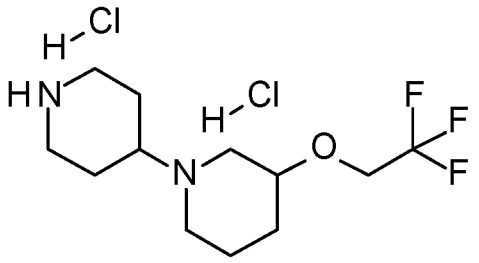


*tert*-Butyl 4-oxopiperidine-1-carboxylate (500 mg, 2.51 mmol) and 3-(2,2,2-trifluoroethoxy)piperidine (*racemic*) (460 mg, 2.51 mmol) formed an initial charge in 15 ml of dichloromethane. Subsequently, concentrated acetic acid (215 µl, 3.76 mmol) was added and the mixture was stirred at room temperature for 2 h. Sodium triacetoxyborohydride (658 mg, 3.01 mmol) was added, and the mixture was stirred at room temperature overnight. The reaction mixture was diluted with dichloromethane and washed with saturated sodium hydrogencarbonate solution. The organic phase was subsequently separated off and filtered through a hydrophobic filter (pleated filter, MN 616 WA 1/4, D = 12.5 cm) and concentrated to dryness under reduced pressure. The residue was purified by preparative HPLC (instrument: Waters Prep LC/MS system, LC-MS: $R_t$ = 2.03 min; MS (ESIpos): m/z = 366 $[M]^+$. Column: XBridge C18 5 µm 100 x 30 mm. Eluent A: water, eluent B: acetonitrile, eluent C: 2% ammonia in water, eluent D: acetonitrile/water (80% by vol. / 20% by

vol.), total flow rate: 80 ml/min, room temperature, wavelength: 200-400 nm, at-column injection (complete injection); gradient profile: eluent A 0 to 2 min 39 ml, eluent B 0 to 2 min 31 ml, eluent A 2 to 10 min from 39 ml to 15 ml and eluent B from 31 ml to 55 ml, 10 to 12 min 0 ml eluent A and 70 ml eluent B. Constant flow rate of eluent C and eluent D of 5 ml/min each over the entire run time). The product-containing fractions were combined and lyophilized. 450 mg (1.23 mmol, 49% of theory) of the target compound was obtained and converted without further analysis.

**Example 43A**

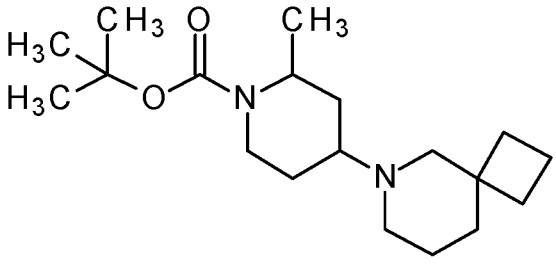
3-(2,2,2-Trifluoroethoxy)-1,4'-bipiperidine dihydrochloride (*racemic*)



To a solution of *tert*-butyl 3-(2,2,2-trifluoroethoxy)[1,4'-bipiperidine]-1'-carboxylate (*racemic*) (446 mg, 1.22 mmol) in 20 ml of dichloromethane was added hydrochloric acid in 1,4-dioxane (1.5 ml, 4.0 M, 6.09 mmol), and the mixture was stirred at room temperature overnight. The reaction mixture was concentrated to dryness under reduced pressure. 399 mg of the target compound was obtained. The target compound was converted further without purification and without analysis.

**Example 44A**

*tert*-Butyl 4-(6-azaspiro[3.5]nonan-6-yl)-2-methylpiperidine-1-carboxylate (diastereomer mixture)



*tert*-Butyl 2-methyl-4-oxopiperidine-1-carboxylate (*racemic*) (100 mg, 0.47 mmol), 6-azaspiro[3.5]nonane hydrochloride (1:1) (83 mg, 0.52 mmol) formed an initial charge in 2 ml of dichloromethane. Subsequently, concentrated acetic acid (40 µl, 0.70 mmol) was added and the mixture was stirred at room temperature overnight. Subsequently, sodium triacetoxyborohydride (119 mg, 0.56 mmol) was added and the mixture was stirred at room temperature for 96 h. The reaction mixture was diluted with dichloromethane and washed with saturated sodium hydrogencarbonate solution. The organic phase was subsequently separated off and filtered through a hydrophobic filter (pleated filter, MN 616 WA 1/4, D = 12.5 cm) and concentrated to dryness under reduced pressure. The residue was purified by preparative HPLC.

Method:

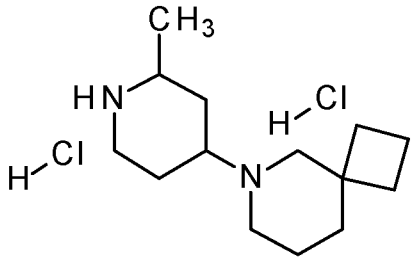
Instrument: Waters Prep LC/MS system, column: XBridge C18 5 µm 100 x 30 mm. Eluent A: water, eluent B: acetonitrile, eluent C: 2% ammonia in water, eluent D: acetonitrile/water (80% by vol. / 20% by vol.), total flow rate: 80 ml/min, room temperature, wavelength: 200-400 nm, at-column injection (complete injection); gradient profile: eluent A 0 to 2 min 23 ml, eluent B 0 to 2 min 47 ml, eluent A 2 to 10 min from 23 ml to 0 ml and eluent B from 47 ml to 70 ml, 10 to 12 min 0 ml eluent A and 70 ml eluent B. Constant flow rate of eluent C and eluent D of 5 ml/min each over the entire run time.

The product-containing fractions were combined and lyophilized. This gave 54 mg (0.16 mmol, 35% of theory) of the target compound.

LC-MS (Method 3): *Diastereomer 1*: $R_t$ = 2.39 min (23.2%); MS (ESIpos): m/z = 323 $[M+H]^+$; *Diastereomer 2*: $R_t$ = 2.42 min (76.8%); MS (ESIpos): m/z = 323 $[M+H]^+$.

**Example 45A**

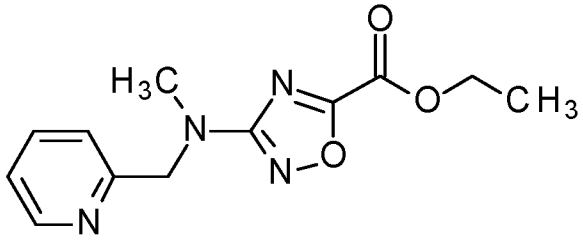
6-(2-Methylpiperidin-4-yl)-6-azaspiro[3.5]nonane dihydrochloride (diastereomer mixture)



To a solution of *tert*-butyl 4-(6-azaspiro[3.5]nonan-6-yl)-2-methylpiperidine-1-carboxylate (*diastereomer mixture*) (53 mg, 0.16 mmol) in 2 ml of dichloromethane was added hydrochloric acid in 1,4-dioxane (1 ml, 4.0 M, 4 mmol), and the mixture was stirred at room temperature overnight. The reaction mixture was concentrated to dryness under reduced pressure. 61 mg of the target compound was obtained. The target compound was converted further without purification and without analysis.

**Example 46A**

Ethyl 3-[methyl(pyridin-2-ylmethyl)amino]-1,2,4-oxadiazole-5-carboxylate

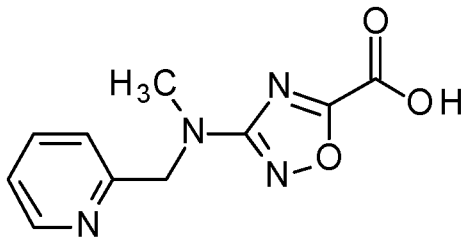


*N*-Methyl-1-(pyridin-2-yl)methanamine (276 mg, 2.26 mmol) was dissolved in 10 ml of acetonitrile, followed by addition of 0.79 ml of *N*,*N*-diisopropylethylamine and ethyl 3-bromo-1,2,4-oxadiazole-5-carboxylate (500 mg, 2.26 mmol). Thereafter, the reaction mixture was stirred at reflux for three hours. After cooling to room temperature, the reaction mixture was concentrated to dryness under reduced pressure. The resulting residue was purified by preparative HPLC (column: Chromatorex C18 10 µm, 125 x 40 mm; wavelength 210 nm; eluent A = water, B = acetonitrile; gradient: 5 min 10% B; 20 min 95% B; flow rate: 100 ml/min; 0.05% formic acid). The product-containing fractions were combined and concentrated and the residue was dried under high vacuum. This gave 181 mg (30% of theory, 0.69 mmol) of the target compound.

LC-MS (Method 1): $R_t$ = 1.22 min; MS (ESIpos): m/z = 263 $[M+H]^+$.

**Example 47A**

3-[Methyl(pyridin-2-ylmethyl)amino]-1,2,4-oxadiazole-5-carboxylic acid



Ethyl 3-[methyl(pyridin-2-ylmethyl)amino]-1,2,4-oxadiazole-5-carboxylate (180 mg, 0.69 mmol) was dissolved in 7 ml of methanol, 3.4 ml of a 1*N* sodium hydroxide solution (1.0 M, 3.4 mmol) was added, and the mixture was stirred at room temperature overnight. Thereafter, the reaction mixture was concentrated to dryness, dissolved completely in water and adjusted to pH 3-4 with a 1*N* hydrochloric acid solution. The resulting solution was concentrated to dryness under reduced pressure. The residue was purified by preparative HPLC.

Method:

Instrument: Waters Prep LC/MS system, column: XBridge C18 5 µm 100 x 30 mm. Eluent A: water, eluent B: acetonitrile, eluent C: 2% ammonia in water, eluent D: acetonitrile/water (80% by vol. / 20% by vol.), total flow rate: 80 ml/min, room temperature, wavelength: 200-400 nm, at-column injection (complete injection); gradient profile: eluent A 0 to 2 min 70 ml, eluent B 0 to 2 min 0 ml, eluent A 2 to 10 min from 70 ml to 55 ml and eluent B from 15 ml to 70 ml, 10 to 12 min 0 ml eluent A and 70 ml eluent B. Constant flow rate of eluent C and eluent D of 5 ml/min each over the entire run time.

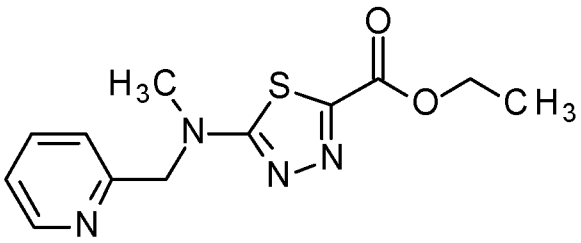
The product-containing fractions were combined and lyophilized. This gave 116 mg (0.49 mmol, 72% of theory) of the target compound.

LC-MS (Method 3): $R_t$ = 0.33 min; MS (ESIpos): m/z = 235 $[M+H]^+$.

$^1$H-NMR (400 MHz, DMSO-d6) δ [ppm]: 2.96 (s, 3H), 4.64 (s, 2H), 7.22 (d, 1H), 7.25-7.32 (m, 1H), 7.72-7.80 (m, 1H), 8.50-8.56 (m, 1H).

**Example 48A**

Ethyl 5-[methyl(pyridin-2-ylmethyl)amino]-1,3,4-thiadiazole-2-carboxylate

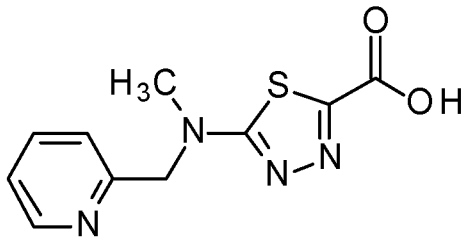


*N*-Methyl-1-(pyridin-2-yl)methanamine (258 mg, 2.11 mmol) was dissolved in 10 ml of acetonitrile, followed by addition of 0.74 ml (4.22 mmol) of *N*,*N*-diisopropylethylamine and ethyl 5-bromo-1,3,4-thiadiazole-2-carboxylate (500 mg, 2.11 mmol). Thereafter, the reaction mixture was stirred at reflux for four hours. After cooling to room temperature, the reaction mixture was concentrated to dryness under reduced pressure. The resulting residue was purified by preparative HPLC (column: Chromatorex C18 10 µm, 125 x 40 mm; wavelength 210 nm; eluent A = water, B = acetonitrile; gradient: 5 min 10% B; 20 min 95% B; flow rate: 100 ml/min; 0.05% formic acid). The product-containing fractions were combined and concentrated and the residue was dried under high vacuum. This gave 539 mg (92% of theory, 1.94 mmol) of the target compound.

LC-MS (Method 1): $R_t$ = 1.17 min; MS (ESIpos): m/z = 279 $[M+H]^+$.

**Example 49A**

5-[Methyl(pyridin-2-ylmethyl)amino]-1,3,4-thiadiazole-2-carboxylic acid



Ethyl 5-[methyl(pyridin-2-ylmethyl)amino]-1,3,4-thiadiazole-2-carboxylate (535 mg, 1.92 mmol) was dissolved in 20 ml of methanol, 9.6 ml of a 1*N* sodium hydroxide solution (1.0 M, 9.6 mmol) was added, and the mixture was stirred at room temperature overnight. Thereafter, the reaction mixture was concentrated to dryness, dissolved completely in water and adjusted to pH 3-4 with a 1*N* hydrochloric acid solution. The resulting solution was concentrated to dryness under reduced pressure. The residue was purified by preparative HPLC.

Method:

Instrument: Waters Prep LC/MS system, column: XBridge C18 5 µm 100 x 30 mm. Eluent A: water, eluent B: acetonitrile, eluent C: 2% ammonia in water, eluent D: acetonitrile/water (80% by vol. / 20% by vol.), total flow rate: 80 ml/min, room temperature, wavelength: 200-400 nm, at-column injection (complete injection); gradient profile: eluent A 0 to 2 min 70 ml, eluent B 0 to 2 min 0 ml, eluent A 2 to 10 min from 70 ml to 55 ml and eluent B from 15 ml to 70 ml, 10 to 12 min 0 ml eluent A and 70 ml eluent B. Constant flow rate of eluent C and eluent D of 5 ml/min each over the entire run time.

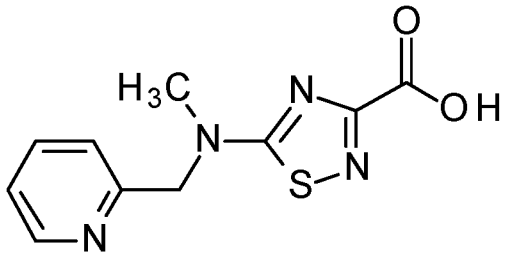
The product-containing fractions were combined and lyophilized. This gave 450 mg (1.80 mmol, 94% of theory) of the target compound.

LC-MS (Method 3): $R_t$ = 0.32 min; MS (ESIpos): m/z = 251 $[M+H]^+$.

$^1$H-NMR (400 MHz, DMSO-d6) δ [ppm]: 3.18 (s, 3H), 4.74 (s, 2H), 7.25-7.33 (m, 2H), 7.77 (td, 1H), 8.53 (d, 1H).

**Example 50A**

5-[Methyl(pyridin-2-ylmethyl)amino]-1,2,4-thiadiazole-3-carboxylic acid



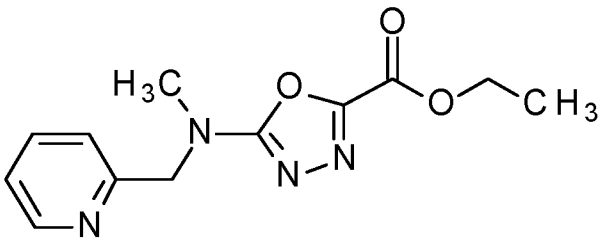
Methyl 5-bromo-1,2,4-thiadiazole-3-carboxylate (500 mg, 2.24 mmol) and *N*-methyl-1-(pyridin-2-yl)methanamine (274 mg, 2.24 mmol) were dissolved in 15 ml of 1-methyl-2-pyrrolidone, and 1.2 ml of *N*,*N*-diisopropylethylamine was added. Thereafter, the reaction mixture (closed vessel) was stirred at 140°C overnight. After cooling to room temperature, the reaction mixture was taken up in ethyl acetate, and washed with water and saturated sodium chloride solution. The organic phase was subsequently separated off and filtered through a hydrophobic filter (pleated filter, MN 616 WA 1/4, D = 12.5 cm) and concentrated to dryness under reduced pressure. The resulting residue was purified by preparative HPLC (column: Chromatorex C18 10 µm, 125 x 40 mm; wavelength 210 nm; eluent A = water, B = acetonitrile; gradient: 5 min 10% B; 20 min 95% B; flow rate: 100 ml/min; 0.05%

formic acid). The product-containing fractions were combined and concentrated and the residue was dried under high vacuum. The resultant residue was dissolved in 20 ml of methanol, 9.6 ml of a 1*N* sodium hydroxide solution (1.0 M, 9.6 mmol) was added, and the mixture was stirred at room temperature overnight. Thereafter, the reaction mixture was concentrated to dryness, dissolved completely in water and adjusted to pH 3-4 with a 1*N* hydrochloric acid solution. The resulting solution was concentrated to dryness under reduced pressure. The residue was repeatedly stirred with methanol and filtered off. The resulting filtrate was concentrated to dryness under reduced pressure. This gave 490 mg (1.82 mmol, 81% of theory) of the target compound.

LC-MS (Method 1): $R_t$ = 0.45 min; MS (ESIpos): m/z = 251 $[M+H]^+$.

**Example 51A**

Ethyl 5-[methyl(pyridin-2-ylmethyl)amino]-1,3,4-oxadiazole-2-carboxylate

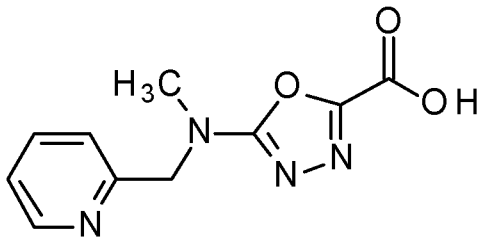


*N*-Methyl-1-(pyridin-2-yl)methanamine (276 mg, 2.26 mmol) was dissolved in 10 ml of acetonitrile, followed by addition of 1.18 ml (6.79 mmol) of *N*,*N*-diisopropylethylamine and ethyl 5-bromo-1,3,4-oxadiazole-2-carboxylate (500 mg, 2.26 mmol). Thereafter, the reaction mixture was stirred at room temperature overnight. The reaction mixture was then concentrated to dryness under reduced pressure. The resulting residue was purified by preparative HPLC (column: Chromatorex C18 10 µm, 125 x 40 mm; wavelength 210 nm; eluent A = water, B = acetonitrile; gradient: 5 min 10% B; 20 min 95% B; flow rate: 100 ml/min; 0.05% formic acid). The product-containing fractions were combined and concentrated and the residue was dried under high vacuum. This gave 324 mg (55% of theory, 1.24 mmol) of the target compound.

LC-MS (Method 4): $R_t$ = 1.09 min; MS (ESIpos): m/z = 263 $[M+H]^+$.

**Example 52A**

5-[Methyl(pyridin-2-ylmethyl)amino]-1,3,4-thiadiazole-2-carboxylic acid



Ethyl 5-[methyl(pyridin-2-ylmethyl)amino]-1,3,4-oxadiazole-2-carboxylate (320 mg, 1.22 mmol) was dissolved in 20 ml of methanol, 6.1 ml of a 1*N* sodium hydroxide solution (1.0 M, 6.1 mmol) was added, and the mixture was stirred at room temperature overnight. Thereafter, the reaction mixture was concentrated to dryness, dissolved completely in water and adjusted to pH 3 with a 1*N* hydrochloric acid solution. The resulting solution was concentrated to dryness under reduced pressure. The residue was purified by preparative HPLC.

Method:

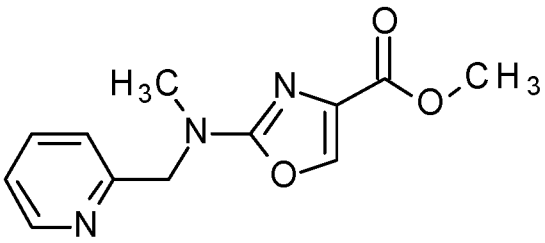
(column: Chromatorex C18 10 µm, 125 x 40 mm; wavelength 210 nm; eluent A = water, B = acetonitrile; gradient: 5 min 10% B; 20 min 95% B; flow rate: 100 ml/min; 0.05% formic acid).

The product-containing fractions were combined and concentrated to dryness under reduced pressure. This gave 412 mg (0.88 mmol, 72% of theory, purity: 50%) of the target compound. The product was converted further without further purification.

LC-MS (Method 1): $R_t$ = 0.25 min; MS (ESIpos): m/z = 235 $[M+H]^+$.

**Example 53A**

Methyl 2-[methyl(pyridin-2-ylmethyl)amino]-1,3-oxazole-4-carboxylate



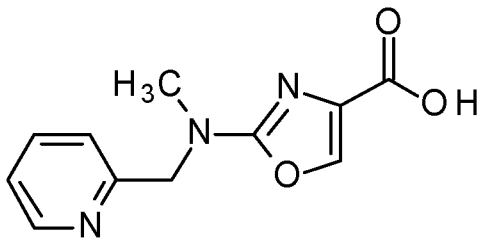
*N*-Methyl-1-(pyridin-2-yl)methanamine (297 mg, 2.43 mmol) was dissolved in 10 ml of acetonitrile, followed by addition of 1.27 ml (7.28 mmol) of *N,N*-diisopropylethylamine and methyl 2-bromo-1,3-oxazole-4-carboxylate (500 mg, 2.43 mmol). Thereafter, the reaction mixture was stirred at room temperature overnight. The reaction mixture was then concentrated to dryness under reduced pressure. The resulting residue was purified by preparative HPLC (column: Chromatorex C18 10 µm, 125 x 40 mm; wavelength 210 nm; eluent A = water, B = acetonitrile; gradient: 5 min 10% B; 20 min 95% B; flow rate: 100 ml/min; 0.05% formic acid). The product-containing fractions were combined and concentrated and the residue was dried under high vacuum. This gave 264 mg (43% of theory, 1.05 mmol; content: 98.8%) of the target compound.

LC-MS (Method 1): $R_t$ = 0.90 min; MS (ESIpos): m/z = 248 $[M+H]^+$.

$^1$H-NMR (400 MHz, DMSO-d6) δ [ppm]: 3.07 (s, 3H), 3.74 (s, 3H), 4.69 (s, 2H), 7.25-7.32 (m, 2H), 7.78 (td, 1H), 8.26 (s, 1H), 8.52 (d, 1H).

**Example 54A**

2-[Methyl(pyridin-2-ylmethyl)amino]-1,3-oxazole-4-carboxylic acid



Methyl 2-[methyl(pyridin-2-ylmethyl)amino]-1,3-oxazole-4-carboxylate (260 mg, 1.05 mmol) was dissolved in 20 ml of methanol, 6.3 ml of a 1*N* sodium hydroxide solution (1.0 M, 5.3 mmol) was added, and the mixture was stirred at room temperature for four hours. Thereafter, the reaction mixture was concentrated to dryness, dissolved completely in water and adjusted to pH 3-4 with a

1*N* hydrochloric acid solution. The resulting solution was concentrated to dryness under reduced pressure. The residue was purified by preparative HPLC.

Method:

Instrument: Waters Prep LC/MS system, column: XBridge C18 5 µm 100 x 30 mm. Eluent A: water, eluent B: acetonitrile, eluent C: 2% ammonia in water, eluent D: acetonitrile/water (80% by vol. / 20% by vol.), total flow rate: 80 ml/min, room temperature, wavelength: 200-400 nm, at-column injection (complete injection); gradient profile: eluent A 0 to 2 min 70 ml, eluent B 0 to 2 min 0 ml, eluent A 2 to 10 min from 70 ml to 55 ml and eluent B from 0 ml to 15 ml, 10 to 12 min 0 ml eluent A and 70 ml eluent B. Constant flow rate of eluent C and eluent D of 5 ml/min each over the entire run time.

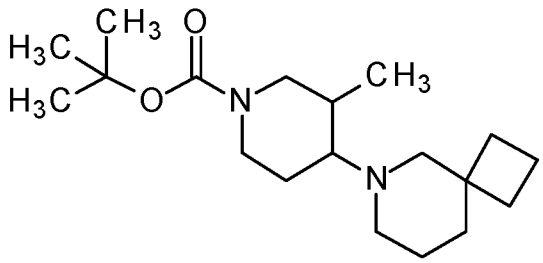
The product-containing fractions were combined and concentrated to dryness under reduced pressure. This gave 156 mg (0.67 mmol, 64% of theory) of the target compound.

LC-MS (Method 1): $R_t$ = 0.60 min; MS (ESIpos): m/z = 234 $[M+H]^+$.

$^1$H-NMR (400 MHz, DMSO-d6) δ [ppm]: 3.02 (s, 3H), 4.66 (s, 2H), 7.24-7.32 (m, 2H), 7.59 (s, 1H), 7.78 (td, 1H), 8.52 (d, 1H).

**Example 55A**

*tert*-Butyl 4-(6-azaspiro[3.5]nonan-6-yl)-3-methylpiperidine-1-carboxylate (diastereomer mixture)



An initial charge of *tert*-butyl 3-methyl-4-oxopiperidine-1-carboxylate (*racemic*) (100 mg, 0.47 mmol), 6-azaspiro[3.5]nonane hydrochloride (1:1) (83 mg, 0.52 mmol), 4 Å molecular sieve and 90 µl (0.52 mmol) of *N*,*N*-diisopropylethylamine in 2 ml of dichloromethane was stirred at room temperature for 10 min. Subsequently, concentrated acetic acid (40 µl, 0.70 mmol) was added and the mixture was stirred at room temperature overnight. Subsequently, sodium triacetoxyborohydride (119 mg, 0.56 mmol) was added and the mixture was stirred at room temperature for 96 h. The

reaction mixture was diluted with dichloromethane and washed with saturated sodium hydrogencarbonate solution. The organic phase was subsequently separated off and filtered through a hydrophobic filter (pleated filter, MN 616 WA 1/4, D = 12.5 cm) and concentrated to dryness under reduced pressure. The residue was purified by preparative HPLC.

Method:

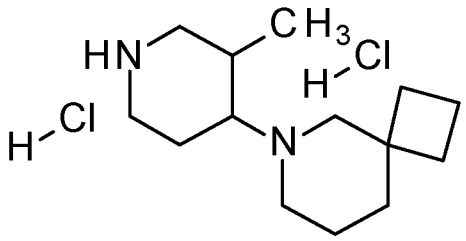
Instrument: Waters Prep LC/MS system, column: XBridge C18 5 µm 100 x 30 mm. Eluent A: water, eluent B: acetonitrile, eluent C: 2% ammonia in water, eluent D: acetonitrile/water (80% by vol. / 20% by vol.), total flow rate: 80 ml/min, room temperature, wavelength: 200-400 nm, at-column injection (complete injection); gradient profile: eluent A 0 to 2 min 23 ml, eluent B 0 to 2 min 47 ml, eluent A 2 to 10 min from 23 ml to 0 ml and eluent B from 47 ml to 70 ml, 10 to 12 min 0 ml eluent A and 70 ml eluent B. Constant flow rate of eluent C and eluent D of 5 ml/min each over the entire run time.

The product-containing fractions were combined and lyophilized. This gave 44 mg (0.14 mmol, 29% of theory) of the target compound.

LC-MS (Method 3): $R_t$ = 2.54 min; MS (ESIpos): m/z = 323 $[M+H]^+$.

**Example 56A**

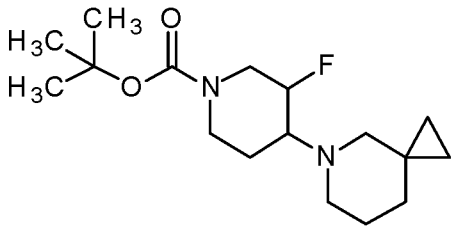
6-(2-Methylpiperidin-4-yl)-6-azaspiro[3.5]nonane dihydrochloride (diastereomer mixture)




To a solution of *tert*-butyl 4-(6-azaspiro[3.5]nonan-6-yl)-3-methylpiperidine-1-carboxylate (diastereomer mixture) (44 mg, 0.14 mmol) in 2 ml of dichloromethane was added hydrochloric acid in 1,4-dioxane (1 ml, 4.0 M, 4 mmol), and the mixture was stirred at room temperature overnight. The reaction mixture was concentrated to dryness under reduced pressure. 55 mg of the target compound was obtained. The target compound was converted further without purification and without analysis.

**Example 57A**

*tert*-Butyl 4-(5-azaspiro[2.5]octan-5-yl)-3-fluoropiperidine-1-carboxylate (*racemic*)



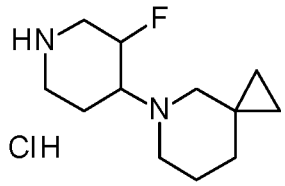
tert-Butyl 3-fluoro-4-oxopiperidine-1-carboxylate (*racemic*) (552 mg, 2.54 mmol), 5-azaspiro[2.5]octane hydrochloride (750 mg, 5.08 mmol) and *N*,*N*-diisopropylethylamine (880 µl, 5.1 mmol) formed an initial charge in 25 ml of dichloromethane. Subsequently, concentrated acetic acid (220 µl, 3.8 mmol) was added and the mixture was stirred at room temperature overnight. Sodium triacetoxyborohydride (646 mg, 3.05 mmol) was added, and stirring of the mixture was continued at room temperature overnight. Water was added to the reaction mixture, which was extracted with dichloromethane. The organic phase was washed with saturated sodium hydrogencarbonate solution and dried over sodium sulfate. The desiccant was filtered off and the filtrate was concentrated. The residue was purified by preparative HPLC (instrument: Waters Prep LC/MS system, column: Phenomenex Kinetex C18 5 µm 100 x 30 mm. Eluent A: water, eluent B: acetonitrile, eluent C: 2% formic acid in water, eluent D: acetonitrile/water (80% by vol./20% by vol.), total flow rate: 80 ml/min, room temperature, wavelength: 200-400 nm, at-column injection (complete injection); gradient profile: eluent A 0 to 2 min 63 ml, eluent B 0 to 2 min 7 ml, eluent A 2 to 10 min from 63 ml to 39 ml and eluent B from 7 ml to 31 ml, 10 to 12 min 0 ml eluent A and 70 ml eluent B. Constant flow rate of eluent C and eluent D of 5 ml/min each over the entire run time). The product-containing fractions were combined and lyophilized. This gave 477 mg (100% purity, 60% of theory) of the target compound.

LC-MS (Method 1): $R_t$ = 0.89 min; MS (ESIpos): m/z = 313 $[M+H]^+$

$^1$H-NMR (400 MHz, DMSO-d6) δ [ppm]: -0.245 (1.80), 0.027 (1.52), 0.999 (0.70), 1.015 (0.67), 1.133 (16.00), 1.328 (0.73), 1.337 (1.03), 1.349 (0.84), 2.086 (1.04), 2.104 (0.83), 2.249 (1.77), 2.254 (3.47), 2.258 (4.67), 2.263 (3.38), 2.267 (1.58), 2.298 (11.37), 2.358 (0.70), 2.371 (0.90), 2.384 (0.60), 2.925 (10.12), 5.507 (1.83), 7.917 (1.62).

**Example 58A**

5-(3-Fluoropiperidin-4-yl)-5-azaspiro[2.5]octane hydrochloride (1:1) (*racemic*)

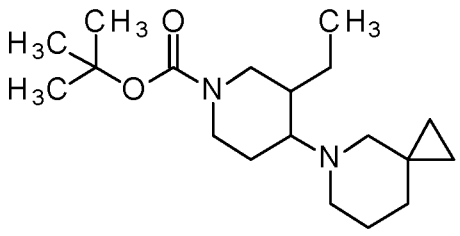



To a solution of *tert*-butyl 4-(5-azaspiro[2.5]octan-5-yl)-3-fluoropiperidine-1-carboxylate (*racemic*) (477 mg, 1.53 mmol) in 15 ml of dichloromethane was added hydrochloric acid in 1,4-dioxane (1.9 ml, 4.0 M, 7.6 mmol), and the mixture was stirred at room temperature overnight. The reaction mixture was concentrated and the residue was dried under high vacuum. This gave 378 mg (100% of theory) of the target compound.

$^1$H-NMR (400 MHz, DMSO-d6) δ [ppm]: 0.463 (8.13), 0.481 (3.22), 0.501 (2.51), 0.525 (2.64), 0.539 (2.24), 0.550 (1.97), 0.627 (1.69), 0.654 (1.89), 0.678 (1.55), 0.985 (1.58), 1.017 (1.40), 1.067 (1.12), 1.100 (1.21), 1.754 (0.69), 1.784 (1.27), 1.820 (2.50), 1.852 (4.13), 1.883 (2.34), 1.983 (1.00), 2.019 (1.17), 2.046 (1.36), 2.077 (1.09), 2.124 (1.24), 2.159 (1.83), 2.191 (1.51), 2.214 (0.64), 2.288 (1.61), 2.319 (2.18), 2.350 (0.96), 2.722 (1.84), 2.751 (3.27), 2.780 (1.63), 2.991 (1.88), 3.022 (1.87), 3.049 (1.30), 3.074 (1.31), 3.103 (1.64), 3.128 (1.53), 3.166 (16.00), 3.219 (1.08), 3.345 (4.01), 3.385 (5.35), 3.501 (1.34), 3.568 (9.70), 3.622 (1.71), 3.655 (3.08), 3.681 (1.86), 3.700 (0.84), 3.714 (0.92), 3.725 (0.87), 3.754 (0.75), 3.806 (1.15), 3.866 (0.69), 3.897 (0.55), 5.613 (1.60), 5.644 (1.31), 5.732 (1.63), 5.760 (3.24), 9.099 (1.20), 10.127 (1.66), 10.747 (1.03), 10.939 (0.87).

**Example 59A**

*tert*-Butyl 4-(5-azaspiro[2.5]octan-5-yl)-3-ethylpiperidine-1-carboxylate (*racemic*)



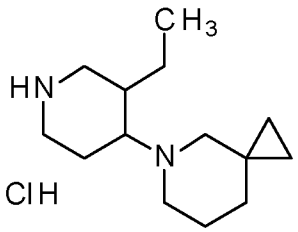
tert-Butyl 3-ethyl-4-oxopiperidine-1-carboxylate (*racemic*) (577 mg, 2.54 mmol), 5-azaspiro[2.5]octane hydrochloride (750 mg, 5.08 mmol) and *N*,*N*-diisopropylethylamine (880 µl, 5.1 mmol) formed an initial charge in 25 ml of dichloromethane. Subsequently, concentrated acetic acid (220 µl, 3.8 mmol) was added and the mixture was stirred at room temperature overnight. Sodium triacetoxyborohydride (646 mg, 3.05 mmol) was added, and stirring of the mixture was continued at room temperature overnight. Water was added to the reaction mixture, which was extracted with dichloromethane. The organic phase was washed with saturated sodium hydrogencarbonate solution and dried over sodium sulfate. The desiccant was filtered off and the filtrate was concentrated. The residue was purified by preparative HPLC (instrument: Waters Prep LC/MS system, column: Phenomenex Kinetex C18 5 µm 100 x 30 mm. Eluent A: water, eluent B: acetonitrile, eluent C: 2% formic acid in water, eluent D: acetonitrile/water (80% by vol./20% by vol.), total flow rate: 80 ml/min, room temperature, wavelength: 200-400 nm, at-column injection (complete injection); gradient profile: eluent A 0 to 2 min 63 ml, eluent B 0 to 2 min 7 ml, eluent A 2 to 10 min from 63 ml to 39 ml and eluent B from 7 ml to 31 ml, 10 to 12 min 0 ml eluent A and 70 ml eluent B. Constant flow rate of eluent C and eluent D of 5 ml/min each over the entire run time). The product-containing fractions were combined and lyophilized. This gave 226 mg (100% purity, 28% of theory) of the target compound.

LC-MS (Method 1): $R_t$ = 1.06 min; MS (ESIpos): m/z = 323 $[M+H]^+$

$^1$H-NMR (400 MHz, DMSO-d6) δ [ppm]: 0.263 (1.70), 0.276 (0.48), 0.869 (0.40), 0.887 (0.76), 0.905 (0.54), 1.380 (16.00), 1.587 (0.46), 1.601 (0.62), 1.615 (0.42), 2.151 (0.73), 2.177 (0.66), 3.169 (6.53), 5.753 (0.62), 8.165 (2.91).

**Example 60A**

5-(3-Ethylpiperidin-4-yl)-5-azaspiro[2.5]octane hydrochloride (1:1) (*racemic*)



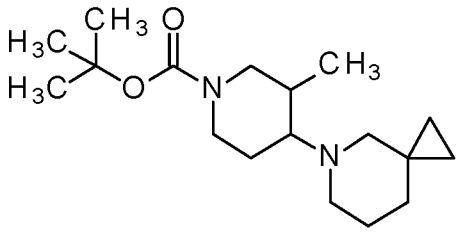

To a solution of *tert*-butyl 4-(5-azaspiro[2.5]octan-5-yl)-3-ethylpiperidine-1-carboxylate (*racemic*) (226 mg, 701 µmol) in 7 ml of dichloromethane was added hydrochloric acid in 1,4-dioxane (880 µl, 4.0 M, 3.5 mmol), and the mixture was stirred at room temperature overnight. The reaction mixture

was concentrated and the residue was dried under high vacuum. This gave 202 mg (111% of theory) of the target compound.

$^1$H-NMR (400 MHz, DMSO-d6) δ [ppm]: 0.475 (0.61), 0.486 (0.53), 0.495 (0.65), 0.525 (0.43), 0.892 (0.66), 0.910 (1.50), 0.928 (1.01), 0.941 (1.21), 0.959 (0.57), 1.800 (0.47), 1.879 (0.42), 2.183 (0.51), 2.838 (0.40), 2.867 (0.47), 3.071 (0.57), 3.399 (0.67), 3.568 (16.00), 5.757 (2.20), 8.145 (0.86).

**Example 61A**

*tert*-Butyl 4-(5-azaspiro[2.5]octan-5-yl)-3-methylpiperidine-1-carboxylate (*racemic*)



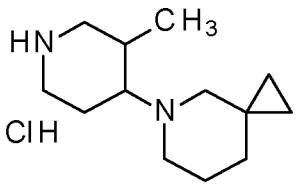
tert-Butyl 3-methyl-4-oxopiperidine-1-carboxylate (*racemic*) (542 mg, 2.54 mmol), 5-azaspiro[2.5]octane hydrochloride (750 mg, 5.08 mmol) and *N*,*N*-diisopropylethylamine (880 µl, 5.1 mmol) formed an initial charge in 25 ml of dichloromethane. Subsequently, concentrated acetic acid (220 µl, 3.8 mmol) was added and the mixture was stirred at room temperature overnight. Sodium triacetoxyborohydride (646 mg, 3.05 mmol) was added, and stirring of the mixture was continued at room temperature overnight. Water was added to the reaction mixture, which was extracted with dichloromethane. The organic phase was washed with saturated sodium hydrogencarbonate solution and dried over sodium sulfate. The desiccant was filtered off and the filtrate was concentrated. The residue was purified by preparative HPLC (instrument: Waters Prep LC/MS system, column: Phenomenex Kinetex C18 5 µm 100 x 30 mm. Eluent A: water, eluent B: acetonitrile, eluent C: 2% formic acid in water, eluent D: acetonitrile/water (80% by vol./20% by vol.), total flow rate: 80 ml/min, room temperature, wavelength: 200-400 nm, at-column injection (complete injection); gradient profile: eluent A 0 to 2 min 63 ml, eluent B 0 to 2 min 7 ml, eluent A 2 to 10 min from 63 ml to 39 ml and eluent B from 7 ml to 31 ml, 10 to 12 min 0 ml eluent A and 70 ml eluent B. Constant flow rate of eluent C and eluent D of 5 ml/min each over the entire run time). The product-containing fractions were combined and lyophilized. This gave 186 mg (100% purity, 24% of theory) of the target compound.

LC-MS (Method 1): $R_t$ = 0.93 min; MS (ESIpos): m/z = 309 $[M+H]^+$

$^1$H-NMR (400 MHz, DMSO-d6) δ [ppm]: 0.268 (1.65), 0.281 (0.64), 0.290 (0.72), 0.305 (0.51), 0.759 (1.44), 0.777 (1.47), 1.380 (16.00), 1.592 (0.49), 1.607 (0.66), 1.620 (0.43), 2.203 (1.77), 3.169 (0.48), 5.754 (0.98), 8.174 (1.37).

**Example 62A**

5-(3-Methylpiperidin-4-yl)-5-azaspiro[2.5]octane hydrochloride (1:1) (*racemic*)



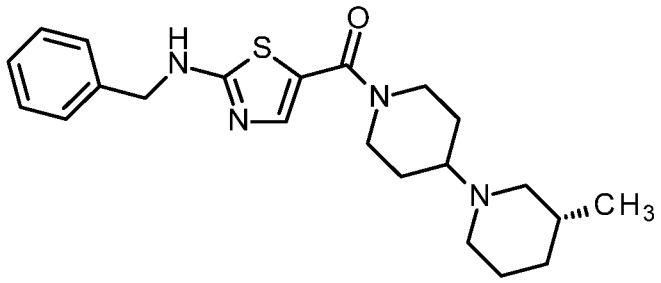

To a solution of *tert*-butyl 4-(5-azaspiro[2.5]octan-5-yl)-3-methylpiperidine-1-carboxylate (*racemic*) (186 mg, 603 µmol) in 6 ml of dichloromethane was added hydrochloric acid in 1,4-dioxane (750 µl, 4.0 M, 3.0 mmol), and the mixture was stirred at room temperature overnight. The reaction mixture was concentrated and the residue was dried under high vacuum. This gave 125 mg (85% of theory) of the target compound.

$^1$H-NMR (400 MHz, DMSO-d6) δ [ppm]: 0.435 (1.48), 0.446 (1.99), 0.462 (2.12), 0.471 (2.80), 0.508 (2.02), 0.520 (1.62), 0.528 (1.53), 0.541 (2.04), 0.551 (1.95), 0.578 (1.29), 0.584 (1.46), 0.596 (1.30), 0.607 (0.80), 0.639 (0.57), 0.651 (0.75), 0.663 (0.88), 0.674 (0.61), 1.029 (1.07), 1.062 (1.20), 1.126 (8.26), 1.144 (8.50), 1.205 (5.77), 1.222 (6.06), 1.632 (0.61), 1.649 (0.61), 1.665 (0.55), 1.768 (0.67), 1.800 (1.62), 1.823 (1.44), 1.858 (1.65), 1.874 (1.70), 1.962 (0.76), 1.995 (1.27), 2.025 (0.98), 2.043 (1.05), 2.055 (0.94), 2.077 (0.96), 2.087 (0.90), 2.133 (0.80), 2.178 (1.40), 2.212 (0.75), 2.584 (0.72), 2.734 (1.31), 2.766 (1.50), 2.809 (1.29), 2.837 (1.88), 2.860 (1.36), 2.955 (0.58), 2.988 (1.56), 3.006 (1.45), 3.021 (1.62), 3.037 (1.89), 3.072 (1.23), 3.089 (1.36), 3.121 (0.53), 3.151 (1.18), 3.167 (16.00), 3.206 (3.19), 3.239 (1.78), 3.287 (1.53), 3.319 (1.42), 3.380 (1.33), 3.490 (1.45), 3.553 (0.73), 3.568 (1.75), 3.626 (1.05), 3.655 (1.64), 3.681 (0.47), 3.700 (0.44), 8.742 (0.87), 9.669 (1.70), 9.956 (0.48).

**Working examples:**

**Example 1**

[2-(Benzylamino)-1,3-thiazol-5-yl][(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone



37 mg (0.10 mmol) of (2-bromo-1,3-thiazol-5-yl)[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone and 21.3 mg (0.2 mmol) of benzylamine were dissolved in 0.8 ml of 1-methyl-2-pyrrolidone in a Zinsser glass vial, and 50 µl of N,N-diisopropylethylamine was added. Thereafter, the vial was placed into a Zinsser metal block, sealed with a sealing mat and agitated at 140°C overnight. After cooling to RT, the solution was filtered and the filtrate was separated into its components by preparative HPLC:

HPLC instrument: Knauer/Labomatik (Chromatorex C18 column, 10 µm, 25*3cm, eluent A: water + 0.1% TFA, eluent B: acetonitrile with gradient; flow rate: 75 ml/min; UV detection: DAD; 210 nm).

The combined fractions were lyophilized and then taken up in ethyl acetate and washed with saturated aqueous sodium hydrogencarbonate solution and then with saturated aqueous sodium chloride solution. The organic phase was separated off, dried over $Mg_2SO_4$ and filtered, and the filtrate was concentrated on a rotary evaporator and dried under high vacuum.

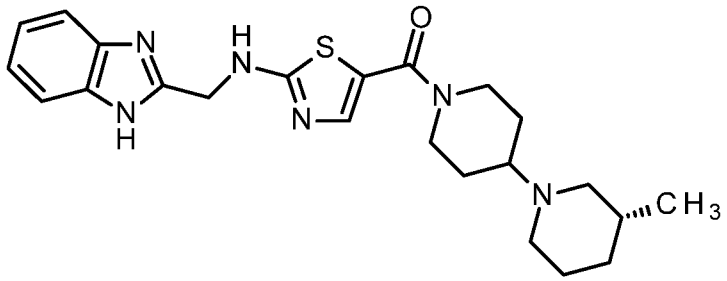
In this way, 20.9 mg (53% of theory, 100% purity) of the title compound was obtained.

LC-MS (Method 2): $R_t$ = 0.58 min; m/z = 399 $(M+H)^+$.

$^1$H.NMR (500 MHz, $(CD_3)_2SO$): δ 8.57 (t, 1H), 7.40 (s, 1H), 7.33 (m, 4H), 7.26 (m, 1H), 4.46 (d, 2H), 4.27 (d, 2H), 2.89 (t, 2H) 2.74 (t, 2H), 2.47 (m, 1H), 2.05 (t, 1H), 1.74 (d, 3H), 1.65 – 1.55 (m, 2H), 1.51 (m, 1H), 1.42 – 1.31 (m, 3H), 0.82 (d, 4H).

**Example 2**

{2-[(1H-Benzimidazol-2-ylmethyl)amino]-1,3-thiazol-5-yl}[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone



37 mg (0.10 mmol) of (2-bromo-1,3-thiazol-5-yl)[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone and 29.4 mg (0.2 mmol) of 1-(1H-benzimidazol-2-yl)methanamine were dissolved in 0.8 ml of 1-methyl-2-pyrrolidone in a Zinsser glass vial, and 50 µl of *N*,*N*-diisopropylethylamine was added. Thereafter, the vial was placed into a Zinsser metal block, sealed with a sealing mat and agitated at 140°C overnight. After cooling to RT, the solution was filtered and the filtrate was separated into its components by preparative LC-MS in accordance with one of the following methods:

Prep. LC-MS methods:

MS instrument: Waters; HPLC instrument: Waters; Waters X-Bridge C18 column, 19 mm x 50 mm, 5 µm, eluent A: water + 0.375% ammonia, eluent B: acetonitrile (ULC) 0.375% ammonia, with gradient; flow rate: 40 ml/min; UV detection: DAD; 210-400 nm.

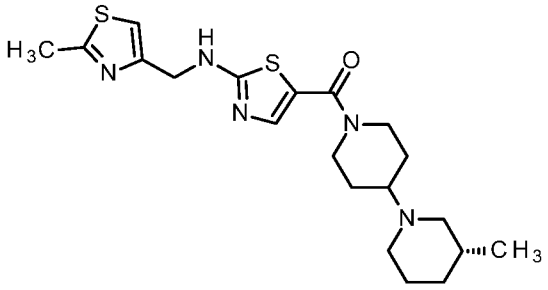
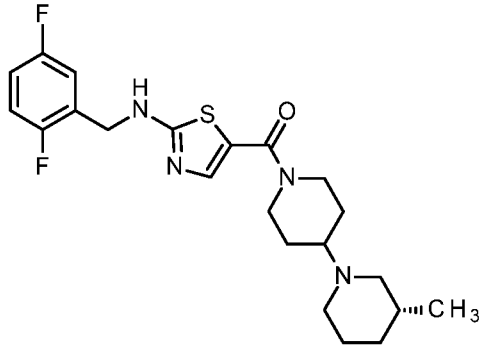
or:

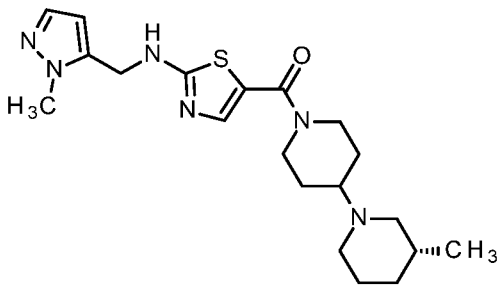
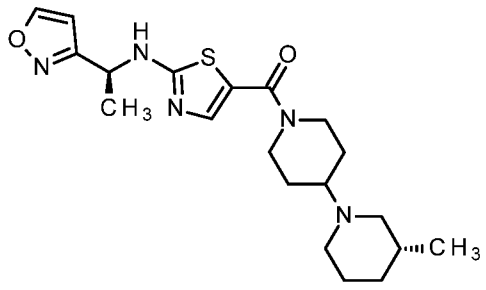
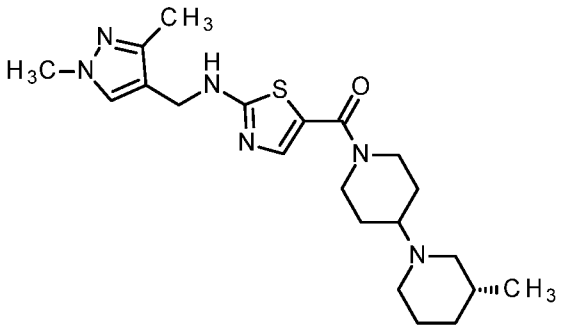
MS instrument: Waters; HPLC instrument: Waters (column: Phenomenex Luna 5µ C18(2) 100A, AXIA Tech. 50 x 21.2 mm), eluent A: water + 0.0375% formic acid, eluent B: acetonitrile (ULC) + 0.0375% formic acid, with gradient; flow rate: 40 ml/min; UV detection: DAD; 210-400 nm.

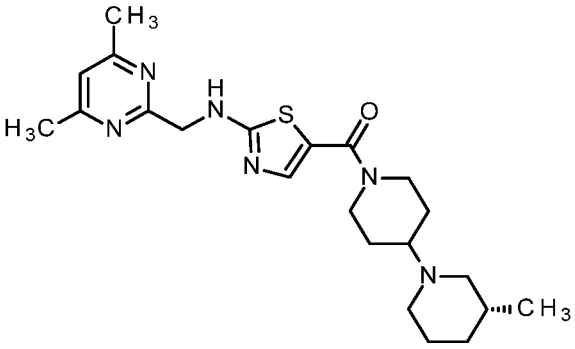
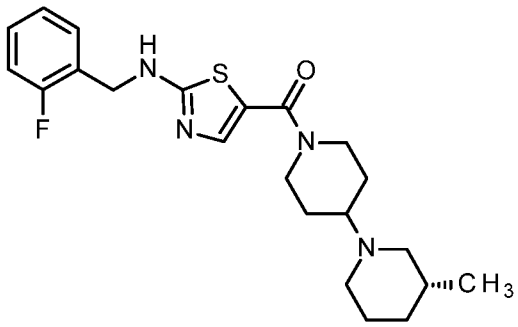
In this way, 15.1 mg (33% of theory, 96% purity) of the title compound was obtained.

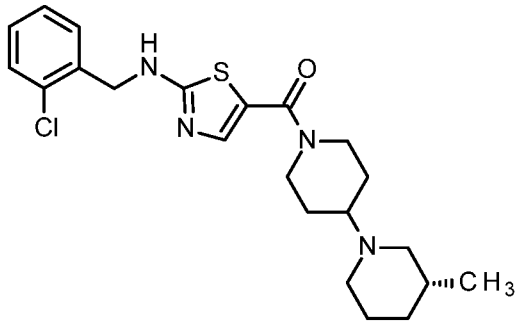
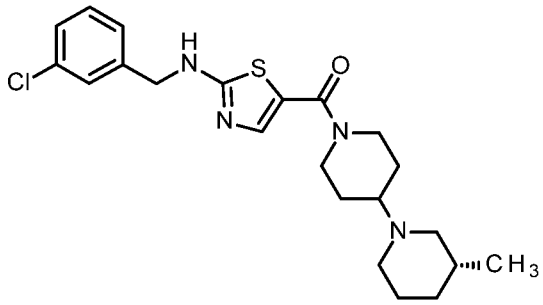
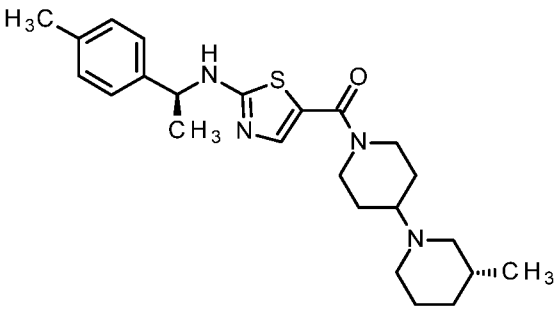
LC-MS (Method 6): $R_t$ = 0.59 min; m/z = 437 $(M-H)^-$.

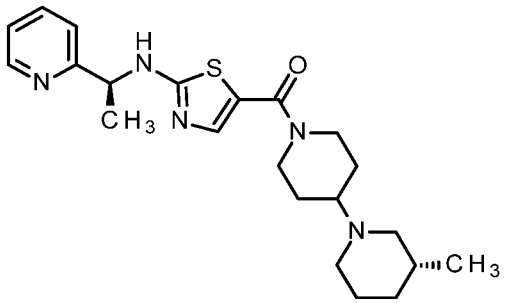
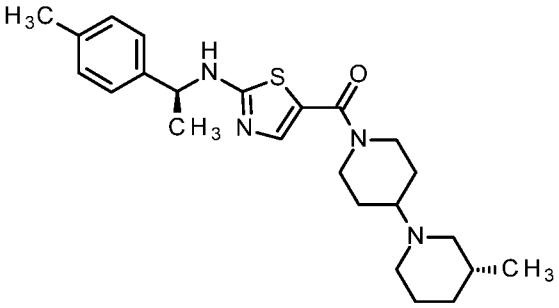
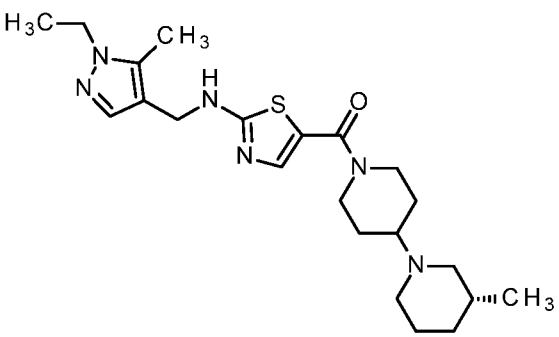
By parallel synthesis analogously to Example 1, the following compounds were prepared proceeding from (2-bromo-1,3-thiazol-5-yl)[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone and the corresponding amine or salt thereof:

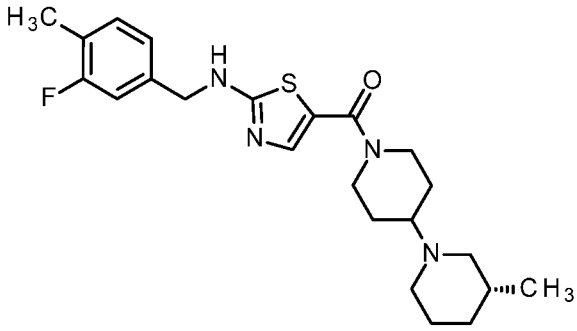
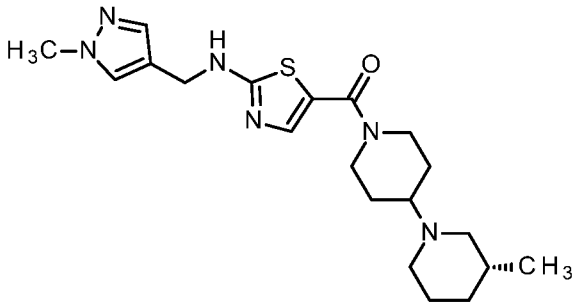
| Example | IUPAC name / structure (yield; purity) | LC-MS (Method 6) |
|---|---|---|
| **3** | [(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl](2-{[(2-methyl-1,3-thiazol-4-yl)methyl]amino}-1,3-thiazol-5-yl)methanone  (5% of theory; 100% purity) | $R_t$ = 0.65 min; m/z = 420 $(M+H)^+$ |
| **4** | {2-[(2,5-difluorobenzyl)amino]-1,3-thiazol-5-yl}[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone  (35% of theory; 100% purity) | $R_t$ = 0.78 min; m/z = 435 $(M+H)^+$ |

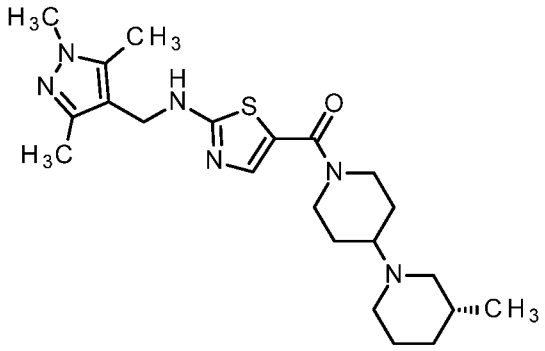
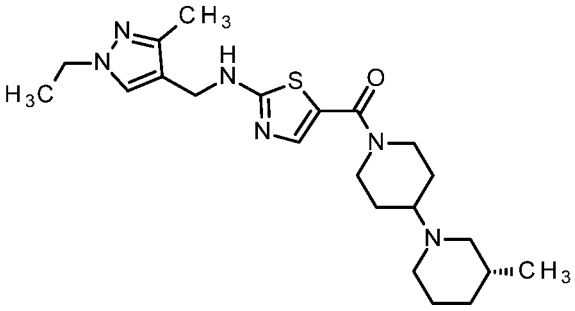
| Example | IUPAC name / structure<br>(yield; purity) | LC-MS (Method 6) |
|---|---|---|
| 5 | [(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl](2-{[(1-methyl-1H-pyrazol-5-yl)methyl]amino}-1,3-thiazol-5-yl)methanone<br>  <br>(38% of theory; 100% purity) | $R_t$ = 0.67 min; m/z = 403 $(M+H)^+$ |
| 6 | rel-[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl](2-{[(1S)-1-(1,2-oxazol-3-yl)ethyl]amino}-1,3-thiazol-5-yl)methanone<br>  <br>(20% of theory; 100% purity) | $R_t$ = 0.68 min; m/z = 404 $(M+H)^+$ |
| 7 | (2-{[(1,3-dimethyl-1H-pyrazol-4-yl)methyl]amino}-1,3-thiazol-5-yl)[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone<br>  <br>(15% of theory; 100% purity) | $R_t$ = 0.68 min; m/z = 417 $(M+H)^+$ |

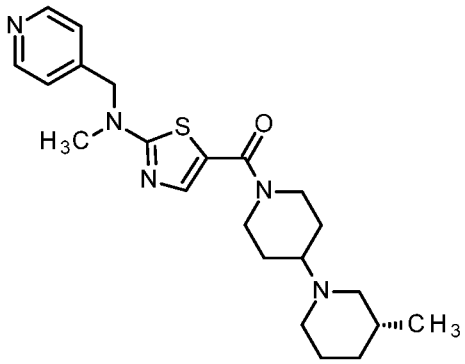
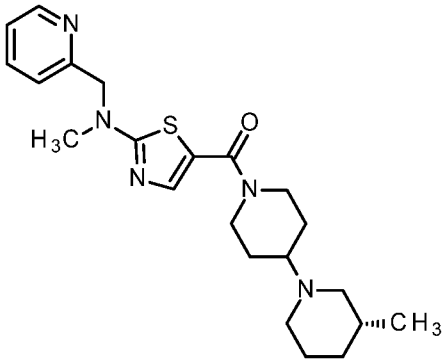
| Example | IUPAC name / structure<br>(yield; purity) | LC-MS (Method 6) |
|---|---|---|
| 8 | (2-{[(4,6-dimethylpyrimidin-2-yl)methyl]amino}-1,3-thiazol-5-yl)[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone<br>  <br>(30% of theory; 100% purity) | $R_t$ = 0.69 min; m/z = 429 $(M+H)^+$ |
| 9 | {2-[(2-fluorobenzyl)amino]-1,3-thiazol-5-yl}[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone<br>  <br>(33% of theory; 100% purity) | $R_t$ = 0.76 min; m/z = 417 $(M+H)^+$ |

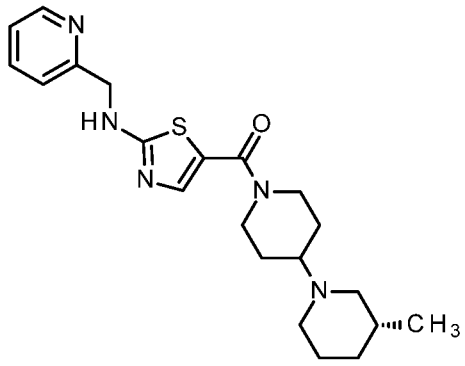
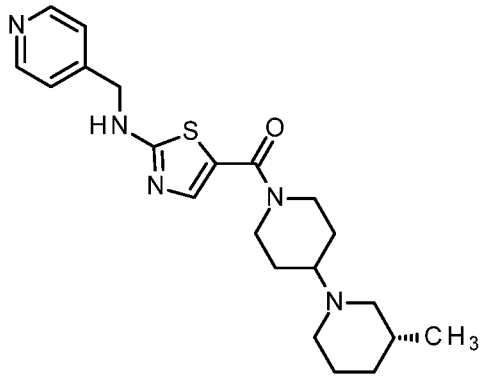
| Example | IUPAC name / structure<br>(yield; purity) | LC-MS (Method 6) |
|---|---|---|
| **10** | {2-[(2-chlorobenzyl)amino]-1,3-thiazol-5-yl}[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone<br>  <br>(7% of theory; 100% purity) | $R_t$ = 0.79 min; m/z = 433 $(M+H)^+$ |
| **11** | N-(2-chloro-4-fluorophenyl)-2-[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]-1,3-thiazole-5-carboxamide<br>  <br>(37% of theory; 99% purity) | $R_t$ = 0.75 min; m/z = 433 $(M+H)^+$ |
| **12** | [(3R)-3-methyl[1,4'-bipiperidine]-1'-yl](2-{[(1*S*)-1-(4-methylphenyl)ethyl]amino}-1,3-thiazol-5-yl)methanone<br>  <br>(26% of theory; 100% purity) | $R_t$ = 0.80 min; m/z = 427 $(M+H)^+$ |

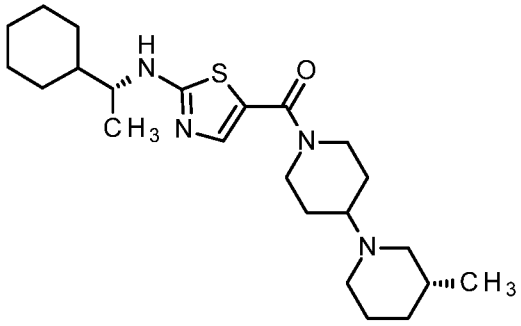
| Example | IUPAC name / structure (yield; purity) | LC-MS (Method 6) |
|---|---|---|
| 13 | rel-[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl](2-{[(1*S*)-1-(pyridin-2-yl)ethyl]amino}-1,3-thiazol-5-yl)methanone  (36% of theory; 100% purity) | $R_t$ = 0.64 min; m/z = 414 $(M+H)^+$ |
| 14 | rel-[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl](2-{[(1*R*)-1-(4-methylphenyl)ethyl]amino}-1,3-thiazol-5-yl)methanone  (38% of theory; 100% purity) | $R_t$ = 0.81 min; m/z = 427 $(M+H)^+$ |
| 15 | (2-{[(1-ethyl-5-methyl-1H-pyrazol-4-yl)methyl]amino}-1,3-thiazol-5-yl)[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone  (24% of theory; 100% purity) | $R_t$ = 0.70 min; m/z = 431 $(M+H)^+$ |

| Example | IUPAC name / structure<br>(yield; purity) | LC-MS (Method 6) |
|---|---|---|
| 16 | {2-[(3-fluoro-4-methylbenzyl)amino]-1,3-thiazol-5-yl}[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone<br>  <br>(46% of theory; 100% purity) | $R_t$ = 0.81 min; m/z = 431 $(M+H)^+$ |
| 17 | [(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl](2-{[(1-methyl-1H-pyrazol-4-yl)methyl]amino}-1,3-thiazol-5-yl)methanone<br>  <br>(33% of theory; 100% purity) | $R_t$ = 0.67 min; m/z = 403 $(M+H)^+$ |

| Example | IUPAC name / structure (yield; purity) | LC-MS (Method 6) |
|---|---|---|
| **18** | [(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl](2-{[(1,3,5-trimethyl-1H-pyrazol-4-yl)methyl]amino}-1,3-thiazol-5-yl)methanone  (36% of theory; 100% purity) | $R_t$ = 0.69 min; m/z = 431 $(M+H)^+$ |
| **19** | (2-{[(1-ethyl-3-methyl-1H-pyrazol-4-yl)methyl]amino}-1,3-thiazol-5-yl)[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone  (30% of theory; 100% purity) | $R_t$ = 0.70 min; m/z = 431 $(M+H)^+$ |

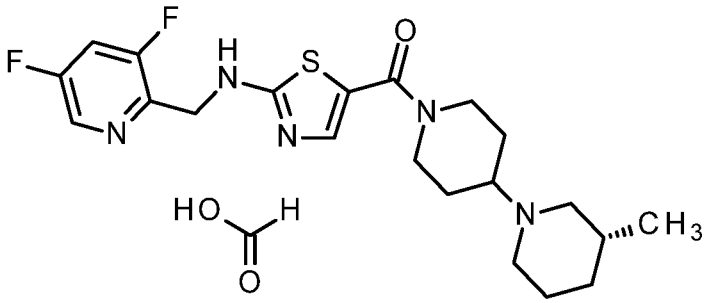
| Example | IUPAC name / structure<br>(yield; purity) | LC-MS (Method 6) |
|---|---|---|
| **20** | [(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]{2-[methyl(pyridin-4-ylmethyl)amino]-1,3-thiazol-5-yl}methanone<br>  <br>(11% of theory; 100% purity) | $R_t$ = 0.61 min; m/z = 414 $(M+H)^+$ |
| **21** | [(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]{2-[methyl(pyridin-2-ylmethyl)amino]-1,3-thiazol-5-yl}methanone<br>  <br>(42% of theory; 100% purity) | $R_t$ = 0.68 min; m/z = 414 $(M+H)^+$ |

| Example | IUPAC name / structure<br>(yield; purity) | LC-MS (Method 6) |
|---|---|---|
| **22** | [(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]{2-[(pyridin-2-ylmethyl)amino]-1,3-thiazol-5-yl}methanone<br>  <br>(22% of theory; 96% purity) | $R_t$ = 0.59 min; m/z = 400 $(M+H)^+$ |
| **23** | [(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]{2-[(pyridin-4-ylmethyl)amino]-1,3-thiazol-5-yl}methanone<br>  <br>(17% of theory; 100% purity) | Rt = 0.57 min; m/z = 400 (M+H)+ |

| Example | IUPAC name / structure (yield; purity) | LC-MS (Method 6) |
|---|---|---|
| 24 | (2-{[(1*S*)-1-cyclohexylethyl]amino}-1,3-thiazol-5-yl)[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone  (13% of theory; 100% purity) | Rt = 0.78 min; m/z = 419 (M+H)+ |

**Example 25**

(2-{[(3,5-Difluoropyridin-2-yl)methyl]amino}-1,3-thiazol-5-yl)[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone formates (1:1)



100 mg (0.25 mmol) of (2-bromo-1,3-thiazol-5-yl)[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone hydrochloride and 88 mg (0.49 mmol) of 1-(3,5-difluoropyridin-2-yl)methanamine hydrochloride (1:1) were suspended in 2 ml of DMF in a 10 ml glass vial, and 0.3 ml of N,N-diisopropylethylamine was added. Thereafter, the reaction mixture was reacted in a CEM microwave at 180°C for 15 min. After cooling to room temperature, water was added to the solution, which was extracted repeatedly with ethyl acetate. The combined organic phases were washed once with water,

dried over magnesium sulfate, filtered and concentrated to dryness. The crude product obtained was purified by prep. HPLC. (Column: Chromatorex C18 10µ 250x20mm, gradient: A = water + 0.5% HCOOH, B = CH3CN, 0 min = 5% B, 3 min = 5% B initial purge without substance, then injection, 5 min = 5% B, 25 min = 50% B, 38 min = 50% B, 38.1 min = 95% B, 43 min= 95% B, 43.01 min= 5% B, 48.0 min= 5% B, flow rate 20 ml/min, wavelength 210 nm.) This gave 12 mg (0.02 mmol, 10% of theory) of the target compound.

$^1$H-NMR (600 MHz, DMSO-$d_6$, δ/ppm):, 0.90 (d, 3H), 1.01-1.16 (m, 1H), 1.54-1.90 (m, 6H), 2.04 (br. d, 2H), 2.44-2.57 (m, 4H, partly hidden by DMSO), 2.80-3.02 (m, 3H), 3.27-3.51 (m, 1H, partly hidden by $H_2O$), 4.39 (br. d, 2H), 4.64 (br. d, 2H), 7.44 (s, 1H), 7.96 (ddd, 1H), 8.50 (d, 1H), 8.69 (t, 1H), 9.10 (br. s, 1H).

LC-MS (Method 2): $R_t$ = 0.57 min; m/z = 436 $(M+H)^+$-($HCO_2H$).

Explorer Discorer SP (CEM)

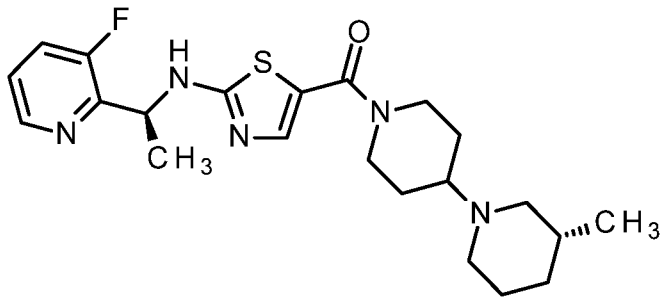
Overall Dimensions: 14.5"W x 17.2"D x 8.7"H (36.2 cm x 43.7 cm x 22.1 cm); Weight: 30lbs;

Electrical Requirements: 90 - 264 VAC 50/60 Hz, 10 Amp @120 VAC, 5 Amps @ 220 VAC;

Magnetron Frequency: 2450 MHz; Power output: 300 W; Pressure: Monitor 0 - 35 Bar, Control 0 - 20 Bar; Temperature: -90°C to 300°C control range; Stirring: In-situ magnetic variable speed; Microwave applicator: Circular, single-mode self-tuning; Ethernet Port: 10 based T, 10 MB/sec; Serial Port: (2) RS-232, 9 pin IBM PC compatible.

**Example 26**

(2-{[(1*S*)-1-(3-Fluoropyridin-2-yl)ethyl]amino}-1,3-thiazol-5-yl)[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone



3 g (8.06 mmol) of (5-bromo-1,3-thiazol-2-yl)[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone and 3.434 g (16.12 mmol) of (1*S*)-1-(3-fluoropyridin-2-yl)ethanamine dihydrochloride were dissolved in 60 ml of 1-methyl-2-pyrrolidone, and 7 ml of N,N-diisopropylethylamine was added. Thereafter, the reaction mixture (closed vessel) was stirred at 140°C overnight. After cooling to room temperature, the solution was diluted with dichloromethane and washed with saturated sodium hydrogencarbonate solution. After the organic phase had been separated off, the solution was filtered through a hydrophobic filter and concentrated to dryness under reduced pressure. Partial epimerization was found, and therefore the resultant residue was purified by chiral prep. HPLC.

1250 mg (0.89 mmol) of the diastereomeric mixture of (2-{[(1*S/R*)-1-(3-fluoropyridin-2-yl)ethyl]amino}-1,3-thiazol-5-yl)[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone was separated into the diastereomers by preparative HPLC on a chiral phase [column: Daicel Chiralpak IG, 5 µm, 250 mm x 20 mm; eluent: ethanol + (0.2% diethylamine) /n-heptane 70:30; flow rate: 15 ml/min; UV detection: 220 nm; temperature: 50°C].

This gave 977 mg (28% of theory, purity > 99%) of the title compound (2-{[(1*S*)-1-(3-fluoropyridin-2-yl)ethyl]amino}-1,3-thiazol-5-yl)[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone and 138 mg of the diastereomer (2-{[(1*R*)-1-(3-fluoropyridin-2-yl)ethyl]amino}-1,3-thiazol-5-yl)[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone.

Analysis of (2-{[(1*S*)-1-(3-fluoropyridin-2-yl)ethyl]amino}-1,3-thiazol-5-yl)[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone:

$R_t$ = 7.39 min; chemical purity > 99%; > 99% de

[Column: Chiralpak IG, 5 µm, 250 mm x 4.6 mm; eluent: n-heptane/ethanol (+0.2% diethylamine) 30:70; flow rate: 1 ml/min; temperature: 70°C; UV detection: 235 nm].

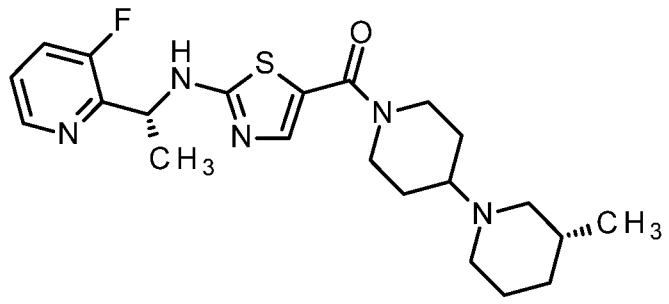
LC-MS (Method 1): $R_t$ = 0.91 min; m/z = 432 $(M+H)^+$.

$^1$H-NMR (600 MHz, DMSO-$d_6$, δ/ppm):, 0.75-0.85 (m, 4H, therein at 0.81 (d, 3H)), 1.29-1.43 (m, 3H), 1.47 (d, 3H), 1.48-1.54. (m, 1H), 1.54-1.59 (m, 1H), 1.54-1.65 (m, 1H), 1.69-1.76 (m, 3H), 2.00-2.08 (m, 1H), 2.43-2.51 (m, 1H, partly hidden by DMSO), 2.69-2.76 (m, 2H), 2.87 (br. t, 2H), 4.23 (br. d, 2H), 5.26-5.32 (m, 1H), 7.33 (s, 1H), 7.39 (dt, 1H), 7.68 (td, 1H), 8.40 (d, 1H), 8.58 (d, 1H).

$[\alpha]_D^{20}$ = -42.79° (c = 0.430, methanol).

**Example 27**

(2-{[(1*R*)-1-(3-Fluoropyridin-2-yl)ethyl]amino}-1,3-thiazol-5-yl)[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone



Yield after separation and purification (see Example 26):

138 mg

Analysis of (2-{[(1*R*)-1-(3-fluoropyridin-2-yl)ethyl]amino}-1,3-thiazol-5-yl)[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone:

$R_t$ = 6.15 min; chemical purity > 99%; > 99% de

[Column: Chiralpak IG, 5 µm, 250 mm x 4.6 mm; eluent: n-heptane/ethanol (+0.2% diethylamine) 30:70; flow rate: 1 ml/min; temperature: 70°C; UV detection: 235 nm].

LC-MS (Method 1): $R_t$ = 0.91 min; m/z = 432 $(M+H)^+$.

$^1$H-NMR (600 MHz, DMSO-$d_6$, δ/ppm):, 0.75-0.85 (m, 4H, therein at 0.81 (d, 3H)), 1.29-1.43 (m, 3H), 1.47 (d, 3H), 1.48-1.54. (m, 1H), 1.54-1.59 (m, 1H), 1.54-1.65 (m, 1H), 1.69-1.76 (m, 3H), 2.00-2.08 (m, 1H), 2.43-2.51 (m, 1H, partly hidden by DMSO), 2.69-2.76 (m, 2H), 2.87 (br. t, 2H), 4.23 (br. d, 2H), 5.29 (br. s, 1H), 7.33 (s, 1H), 7.39 (dt, 1H), 7.68 (t, 1H), 8.40 (d, 1H), 8.57 (br. d, 1H).

Preparation method 2:

120 mg (0.32 mmol) of (5-bromo-1,3-thiazol-2-yl)[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone and 137 mg (0.64 mmol) of (1*R*)-1-(3-fluoropyridin-2-yl)ethanamine dihydrochloride were dissolved in 2.4 ml of 1-methyl-2-pyrrolidone, and 0.28 ml of *N*,*N*-diisopropylethylamine was added. Thereafter, the reaction mixture (closed vessel) was stirred at 140°C overnight. After cooling to room temperature, the solution was diluted with dichloromethane and washed with saturated

sodium hydrogencarbonate solution. After the organic phase had been separated off, the solution was filtered through a hydrophobic filter and concentrated to dryness under reduced pressure. The resultant residue was purified by preparative HPLC.

Method:

Instrument: Waters Prep LC/MS system, column: Phenomenex Kinetex C18 5µm 100 x 30 mm. Eluent A: water, eluent B: acetonitrile, eluent C: 2% formic acid in water, eluent D: acetonitrile/water (80% by vol./20% by vol.), total flow rate: 80 ml/min, room temperature, wavelength: 200-400 nm, at-column injection (complete injection); gradient profile: eluent A 0 to 2 min 70 ml, eluent B 0 to 2 min 0 ml, eluent A 2 to 10 min from 70 ml to 55 ml and eluent B from 0 ml to 15 ml, 10 to 12 min 0 ml eluent A and 70 ml eluent B. Constant flow rate of eluent C and eluent D of 5 ml/min each over the entire run time.

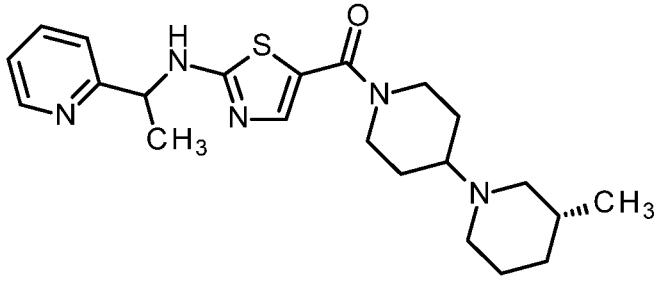
73 mg of a yellow foam was isolated. The foam was dissolved in dichloromethane and washed with saturated sodium hydrogencarbonate solution, and the organic phase was separated off, then filtered through a hydrophobic filter and concentrated to dryness under reduced pressure. This gave 71 mg (51% of theory, 0.16 mmol, purity > 99%) of the title compound as a yellow foam.
LC-MS (Method 1): $R_t$ = 0.84 min; m/z = 432 $(M+H)^+$.

$^1$H-NMR (400 MHz, DMSO-$d_6$, δ/ppm): 0.74-0.87 (m, 4H, therein at 0.81 (d, 3H)), 1.27-1.42 (m, 3H), 1.42-1.66 (m, 6H, therein at 1.46 (d, 3H)), 1.67-1.78 (m, 3H), 1.98-2.08 (m, 1H), 2.42-2.53 (m, 1H, partly hidden by DMSO), 2.69-2.77 (m, 2H), 2.87 (br. t, 2H), 4.23 (br. d, 2H), 5.24-5.34 (m, 1H), 7.33 (s, 1H), 7.39 (dt, 1H), 7.69 (ddd, 1H), 8.40 (dt, 1H), 8.61 (d, 1H).

$[\alpha]_D^{20}$ = +34.25° (c = 0.365, methanol).

**Example 28 and Example 29**

[(3*R*)-3-Methyl[1,4'-bipiperidine]-1'-yl](2-{[1-(pyridin-2-yl)ethyl]amino}-1,3-thiazol-5-yl)methanone (*diastereomers 1 and 2*)



324 mg (0.78 mmol) of the diastereomer mixture [(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl](2-{[1-(pyridin-2-yl)ethyl]amino}-1,3-thiazol-5-yl)methanone (Example 13) was separated into the enantiomers by preparative HPLC on a chiral phase [column: Daicel Chiralcel OZ-H, 5 µm, 250 mm x 20 mm; eluent: ethanol + 0.2% diethylamine/n-heptane 50:50; flow rate: 25 ml/min; UV detection: 220 nm; temperature: 30°C]:

Example 28 (*diastereomer 1*):

[(3*R*)-3-Methyl[1,4'-bipiperidine]-1'-yl](2-{[1-(pyridin-2-yl)ethyl]amino}-1,3-thiazol-5-yl)methanone

Yield: 123 mg

$R_t$ = 3.41 min; chemical purity > 99%; > 99% de

[Column: Chiraltek OZ-3, 3 µm, 100 mm x 4.6 mm; eluent: isohexane/ethanol +0.2% diethylamine 50:50; flow rate: 1 ml/min; temperature: 25°C; UV detection: 220 nm].

LC-MS (Method 1): $R_t$ = 0.68 min; m/z = 412 $(M-H)^-$.

$^1$H-NMR (400 MHz, DMSO-$d_6$, δ/ppm): 0.74-0.91 (m, 4H, therein at 0.81 (d, 3H)), 1.21-1.67 (m, 10H, therein at 1.46 (d, 3H)), 1.68-1.83 (m, 3H), 2.06 (br. t, 1H), 2.69-2.80 (m, 2H), 2.88 (br. t, 2H), 4.24 (br. d, 2H), 4.83-4.93 (m, 1H), 7.26 (ddd, 1H), 7.35 (s, 1H), 7.37 (d, 1H), 7.75 (td, 1H), 8.52 (d, 1H), 8.61 (d, 1H).

$[\alpha]_D^{20}$ = -15.98° (c = 0.290, methanol).

Example 29 (*diastereomer 2*):

[(3*R*)-3-Methyl[1,4'-bipiperidine]-1'-yl](2-{[1-(pyridin-2-yl)ethyl]amino}-1,3-thiazol-5-yl)methanone

Yield: 133 mg

$R_t$ = 4.39 min; chemical purity > 99%; > 94% de

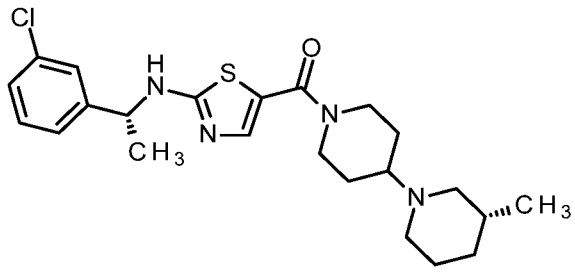
[Column: Chiraltek OZ-3, 3 µm, 100 mm x 4.6 mm; eluent: isohexane/ethanol +0.2% diethylamine 50:50; flow rate: 1 ml/min; temperature: 25°C; UV detection: 220 nm].

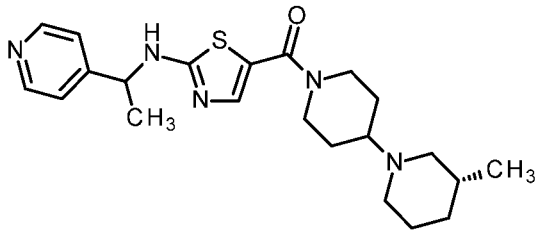
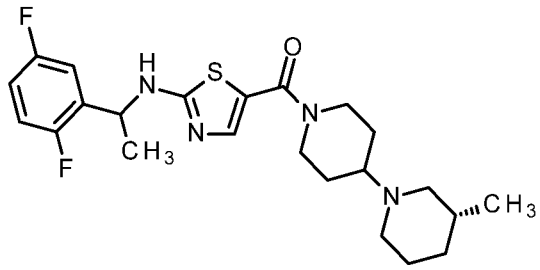
LC-MS (Method 1): $R_t$ = 0.69 min; m/z = 412 $(M-H)^-$.

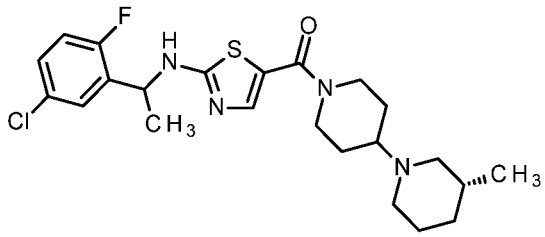
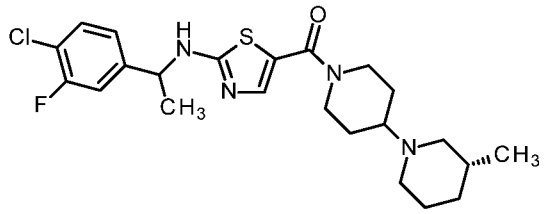
$^1$H-NMR (400 MHz, DMSO-$d_6$, δ/ppm): 0.74-0.90 (m, 4H, therein at 0.82 (d, 3H)), 1.21-1.67 (m, 10H, therein at 1.46 (d, 3H)), 1.74 (br. d, 3H), 2.01-2.14 (m, 1H), 2.69-2.81 (m, 2H), 2.88 (br. t, 2H), 4.24 (br. d, 2H), 4.88 (quin., 1H), 7.26 (ddd, 1H), 7.35 (s, 1H), 7.37 (d, 1H), 7.76 (td, 1H), 8.52 (d, 1H), 8.61 (d, 1H).

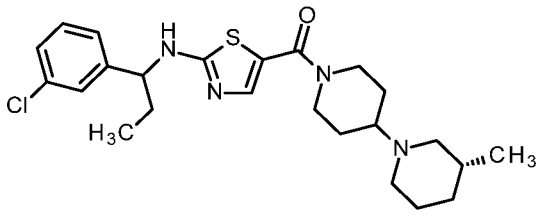
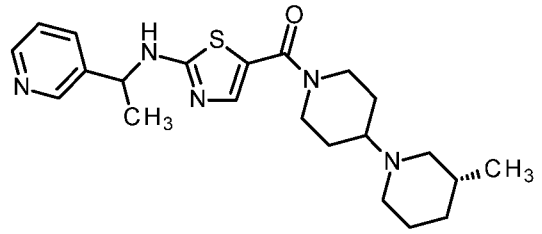
$[\alpha]_D^{20}$ = +14.85° (c = 0.330, methanol).

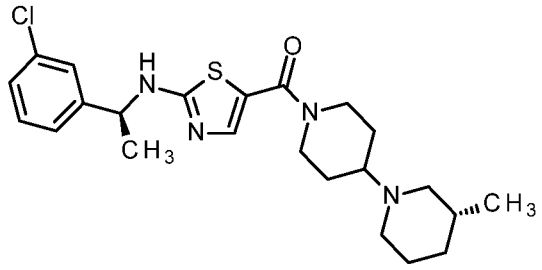
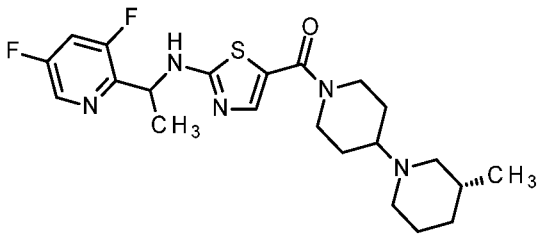
Analogously to Examples 1, 2 and 25 to 27, the following compounds of Examples 30 to 56 were prepared from the respectively specified starting materials:

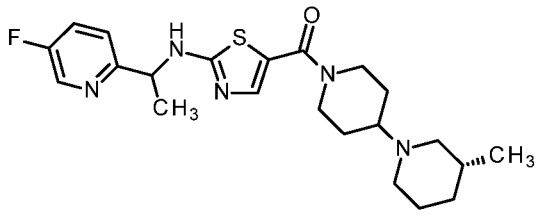
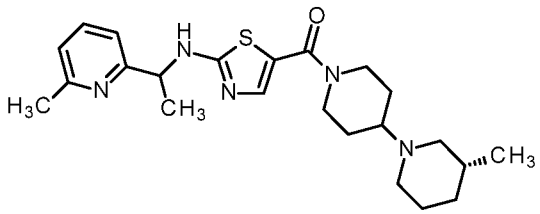
| Example | Name / Structure / Starting material | Analytical data |
|---|---|---|
| **30** | (2-{[(1*R*)-1-(3-chlorophenyl)ethyl]amino}-1,3-thiazol-5-yl)[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone<br>  <br>from (5-bromo-1,3-thiazol-2-yl)[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone and (1*R*)-1-(3-chlorophenyl)ethanamine | $^1$H-NMR (400 MHz, DMSO-$d_6$, δ/ppm): 0.76-0.86 (m, 4H, therein at 0.81 (d, 3H)), 1.29-1.41 (m, 3H), 1.44 (d, 3H), 1.46-1.54 (m, 1H), 1.54-1.59 (m, 1H), 1.59-1.65 (m, 1H), 1.68-1.77 (m, 3H), 2.00-2.07 (m, 1H), 2.43-2.52 (m, 1H, partly hidden by DMSO), 2.68-2.76 (m, 2H), 2.88 (br. t, 2H), 4.23 (br. d, 2H), 4.76-4.83 (m, 1H), 7.27-7.38 (m, 4H), 7.41 (s, 1H), 8.58 (d, 1H).<br>LC-MS (Method 5):<br>$R_t$ = 1.90 min; m/z = 447/449 $(M+H)^+$. |

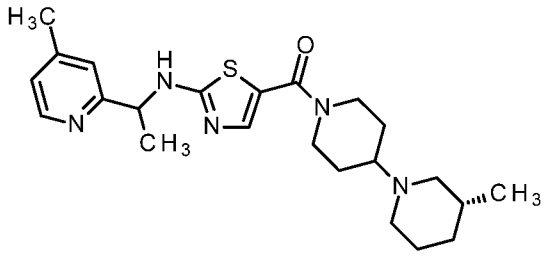
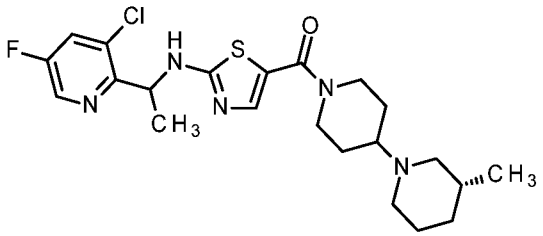
| Example | Name / Structure / Starting material | Analytical data |
|---|---|---|
| **31** | [(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl](2-{[1-(pyridin-4-yl)ethyl]amino}-1,3-thiazol-5-yl)methanone (diastereomer mixture)<br>  <br>from (5-bromo-1,3-thiazol-2-yl)[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone and *rac*-1-(pyridin-4-yl)ethanamine | LC-MS (Method 5):<br>$R_t$ = 1.40 min; m/z = 414 $(M+H)^+$. |
| **32** | (2-{[1-(2,5-difluorophenyl)ethyl]amino}-1,3-thiazol-5-yl)[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone (diastereomer mixture)<br>  <br>from (5-bromo-1,3-thiazol-2-yl)[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone and *rac*-1-(2,5-difluorophenyl)ethanamine | LC-MS (Method 5):<br>$R_t$ = 1.81 min; m/z = 449 $(M+H)^+$. |

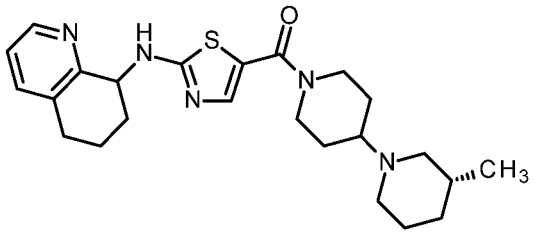
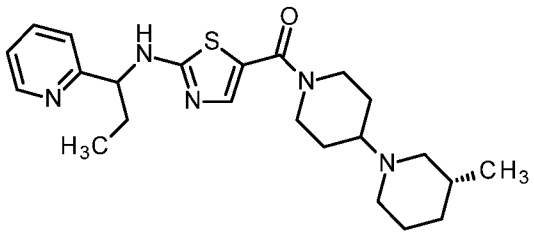
| Example | Name / Structure / Starting material | Analytical data |
|---|---|---|
| **33** | (2-{[1-(5-chloro-2-fluorophenyl)ethyl]amino}-1,3-thiazol-5-yl)[(3R)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone (diastereomer mixture)<br>  <br>from (5-bromo-1,3-thiazol-2-yl)[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone and *rac*-1-(5-chloro-2-fluorophenyl)ethanamine | LC-MS (Method 5):<br>$R_t$ = 1.91 min; m/z = 465/467 $(M+H)^+$. |
| **34)** | (2-{[1-(4-chloro-3-fluorophenyl)ethyl]amino}-1,3-thiazol-5-yl)[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone (diastereomer mixture)<br>  <br>from (5-bromo-1,3-thiazol-2-yl)[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone and *rac*-1-(3-chloro-4-fluorophenyl)ethanamine | LC-MS (Method 5):<br>$R_t$ = 1.92 min; m/z = 465/467 $(M+H)^+$. |

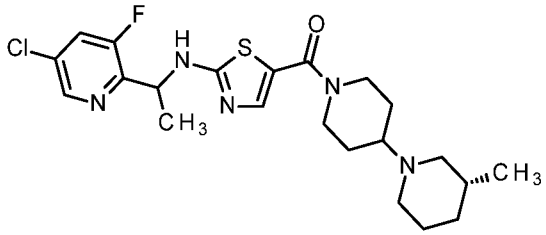
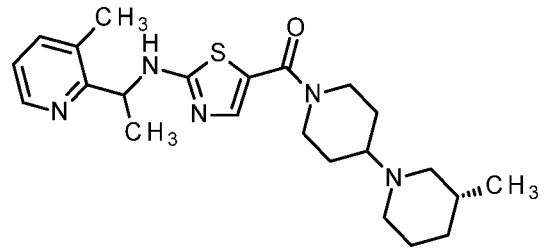
| Example | Name / Structure / Starting material | Analytical data |
|---|---|---|
| **35** | (2-{[1-(3-chlorophenyl)propyl]amino}-1,3-thiazol-5-yl)[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone (diastereomer mixture)<br>  <br>from (5-bromo-1,3-thiazol-2-yl)[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone and *rac*-1-(3-chlorophenyl)propan-1-amine | LC-MS (Method 5):<br>$R_t$ = 2.01 min; m/z = 461/463 $(M+H)^+$. |
| **36** | [(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl](2-{[1-(pyridin-3-yl)ethyl]amino}-1,3-thiazol-5-yl)methanone (diastereomer mixture)<br>  <br>from (5-bromo-1,3-thiazol-2-yl)[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone and *rac*-1-(pyridin-3-yl)ethanamine | LC-MS (Method 5):<br>$R_t$ = 1.43 min; m/z = 414 $(M+H)^+$. |

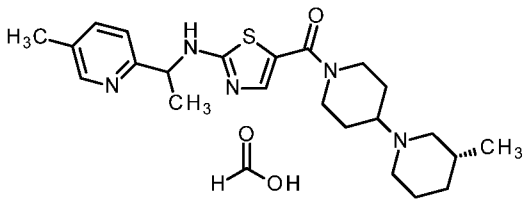
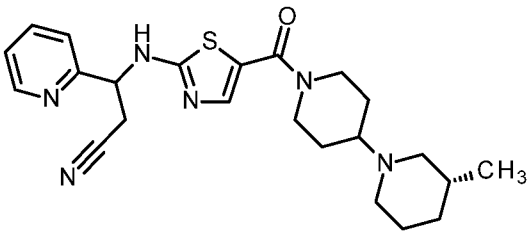
| Example | Name / Structure / Starting material | Analytical data |
|---|---|---|
| **37** | (2-{[(1*S*)-1-(3-chlorophenyl)ethyl]amino}-1,3-thiazol-5-yl)[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone<br>  <br>from (5-bromo-1,3-thiazol-2-yl)[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone and (1*S*)-1-(3-chlorophenyl)ethanamine | $^1$H-NMR (600 MHz, DMSO-$d_6$, δ/ppm): 0.76-0.85 (m, 4H, therein at 0.81 (d, 3H)), 1.28-1.41 (m, 3H), 1.44 (d, 3H), 1.46-1.54 (m, 1H), 1.54-1.59 (m, 1H), 1.59-1.65 (m, 1H), 1.68-1.77 (m, 3H), 2.00-2.07 (m, 1H), 2.43-2.52 (m, 1H, partly hidden by DMSO), 2.69-2.77 (m, 2H), 2.88 (br. t, 2H), 4.23 (br. d, 2H), 4.76-4.83 (m, 1H), 7.27-7.38 (m, 4H), 7.41 (s, 1H), 8.58 (d, 1H).<br>LC-MS (Method 5):<br>$R_t$ = 1.91 min; m/z = 447/449 $(M+H)^+$. |
| **38** | (2-{[1-(3,5-difluoropyridin-2-yl)ethyl]amino}-1,3-thiazol-5-yl)[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone (diastereomer mixture)<br>  <br>from (5-bromo-1,3-thiazol-2-yl)[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone and rac-1-(3,5-difluoropyridin-2-yl)ethanamine hydrochloride (1:1) | LC-MS (Method 1):<br>$R_t$ = 0.90 min; m/z = 450 $(M+H)^+$. |

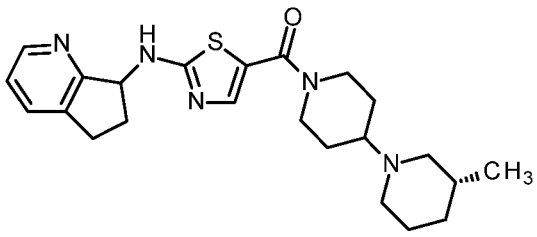
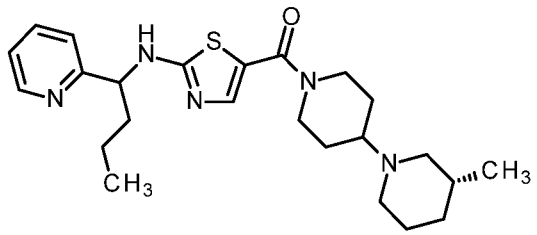
| Example | Name / Structure / Starting material | Analytical data |
|---|---|---|
| **39** | (2-{[1-(5-fluoropyridin-2-yl)ethyl]amino}-1,3-thiazol-5-yl)[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone (diastereomer mixture)<br>  <br>from (5-bromo-1,3-thiazol-2-yl)[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone and rac-1-(5-fluoropyridin-2-yl)ethanamine | LC-MS (Method 1):<br>$R_t$ = 0.84 min; m/z = 432 $(M+H)^+$. |
| **40** | [(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl](2-{[1-(6-methylpyridin-2-yl)ethyl]amino}-1,3-thiazol-5-yl)methanone (diastereomer mixture)<br>  <br>from (5-bromo-1,3-thiazol-2-yl)[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone and rac-1-(6-methylpyridin-2-yl)ethanamine | LC-MS (Method 1):<br>$R_t$ = 0.67 min; m/z = 426 $(M-H)^-$. |

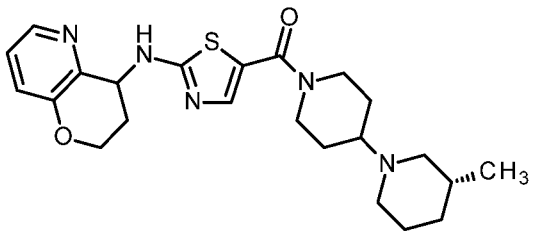
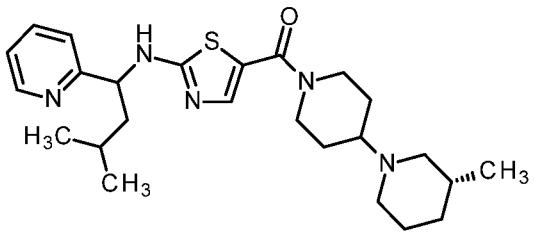
| Example | Name / Structure / Starting material | Analytical data |
|---|---|---|
| **41** | [(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl](2-{[1-(4-methylpyridin-2-yl)ethyl]amino}-1,3-thiazol-5-yl)methanone (diastereomer mixture)<br>  <br>from (5-bromo-1,3-thiazol-2-yl)[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone and rac-1-(4-methylpyridin-2-yl)ethanamine dihydrochloride | LC-MS (Method 1):<br>$R_t$ = 0.63 min; m/z = 426 $(M-H)^-$. |
| **42** | (2-{[1-(3-chloro-5-fluoropyridin-2-yl)ethyl]amino}-1,3-thiazol-5-yl)[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone (diastereomer mixture)<br>  <br>from (5-bromo-1,3-thiazol-2-yl)[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone and rac-1-(3-chloro-5-fluoropyridin-2-yl)ethanamine hydrochloride (1:1) | LC-MS (Method 1):<br>$R_t$ = 1.04 min; m/z = 466/468 $(M+H)^+$. |

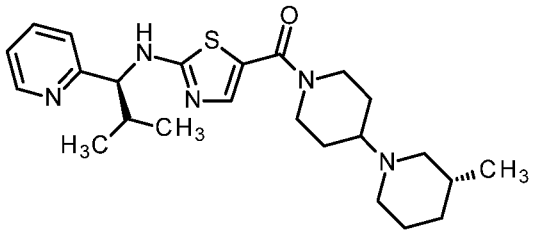
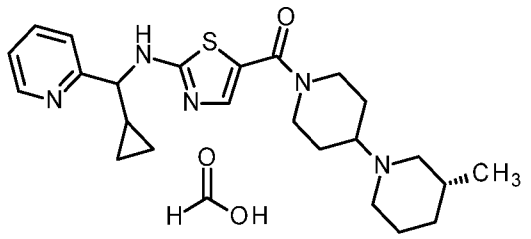
| Example | Name / Structure / Starting material | Analytical data |
|---|---|---|
| **43** | [(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl][2-(5,6,7,8-tetrahydroquinolin-8-ylamino)-1,3-thiazol-5-yl]methanone (diastereomer mixture)<br>  <br>from (5-bromo-1,3-thiazol-2-yl)[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone and rac-5,6,7,8-tetrahydroquinoline-8-amine | LC-MS (Method 2):<br>$R_t$ = 0.39 min; m/z = 440 $(M+H)^+$. |
| **44** | [(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl](2-{[1-(pyridin-2-yl)propyl]amino}-1,3-thiazol-5-yl)methanone (diastereomer mixture)<br>  <br>from (5-bromo-1,3-thiazol-2-yl)[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone and rac-1-(pyridin-2-yl)propane-1-amine | LC-MS (Method 1):<br>$R_t$ = 1.04 min; m/z = 426 $(M-H)^-$. |

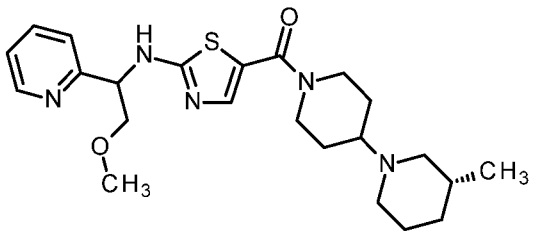
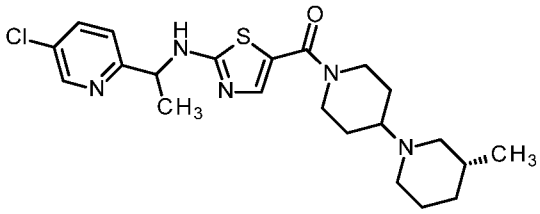
| Example | Name / Structure / Starting material | Analytical data |
|---|---|---|
| 45 | {2-[1-(5-chloro-3-fluoropyridin-2-yl)ethyl]-1,3-thiazol-5-yl}[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone (diastereomer mixture)<br>  <br>from (5-bromo-1,3-thiazol-2-yl)[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone and rac-1-(5-chloro-3-fluoropyridin-2-yl)ethanamine | LC-MS (Method 1):<br>$R_t$ = 1.06 min; m/z = 466/468 $(M+H)^+$. |
| 46 | [(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]{2-[1-(3-methylpyridin-2-yl)ethyl]-1,3-thiazol-5-yl}methanone (diastereomer mixture)<br>  <br>from (5-bromo-1,3-thiazol-2-yl)[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone and rac-1-(3-methylpyridin-2-yl)ethanamine | LC-MS (Method 1):<br>$R_t$ = 0.73 min; m/z = 426 $(M-H)^-$. |

| Example | Name / Structure / Starting material | Analytical data |
|---|---|---|
| **47** | [(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl](2-{[1-(5-methylpyridin-2-yl)ethyl]amino}-1,3-thiazol-5-yl)methanone formate (1:1) (diastereomer mixture)<br>  <br>from (5-bromo-1,3-thiazol-2-yl)[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone and rac-1-(5-methylpyridin-2-yl)ethanamine | LC-MS (Method 1):<br>$R_t$ = 0.72 min; m/z = 426 $(M\text{-}H\text{-}CO_2H_2)^-$. |
| **48** | 3-[(5-{[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]carbonyl}-1,3-thiazol-2-yl)amino]-3-(pyridin-2-yl)propanenitrile (diastereomer mixture)<br>  <br>from (5-bromo-1,3-thiazol-2-yl)[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone and rac-3-amino-3-(pyridin-2-yl)propanenitrile hydrochloride (1:1) | LC-MS (Method 1):<br>$R_t$ = 0.75 min; m/z = 439 $(M+H)^+$. |

| Example | Name / Structure / Starting material | Analytical data |
|---|---|---|
| **49** | {2-[6,7-dihydro-5H-cyclopenta[b]pyridin-7-ylamino]-1,3-thiazol-5-yl}[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone (diastereomer mixture)<br>  <br>from (5-bromo-1,3-thiazol-2-yl)[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone and rac-6,7-dihydro-5H-cyclopenta[b]pyridine-7-amine hydrochloride (1:1) | LC-MS (Method 1):<br>$R_t$ = 0.73 min; m/z = 424 $(M-H)^-$. |
| **50** | [(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl](2-{[1-(pyridin-2-yl)butyl]amino}-1,3-thiazol-5-yl)methanone (diastereomer mixture)<br>  <br>from (5-bromo-1,3-thiazol-2-yl)[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone and rac-1-(pyridin-2-yl)butane-1-amine | LC-MS (Method 1):<br>$R_t$ = 0.89 min; m/z = 440 $(M+H)^+$. |

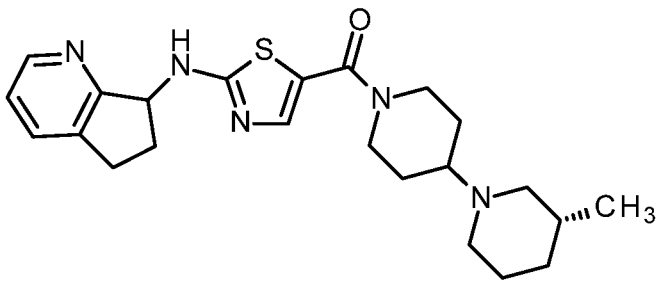
| Example | Name / Structure / Starting material | Analytical data |
|---|---|---|
| **51** | {2-[3,4-dihydro-2*H*-pyrano[3,2-b]pyridin-4-ylamino]-1,3-thiazol-5-yl}[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone (diastereomer mixture)<br>  <br>from (5-bromo-1,3-thiazol-2-yl)[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone and rac-3,4-dihydro-2H-pyrano[3,2-b]pyridine-4-amine | LC-MS (Method 1):<br>$R_t$ = 0.76 min; m/z = 440 $(M-H)^-$. |
| **52** | [(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl](2-{[3-methyl-1-(pyridin-2-yl)butyl]amino}-1,3-thiazol-5-yl)methanone (diastereomer mixture)<br>  <br>from (5-bromo-1,3-thiazol-2-yl)[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone and rac-3-methyl-1-(pyridin-2-yl)butane-1-amine | LC-MS (Method 1):<br>$R_t$ = 0.99 min; m/z = 454 $(M-H)^-$. |

| Example | Name / Structure / Starting material | Analytical data |
|---|---|---|
| **53** | [(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl](2-{[(1*S*)-2-methyl-1-(pyridin-2-yl)propyl]amino}-1,3-thiazol-5-yl)methanone<br>  <br>from (5-bromo-1,3-thiazol-2-yl)[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone and (1*S*)-2-methyl-1-(pyridin-2-yl)propane-1-amine | $^1$H-NMR (400 MHz, DMSO-$d_6$, δ/ppm): 0.73-0.86 (m, 7H, therein at 0.78 (d, 3H) and at 0.81 (d, 3H)), 0.94 (d, 3H), 1.27-1.44 (m, 3H), 1.45-1.66 (m, 3H), 1.67-1.78 (m, 3H), 1.98-2.07 (m, 1H), 2.15-2.27 (m, 1H), 2.42-2.52 (m, 1H, partly hidden by DMSO), 2.68-2.77 (m, 2H), 2.87 (br. t, 2H), 4.24 (br. d, 2H), 4.61 (t, 1H), 7.23-7.28 (m, 1H), 7.32 (s, 1H), 7.34 (d, 1H), 7.75 (td, 1H), 8.51-8.58 (m, 1H).<br>LC-MS (Method 1):<br>$R_t$ = 0.81 min; m/z = 442 $(M+H)^+$. |
| **54** | (2-{[cyclopropyl(pyridin-2-yl)methyl]amino}-1,3-thiazol-5-yl)[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone formate (1:1) (diastereomer mixture)<br>  <br>from (5-bromo-1,3-thiazol-2-yl)[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone and rac-1-cyclopropyl-1-(pyridin-2-yl)methanamine | LC-MS (Method 1):<br>$R_t$ = 0.80 min; m/z = 438 $(M-H-CO_2H_2)^-$. |

| Example | Name / Structure / Starting material | Analytical data |
|---|---|---|
| **55** | (2-{[2-methoxy-1-(pyridin-2-yl)ethyl]amino}-1,3-thiazol-5-yl)[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone (diastereomer mixture)<br>  <br>from (5-bromo-1,3-thiazol-2-yl)[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone and rac-2-methoxy-1-(pyridin-2-yl)ethanamine dihydrochloride | LC-MS (Method 1):<br>$R_t$ = 0.70 min; m/z = 442 $(M-H)^-$. |
| **56** | (2-{[1-(5-chloropyridin-2-yl)ethyl]amino}-1,3-thiazol-5-yl)[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone (diastereomer mixture)<br>  <br>from (5-bromo-1,3-thiazol-2-yl)[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone and rac-1-(5-chloropyridin-2-yl)ethanamine hydrochloride (1:1) | LC-MS (Method 1):<br>$R_t$ = 0.95 min; m/z = 448/450 $(M+H)^+$. |

**Example 57 and Example 58**

{2-[6,7-Dihydro-5H-cyclopenta[b]pyridin-7-ylamino]-1,3-thiazol-5-yl}[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone (*diastereomers 1 and 2*)



195 mg (0.78 mmol) of the diastereomer mixture of {2-[(6,7-dihydro-5H-cyclopenta[b]pyridin-7-ylamino]-1,3-thiazol-5-yl}[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone (Example 49) was separated into the diastereomers by preparative HPLC on a chiral phase [column: YMC Chiralart Amylose SA, 5 µm, 250 mm x 20 mm; eluent: ethanol + 0.2% diethylamine/n-heptane 50:50; flow rate: 18 ml/min; UV detection: 220 nm; temperature: 40°C]:

Example 57 (*diastereomer 1*):

{2-[6,7-Dihydro-5H-cyclopenta[b]pyridin-7-ylamino]-1,3-thiazol-5-yl}[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone

Yield: 64 mg

$R_t$ = 7,405 min; chemical purity > 99%; > 99% de

[Column: YMC Chiralart Amylose SA, 5 µm, 250 mm x 4.6 mm; eluent: n-heptane/ethanol + 0.2% diethylamine 50:50; flow rate: 1 ml/min; temperature: 40°C; UV detection: 220 nm].

LC-MS (Method 1): $R_t$ = 0.73 min; m/z = 424 $(M-H)^-$.

$^1$H-NMR (400 MHz, DMSO-$d_6$, δ/ppm): 0.75-0.88 (m, 4H, therein at 0.82 (d, 3H)), 1.31-1.46 (m, 3H), 1.47-1.68 (m, 3H), 1.71-1.81 (m, 3H), 1.85-1.97 (m, 1H), 2.01-2.10 (m, 1H), 2.44-2.55 (m, 1H, partly hidden by DMSO), 2.55-2.64 (m, 1H), 2.71-2.79 (m, 2H), 2.80-3.01 (m, 4H), 4.29 (br. d, 2H), 5.15-5.24 (m, 1H), 7.24 (dd, 1H), 7.42 (s, 1H), 7.69 (d, 1H), 8.38 (d, 1H), 8.44 (d, 1H).

$[\alpha]_D^{20}$ = -15.41° (c = 0.305, methanol).

Example 58 (*diastereomer 2*):

{2-[6,7-Dihydro-5H-cyclopenta[b]pyridin-7-ylamino]-1,3-thiazol-5-yl}[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone

Yield: 64 mg

$R_t$ = 8.009 min; chemical purity > 99%; > 99% de

[Column: YMC Chiralart Amylose SA, 5 µm, 250 mm x 4.6 mm; eluent: n-heptane/ethanol + 0.2% diethylamine 50:50; flow rate: 1 ml/min; temperature: 40°C; UV detection: 220 nm].

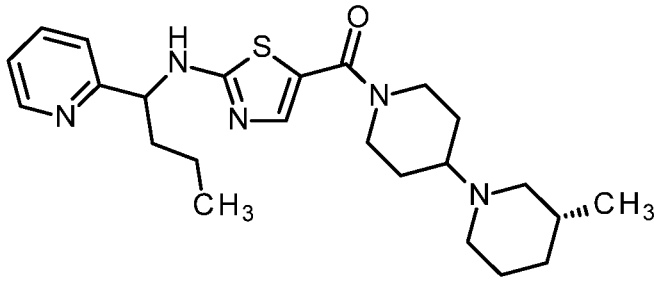
LC-MS (Method 1): $R_t$ = 0.73 min; m/z = 424 $(M-H)^-$.

$^1$H-NMR (400 MHz, DMSO-$d_6$, δ/ppm): 0.75-0.88 (m, 4H, therein at 0.82 (d, 3H)), 1.31-1.47 (m, 3H), 1.47-1.68 (m, 3H), 1.71-1.81 (m, 3H), 1.85-1.97 (m, 1H), 2.01-2.11 (m, 1H), 2.45-2.55 (m, 1H, partly hidden by DMSO), 2.55-2.64 (m, 1H), 2.70-2.79 (m, 2H), 2.80-3.01 (m, 4H), 4.29 (br. d, 2H), 5.15-5.24 (m, 1H), 7.24 (dd, 1H), 7.42 (s, 1H), 7.69 (d, 1H), 8.38 (d, 1H), 8.44 (d, 1H).

$[\alpha]_D^{20}$ = +8.12° (c = 0.275, methanol).

**Example 59 and Example 60**

[(3*R*)-3-Methyl[1,4'-bipiperidine]-1'-yl](2-{[1-(pyridin-2-yl)butyl]amino}-1,3-thiazol-5-yl)methanone (*diastereomers 1 and 2*)



167 mg (0.38 mmol) of the diastereomer mixture [(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl](2-{[1-(pyridin-2-yl)butyl]amino}-1,3-thiazol-5-yl)methanone (Example 50) was separated into the diastereomers by preparative HPLC on a chiral phase [column: YMC Chiralart Amylose SA, 5 µm, 250 mm x 20 mm; eluent: ethanol + 0.2% diethylamine/n-heptane 50:50; flow rate: 18 ml/min; UV detection: 220 nm; temperature: 40°C]:

Example 59 (*diastereomer 1*):

[(3*R*)-3-Methyl[1,4'-bipiperidine]-1'-yl](2-{[1-(pyridin-2-yl)butyl]amino}-1,3-thiazol-5-yl)methanone

Yield: 68 mg

$R_t$ = 4.714 min; chemical purity > 99%; > 99% de

[Column: YMC Chiralart Amylose SA, 5 µm, 250 mm x 4.6 mm; eluent: n-heptane/ethanol + 0.2% diethylamine 50:50; flow rate: 1 ml/min; temperature: 40°C; UV detection: 220 nm].

LC-MS (Method 1): $R_t$ = 0.90 min; m/z = 440 $(M-H)^-$.

$^1$H-NMR (400 MHz, DMSO-$d_6$, δ/ppm): 0.74-0.84 (m, 4H, therein at 0.81 (d, 3H)), 0.88 (t, 3H), 1.21-1.45 (m, 5H), 1.45-1.66 (m, 3H), 1.68-1.83 (m, 5H), 1.98-2.07 (m, 1H), 2.41-2.53 (m, 1H, partly hidden by DMSO), 2.68-2.77 (m, 2H), 2.87 (br. t, 2H), 4.24 (br. d, 2H), 4.72-4.81 (m, 1H), 7.25 (ddd, 1H), 7.33 (s, 1H), 7.36 (d, 1H), 7.75 (td, 1H), 8.52 (dt, 1H), 8.60 (d, 1H).

$[\alpha]_D^{20}$ = +26.82° (c = 0.450, methanol).

Example 60 (*diastereomer 2*):

[(3*R*)-3-Methyl[1,4'-bipiperidine]-1'-yl](2-{[1-(pyridin-2-yl)butyl]amino}-1,3-thiazol-5-yl)methanone

Yield: 71 mg

$R_t$ = 7.813 min; chemical purity > 99%; > 99% de

[Column: YMC Chiralart Amylose SA, 5 µm, 250 mm x 4.6 mm; eluent: n-heptane/ethanol + 0.2% diethylamine 50:50; flow rate: 1 ml/min; temperature: 40°C; UV detection: 220 nm].

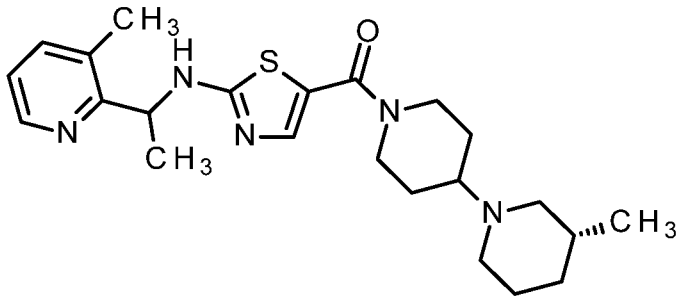
LC-MS (Method 1): $R_t$ = 0.90 min; m/z = 440 $(M-H)^-$.

$^1$H-NMR (400 MHz, DMSO-$d_6$, δ/ppm): 0.73-0.85 (m, 4H, therein at 0.81 (d, 3H)), 0.88 (t, 3H), 1.21-1.45 (m, 5H), 1.45-1.66 (m, 3H), 1.68-1.83 (m, 5H), 1.98-2.07 (m, 1H), 2.42-2.53 (m, 1H, partly hidden by DMSO), 2.68-2.78 (m, 2H), 2.87 (br. t, 2H), 4.24 (br. d, 2H), 4.73-4.82 (m, 1H), 7.25 (ddd, 1H), 7.33 (s, 1H), 7.36 (d, 1H), 7.72-7.78 (m, 1H), 8.50-8.54 (m, 1H), 8.60 (d, 1H).

$[\alpha]_D^{20}$ = -37.69° (c = 0.260, methanol).

**Example 61 and Example 62**

[(3*R*)-3-Methyl[1,4'-bipiperidine]-1'-yl](2-{[1-(3-methylpyridin-2-yl)ethyl]amino}-1,3-thiazol-5-yl)methanone (*diastereomers 1 and 2*)



66 mg (0.15 mmol) of the diastereomer mixture [(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl](2-{[1-(3-methylpyridin-2-yl)ethyl]amino}-1,3-thiazol-5-yl)methanone (Example 46) was separated into the diastereomers by preparative HPLC on a chiral phase [column: Daicel Chiralpak ID, 5 µm, 250 mm x 20 mm; eluent: ethanol + 0.2% diethylamine/n-heptane 50:50; flow rate: 15 ml/min; UV detection: 210 nm; temperature: 40°C]:

Example 61 (*diastereomer 1*):

[(3*R*)-3-Methyl[1,4'-bipiperidine]-1'-yl](2-{[1-(3-methylpyridin-2-yl)ethyl]amino}-1,3-thiazol-5-yl)methanone

Yield: 27 mg

$R_t$ = 2.007 min; chemical purity > 99%; > 99% de

[Column: Daicel Chiralpak ID-3, 3 µm, 50 mm x 4.6 mm; eluent: n-heptane/ethanol + 0.2% diethylamine 50:50; flow rate: 1 ml/min; temperature: 30°C; UV detection: 220 nm].

LC-MS (Method 1): $R_t$ = 0.70 min; m/z = 426 $(M-H)^-$.

$^1$H-NMR (400 MHz, DMSO-$d_6$, δ/ppm): 0.72-0.90 (m, 4H, therein at 0.81 (d, 3H)), 1.15-1.45 (m, 6H, therein at 1.42 (d, 3H)), 1.45-1.66 (m, 3H), 1.67-1.79 (m, 3H), 1.99-2.10 (m, 1H), 2.39 (s, 3H), 2.42-2.53 (m, 1H, partly hidden by DMSO), 2.67-2.78 (m, 2H), 2.87 (br. t, 2H), 4.24 (br. d, 2H), 5.21 (quin., 1H), 7.19 (dd, 1H), 7.34 (s, 1H), 7.56 (d, 1H), 8.38 (d, 1H), 8.51 (d, 1H).

$[\alpha]_D^{20}$ = +19.60° (c = 0.250, methanol).

Example 62 (*diastereomer 2*):

[(3*R*)-3-Methyl[1,4'-bipiperidine]-1'-yl](2-{[1-(3-methylpyridin-2-yl)ethyl]amino}-1,3-thiazol-5-yl)methanone

Yield: 29 mg

$R_t$ = 2.958 min; chemical purity > 99%; > 99% de

[Column: Daicel Chiralpak ID-3, 3 µm, 50 mm x 4.6 mm; eluent: n-heptane/ethanol + 0.2% diethylamine 50:50; flow rate: 1 ml/min; temperature: 30°C; UV detection: 220 nm].

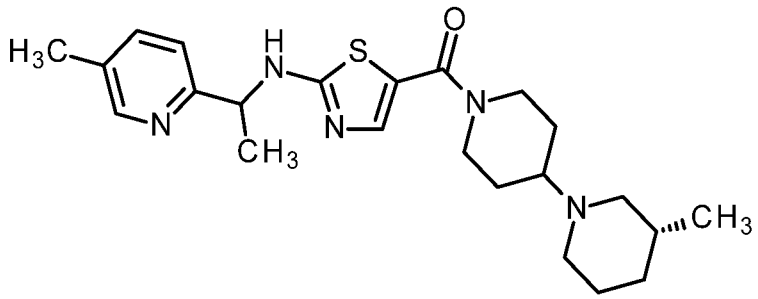
LC-MS (Method 1): $R_t$ = 0.70 min; m/z = 426 $(M-H)^-$.

$^1$H-NMR (400 MHz, DMSO-$d_6$, δ/ppm): 0.72-0.90 (m, 4H, therein at 0.81 (d, 3H)), 1.14-1.46 (m, 6H, therein at 1.42 (d, 3H)), 1.46-1.66 (m, 3H), 1.67-1.79 (m, 3H), 1.99-2.10 (m, 1H), 2.39 (s, 3H), 2.42-2.53 (m, 1H, partly hidden by DMSO), 2.72 (br. d, 2H), 2.87 (br. t, 2H), 4.24 (br. d, 2H), 5.21 (quin., 1H), 7.19 (dd, 1H), 7.34 (s, 1H), 7.56 (d, 1H), 8.38 (d, 1H), 8.51 (d, 1H).

$[\alpha]_D^{20}$ = -25.33° (c = 0.250, methanol).

**Example 63 and Example 64**

[(3*R*)-3-Methyl[1,4'-bipiperidine]-1'-yl](2-{[1-(5-methylpyridin-2-yl)ethyl]amino}-1,3-thiazol-5-yl)methanone (*diastereomers 1 and 2*)




195 mg (0.41 mmol) of the diastereomer mixture [(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl](2-{[1-(5-methylpyridin-2-yl)ethyl]amino}-1,3-thiazol-5-yl)methanone formate (1:1) (Example 47) was separated into the diastereomers by preparative HPLC on a chiral phase [column: YMC Chiralart

Amylose SA, 5 µm, 250 mm x 20 mm; eluent: ethanol + 0.2% diethylamine/n-heptane 50:50; flow rate: 20 ml/min; UV detection: 300 nm; temperature: 40°C]:

Example 63 (*diastereomer 1*):

[(3*R*)-3-Methyl[1,4'-bipiperidine]-1'-yl](2-{[1-(5-methylpyridin-2-yl)ethyl]amino}-1,3-thiazol-5-yl)methanone

Yield: 64 mg

$R_t$ = 5.066 min; chemical purity > 99%; > 99% de

[Column: YMC Chiralart Amylose SA, 5 µm, 250 mm x 4.6 mm; eluent: n-heptane/ethanol + 0.2% diethylamine 50:50; flow rate: 1 ml/min; temperature: 40°C; UV detection: 300 nm].

LC-MS (Method 1): $R_t$ = 0.72 min; m/z = 426 $(M-H)^-$.

$^1$H-NMR (400 MHz, DMSO-$d_6$, δ/ppm): 0.73-0.87 (m, 4H, therein at 0.81 (d, 3H)), 1.26-1.47 (m, 6H, therein at 1.44 (d, 3H)), 1.47-1.66 (m, 3H), 1.67-1.79 (m, 3H), 1.98-2.08 (m, 1H), 2.26 (s, 3H), 2.41-2.53 (m, 1H, partly hidden by DMSO), 2.67-2.78 (m, 2H), 2.88 (br. t, 2H), 4.24 (br. d, 2H), 4.77-4.87 (m, 1H), 7.26 (d, 1H), 7.34 (s, 1H), 7.56 (dd, 1H), 8.35 (d, 1H), 8.58 (d, 1H).

$[\alpha]_D^{20}$ = +32.00° (c = 0.250, methanol).

Example 64 (*diastereomer 2*):

[(3*R*)-3-Methyl[1,4'-bipiperidine]-1'-yl](2-{[1-(5-methylpyridin-2-yl)ethyl]amino}-1,3-thiazol-5-yl)methanone

Yield: 61 mg

$R_t$ = 17.061 min; chemical purity > 99%; > 99% de

[Column: YMC Chiralart Amylose SA, 5 µm, 250 mm x 4.6 mm; eluent: n-heptane/ethanol + 0.2% diethylamine 50:50; flow rate: 1 ml/min; temperature: 40°C; UV detection: 300 nm].

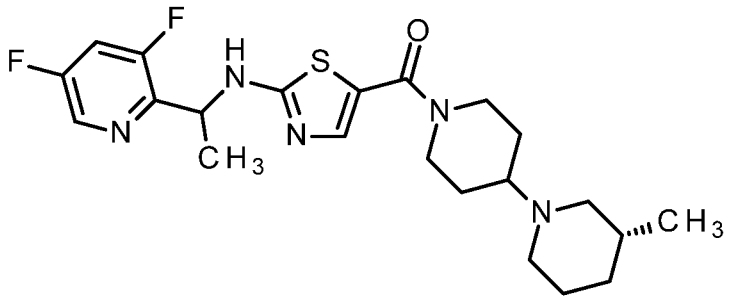
LC-MS (Method 1): $R_t$ = 0.72 min; m/z = 426 $(M-H)^-$.

$^1$H-NMR (400 MHz, DMSO-$d_6$, δ/ppm): 0.73-0.88 (m, 4H, therein at 0.81 (d, 3H)), 1.26-1.47 (m, 6H, therein at 1.44 (d, 3H)), 1.47-1.67 (m, 3H), 1.67-1.78 (m, 3H), 1.98-2.08 (m, 1H), 2.26 (s, 3H), 2.41-2.53 (m, 1H, partly hidden by DMSO), 2.69-2.77 (m, 2H), 2.87 (br. t, 2H), 4.24 (br. d, 2H), 4.78-4.88 (m, 1H), 7.27 (d, 1H), 7.34 (s, 1H), 7.56 (dd, 1H), 8.35 (d, 1H), 8.58 (d, 1H).

$[\alpha]_D^{20}$ = -42.57° (c = 0.350, methanol).

**Example 65 and Example 66**

(2-{[1-(3,5-Difluoropyridin-2-yl)ethyl]amino}-1,3-thiazol-5-yl)[(3R)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone (*diastereomers 1 and 2*)



95 mg (0.21 mmol) of the diastereomer mixture (2-{[1-(3,5-difluoropyridin-2-yl)ethyl]amino}-1,3-thiazol-5-yl)[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone (Example 38) was separated into the diastereomers by preparative HPLC on a chiral phase [column: YMC Chiralart Amylose SA, 5 µm, 250 mm x 20 mm; eluent: ethanol + 0.2% diethylamine/n-heptane 40:60; flow rate: 18 ml/min; UV detection: 300 nm; temperature: 30°C]:

Example 65 (*diastereomer 1*):

(2-{[1-(3,5-Difluoropyridin-2-yl)ethyl]amino}-1,3-thiazol-5-yl)[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone

Yield: 39 mg

$R_t$ = 5.53 min; chemical purity > 99%; > 99% de

[Column: YMC Chiralart Amylose SA, 5 µm, 250 mm x 4.6 mm; eluent: n-heptane/ethanol + 0.2% diethylamine 60:40; flow rate: 1 ml/min; temperature: 30°C; UV detection: 300 nm].

LC-MS (Method 1): $R_t$ = 0.91 min; m/z = 448 $(M-H)^-$.

$^1$H-NMR (400 MHz, DMSO-$d_6$, δ/ppm): 0.73-0.88 (m, 4H, therein at 0.81 (d, 3H)), 1.27-1.42 (m, 3H), 1.42-1.67 (m, 6H, therein at 1.46 (d, 3H)), 1.68-1.78 (m, 3H), 1.98-2.08 (m, 1H), 2.42-2.53 (m, 1H, partly hidden by DMSO), 2.68-2.77 (m, 2H), 2.87 (br. t, 2H), 4.23 (br. d, 2H), 5.20-5.30 (m, 1H), 7.33 (s, 1H), 7.86-7.95 (m, 1H), 8.48 (d, 1H), 8.62 (d, 1H).

$[\alpha]_D^{20}$ = +27.38° (c = 0.280, methanol).

Example 66 (*diastereomer 2*):

(2-{[1-(3,5-Difluoropyridin-2-yl)ethyl]amino}-1,3-thiazol-5-yl)[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone

Yield: 39 mg

$R_t$ = 7.683 min; chemical purity > 99%; > 99% de

[Column: YMC Chiralart Amylose SA, 5 µm, 250 mm x 4.6 mm; eluent: n-heptane/ethanol + 0.2% diethylamine 60:40; flow rate: 1 ml/min; temperature: 30°C; UV detection: 300 nm].

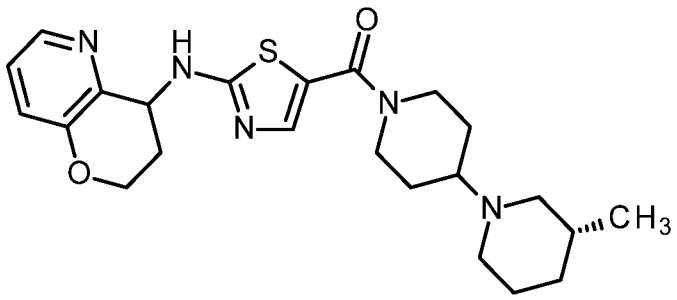
LC-MS (Method 1): $R_t$ = 0.91 min; m/z = 448 $(M-H)^-$.

$^1$H-NMR (400 MHz, DMSO-$d_6$, δ/ppm): 0.72-0.88 (m, 4H, therein at 0.81 (d, 3H)), 1.27-1.42 (m, 3H), 1.42-1.67 (m, 6H, therein at 1.46 (d, 3H)), 1.68-1.78 (m, 3H), 1.98-2.08 (m, 1H), 2.42-2.53 (m, 1H, partly hidden by DMSO), 2.68-2.78 (m, 2H), 2.87 (br. t, 2H), 4.23 (br. d, 2H), 5.20-5.30 (m, 1H), 7.33 (s, 1H), 7.86-7.95 (m, 1H), 8.48 (d, 1H), 8.62 (d, 1H).

$[\alpha]_D^{20}$ = -37.82° (c = 0.275, methanol).

**Example 67 and Example 68**

{2-[3,4-Dihydro-2*H*-pyrano[3,2-b]pyridin-4-ylamino]-1,3-thiazol-5-yl}[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone (*diastereomers 1 and 2*)



111 mg (0.25 mmol) of the diastereomer mixture {2-[3,4-dihydro-2*H*-pyrano[3,2-b]pyridin-4-ylamino]-1,3-thiazol-5-yl}[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone (Example 51) was separated into the diastereomers by preparative HPLC on a chiral phase [column: Daical Chiracel OX-H, 5 µm, 250 mm x 20 mm; eluent: ethanol + 0.2% diethylamine/n-heptane 40:60; flow rate: 16 ml/min; UV detection: 300 nm; temperature: 30°C]:

Example 67 (*diastereomer 1*):

{2-[3,4-Dihydro-2*H*-pyrano[3,2-b]pyridin-4-ylamino]-1,3-thiazol-5-yl}[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone

Yield: 45 mg

$R_t$ = 15.14 min; chemical purity > 99%; > 99% de

[Column: Chiracel OX-H, 5 µm, 250 mm x 4.6 mm; eluent: n-heptane/ethanol + 0.2% diethylamine 60:40; flow rate: 1 ml/min; temperature: 30°C; UV detection: 300 nm].

LC-MS (Method 1): $R_t$ = 0.75 min; m/z = 440 $(M-H)^-$.

$^1$H-NMR (400 MHz, DMSO-$d_6$, δ/ppm): 0.75-0.88 (m, 4H, therein at 0.81 (d, 3H)), 1.31-1.47 (m, 3H), 1.47-1.68 (m, 3H), 1.70-1.81 (m, 3H), 2.00-2.11 (m, 1H), 2.12-2.21 (m, 1H), 2.22-2.32 (m, 1H), 2.44-2.56 (m, 1H, partly hidden by DMSO), 2.70-2.80 (m, 2H), 2.92 (br. t, 2H), 4.14-4.23 (m, 1H), 4.25-4.36 (m, 3H), 4.93-5.00 (m, 1H), 7.26 (d, 2H), 7.43 (s, 1H), 8.16 (t, 1H), 8.54 (d, 1H).

$[\alpha]_D^{20}$ = +20.25° (c = 0.260, methanol).

Example 68 (*diastereomer 2*):

{2-[3,4-Dihydro-2*H*-pyrano[3,2-b]pyridin-4-ylamino]-1,3-thiazol-5-yl}[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone

Yield: 44 mg

$R_t$ = 16.11 min; chemical purity > 99%; > 99% de

[Column: Chiracel OX-H, 5 µm, 250 mm x 4.6 mm; eluent: n-heptane/ethanol + 0.2% diethylamine 60:40; flow rate: 1 ml/min; temperature: 30°C; UV detection: 300 nm].

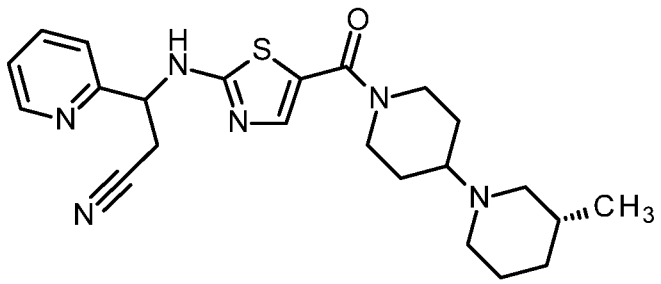
LC-MS (Method 1): $R_t$ = 0.75 min; m/z = 440 $(M-H)^-$.

$^1$H-NMR (400 MHz, DMSO-$d_6$, δ/ppm): 0.73-0.89 (m, 4H, therein at 0.82 (d, 3H)), 1.31-1.46 (m, 3H), 1.46-1.69 (m, 3H), 1.70-1.81 (m, 3H), 2.01-2.11 (m, 1H), 2.12-2.21 (m, 1H), 2.22-2.32 (m, 1H), 2.44-2.56 (m, 1H, partly hidden by DMSO), 2.70-2.80 (m, 2H), 2.92 (br. t, 2H), 4.13-4.23 (m, 1H), 4.25-4.36 (m, 3H), 4.93-5.00 (m, 1H), 7.26 (d, 2H), 7.43 (s, 1H), 8.16 (t, 1H), 8.54 (d, 1H).

$[\alpha]_D^{20}$ = -32.53° (c = 0.250, methanol).

**Example 69 and Example 70**

3-[(5-{[(3*R*)-3-Methyl[1,4'-bipiperidine]-1'-yl]carbonyl}-1,3-thiazol-2-yl)amino]-3-(pyridin-2-yl)propanenitrile (*diastereomers 1 and 2*)



65 mg (0.15 mmol) of the diastereomer mixture of 3-[(5-{[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]carbonyl}-1,3-thiazol-2-yl)amino]-3-(pyridin-2-yl)propanenitrile (Example 48) was separated into the diastereomers by preparative HPLC on a chiral phase [column: Daicel Chiralcel OX-H, 5 µm, 250 mm x 20 mm; eluent: ethanol + 0.2% diethylamine/n-heptane 50:50; flow rate: 15 ml/min; UV detection: 210 nm; temperature: 40°C]:

Example 69 (*diastereomer 1*):

3-[(5-{[(3*R*)-3-Methyl[1,4'-bipiperidine]-1'-yl]carbonyl}-1,3-thiazol-2-yl)amino]-3-(pyridin-2-yl)propanenitrile

Yield: 26 mg

$R_t$ = 2.02 min; chemical purity > 99%; > 99% de

[Column: Daicel Chiracel OX-3, 3 µm, 50 mm x 4.6 mm; eluent: n-heptane/ethanol + 0.2% diethylamine 50:50; flow rate: 1 ml/min; temperature: 30°C; UV detection: 220 nm].

LC-MS (Method 1): $R_t$ = 0.75 min; m/z = 437 $(M-H)^-$.

$^1$H-NMR (400 MHz, DMSO-$d_6$, δ/ppm): 0.73-0.90 (m, 4H, therein at 0.82 (d, 3H)), 1.28-1.46 (m, 3H), 1.46-1.67 (m, 3H), 1.68-1.80 (m, 3H), 1.98-2.10 (m, 1H), 2.43-2.56 (m, 1H, partly hidden by DMSO), 2.69-2.79 (m, 2H), 2.91 (br. t, 2H), 3.10-3.27 (m, 2H), 4.26 (br. d, 2H), 5.26-5.36 (m, 1H), 7.34-7.40 (m, 1H), 7.42 (s, 1H), 7.50 (d, 1H), 7.84 (td, 1H), 8.60 (d, 1H), 8.86 (br. d, 1H).

$[\alpha]_D^{20}$ = +19.74° (c = 0.260, methanol).

Example 70 (*diastereomer 2*):

3-[(5-{[(3*R*)-3-Methyl[1,4'-bipiperidine]-1'-yl]carbonyl}-1,3-thiazol-2-yl)amino]-3-(pyridin-2-yl)propanenitrile

Yield: 27 mg

$R_t$ = 2.43 min; chemical purity > 99%; > 99% de

[Column: Daicel Chiracel OX-3, 3 µm, 50 mm x 4.6 mm; eluent: n-heptane/ethanol + 0.2% diethylamine 50:50; flow rate: 1 ml/min; temperature: 30°C; UV detection: 220 nm].

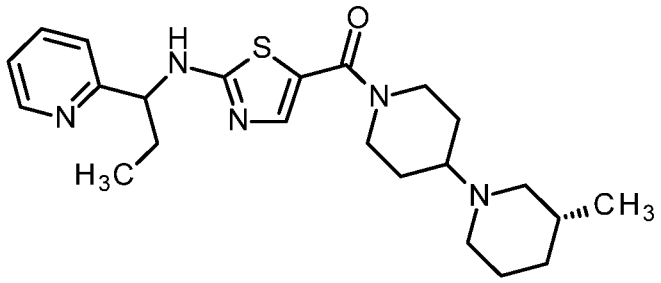
LC-MS (Method 1): $R_t$ = 0.76 min; m/z = 437 $(M-H)^-$.

$^1$H-NMR (400 MHz, DMSO-$d_6$, δ/ppm): 0.74-0.89 (m, 4H, therein at 0.81 (d, 3H)), 1.29-1.45 (m, 3H), 1.46-1.68 (m, 3H), 1.69-1.80 (m, 3H), 1.99-2.09 (m, 1H), 2.43-2.56 (m, 1H, partly hidden by DMSO), 2.69-2.79 (m, 2H), 2.91 (br. t, 2H), 3.10-3.26 (m, 2H), 4.26 (br. d, 2H), 5.26-5.35 (m, 1H), 7.34-7.40 (m, 1H), 7.42 (s, 1H), 7.50 (d, 1H), 7.84 (td, 1H), 8.60 (d, 1H), 8.86 (br. d, 1H).

$[\alpha]_D^{20}$ = -30.77° (c = 0.260, methanol).

**Example 71 and Example 72**

[(3*R*)-3-Methyl[1,4'-bipiperidine]-1'-yl](2-{[1-(pyridin-2-yl)propyl]amino}-1,3-thiazol-5-yl)methanone (*diastereomers 1 and 2*)



54 mg (0.13 mmol) of the diastereomer mixture of [(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl](2-{[1-(pyridin-2-yl)propyl]amino}-1,3-thiazol-5-yl)methanone (Example 44) was separated into the diastereomers by preparative HPLC on a chiral phase [column: Daicel Chiralpak IG, 5 µm, 250 mm x 20 mm; eluent: ethanol + 0.2% diethylamine/n-heptane 50:50; flow rate: 20 ml/min; UV detection: 210 nm; temperature: 50°C]:

Example 71 (*diastereomer 1*):

[(3*R*)-3-Methyl[1,4'-bipiperidine]-1'-yl](2-{[1-(pyridin-2-yl)propyl]amino}-1,3-thiazol-5-yl)methanone

Yield: 19 mg

$R_t$ = 4.03 min; chemical purity > 99%; > 99% de

[Column: Daicel Chiralpak IG-3, 3 µm, 50 mm x 4.6 mm; eluent: n-heptane/ethanol + 0.2% diethylamine 50:50; flow rate: 1 ml/min; temperature: 30°C; UV detection: 220 nm].

LC-MS (Method 1): $R_t$ = 0.78 min; m/z = 426 $(M-H)^-$.

$^1$H-NMR (400 MHz, DMSO-$d_6$, δ/ppm): 0.71-0.93 (m, 7H, therein at 0.81 (d, 3H) and at 0.88 (t, 3H)), 1.27-1.46 (m, 3H), 1.46-1.67 (m, 3H), 1.68-1.78 (m, 3H), 1.78-1.93 (m, 2H), 1.98-2.09 (m, 1H), 2.41-2.57 (m, 1H, partly hidden by DMSO), 2.68-2.78 (m, 2H), 2.87 (br. t, 2H), 4.24 (br. d, 2H), 4.64-4.74 (m, 1H), 7.26 (ddd, 1H), 7.34 (s, 1H), 7.36 (d, 1H), 7.72-7.80 (m, 1H), 8.52 (d, 1H), 8.59 (d, 1H).

$[\alpha]_D^{20}$ = +31.70° (c = 0.265, methanol).

Example 72 (*diastereomer 2*):

[(3*R*)-3-Methyl[1,4'-bipiperidine]-1'-yl](2-{[1-(pyridin-2-yl)propyl]amino}-1,3-thiazol-5-yl)methanone

Yield: 19 mg

$R_t$ = 7.25 min; chemical purity > 99%; > 99% de

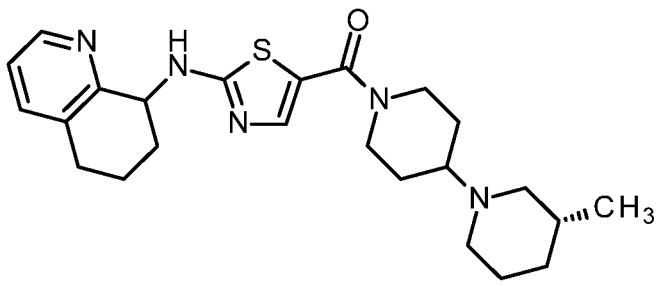
[Column: Daicel Chiralpak IG-3, 3 µm, 50 mm x 4.6 mm; eluent: n-heptane/ethanol + 0.2% diethylamine 50:50; flow rate: 1 ml/min; temperature: 30°C; UV detection: 220 nm].

LC-MS (Method 1): $R_t$ = 0.77 min; m/z = 426 $(M-H)^-$.

$^1$H-NMR (400 MHz, DMSO-$d_6$, δ/ppm): 0.72-0.93 (m, 7H, therein at 0.81 (d, 3H) and at 0.88 (t, 3H)), 1.27-1.44 (m, 3H), 1.45-1.66 (m, 3H), 1.68-1.78 (m, 3H), 1.78-1.93 (m, 2H), 1.98-2.09 (m, 1H), 2.41-2.57 (m, 1H, partly hidden byh DMSO), 2.68-2.78 (m, 2H), 2.87 (br. t, 2H), 4.24 (br. d, 2H), 4.63-4.73 (m, 1H), 7.26 (ddd, 1H), 7.33 (s, 1H), 7.36 (d, 1H), 7.71-7.80 (m, 1H), 8.53 (d, 1H), 8.59 (d, 1H).

**Example 73 and Example 74**

[(3*R*)-3-Methyl[1,4'-bipiperidine]-1'-yl]{2-[5,6,7,8-tetrahydroquinolin-8-ylamino]-1,3-thiazol-5-yl}methanone (*diastereomers 1 and 2*)



66 mg (0.15 mmol) of the diastereomer mixture [(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]{2-[5,6,7,8-tetrahydroquinolin-8-ylamino]-1,3-thiazol-5-yl}methanone (Example 43) was separated into the diastereomers by preparative HPLC on a chiral phase [column: Daicel Chiralcel OX-H, 5 µm,

250 mm x 20 mm; eluent: isopropanol + 0.2% diethylamine/n-heptane 40:60; flow rate: 20 ml/min; UV detection: 220 nm; temperature: 50°C]:

Example 73 (*diastereomer 1*):

[(3*R*)-3-Methyl[1,4'-bipiperidine]-1'-yl]{2-[5,6,7,8-tetrahydroquinolin-8-ylamino]-1,3-thiazol-5-yl}methanone

Yield: 24 mg

$R_t$ = 3.52 min; chemical purity > 99%; > 99% de

[Column: Daicel Chiralpak OX-3, 3 µm, 50 mm x 4.6 mm; eluent: n-heptane/isopropanol + 0.2% diethylamine 50:50; flow rate: 1 ml/min; temperature: 30°C; UV detection: 220 nm].

LC-MS (Method 1): $R_t$ = 0.74 min; m/z = 438 $(M-H)^-$.

$^1$H-NMR (400 MHz, DMSO-$d_6$, δ/ppm): 0.75-0.89 (m, 4H, therein at 0.82 (d, 3H)), 1.31-1.47 (m, 3H), 1.47-1.68 (m, 3H), 1.71-1.91 (m, 5H), 1.91-2.01 (m, 1H), 2.01-2.12 (m, 2H), 2.44-2.57 (m, 1H, partly hidden by DMSO), 2.69-2.86 (m, 4H), 2.91 (br. t, 2H), 4.29 (br. d, 2H), 4.85-4.94 (m, 1H), 7.24 (dd, 1H), 7.41 (s, 1H), 7.55 (d, 1H), 8.34-8.44 (m, 2H).

$[\alpha]_D^{20}$ = +55.07° (c = 0.250, methanol).

Example 74 (*diastereomer 2*):

[(3*R*)-3-Methyl[1,4'-bipiperidine]-1'-yl]{2-[5,6,7,8-tetrahydroquinolin-8-ylamino]-1,3-thiazol-5-yl}methanone

Yield: 31 mg

$R_t$ = 4.63 min; chemical purity > 99%; > 99% de

[Column: Daicel Chiralpak OX-3, 3 µm, 50 mm x 4.6 mm; eluent: n-heptane/isopropanol + 0.2% diethylamine 50:50; flow rate: 1 ml/min; temperature: 30°C; UV detection: 220 nm].

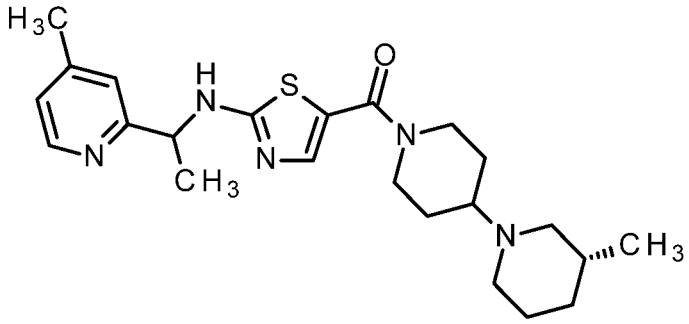
LC-MS (Method 1): $R_t$ = 0.74 min; m/z = 438 $(M-H)^-$.

$^1$H-NMR (400 MHz, DMSO-$d_6$, δ/ppm): 0.75-0.89 (m, 4H, therein at 0.82 (d, 3H)), 1.31-1.46 (m, 3H), 1.46-1.68 (m, 3H), 1.70-1.91 (m, 5H), 1.92-2.01 (m, 1H), 2.01-2.12 (m, 2H), 2.45-2.56 (m, 1H, partly hidden by DMSO), 2.69-2.86 (m, 4H), 2.91 (br. t, 2H), 4.29 (br. d, 2H), 4.86-4.94 (m, 1H), 7.24 (dd, 1H), 7.41 (s, 1H), 7.55 (d, 1H), 8.36-8.43 (m, 2H).

$[\alpha]_D^{20}$ = -68.36° (c = 0.275, methanol).

**Example 75 and Example 76**

[(3*R*)-3-Methyl[1,4'-bipiperidine]-1'-yl](2-{[1-(4-methylpyridin-2-yl)ethyl]amino}-1,3-thiazol-5-yl)methanone (*diastereomers 1 and 2*)



132 mg (0.31 mmol) of the diastereomer mixture [(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl](2-{[1-(4-methylpyridin-2-yl)ethyl]amino}-1,3-thiazol-5-yl)methanone (Example 41) was separated into the diastereomers by preparative HPLC on a chiral phase [column: Daicel Chiralpak IE, 5 µm, 250 mm x 20 mm; eluent: ethanol + 0.2% diethylamine/n-heptane 50:50; flow rate: 18 ml/min; UV detection: 220 nm; temperature: 50°C]:

Example 75 (*diastereomer 1*):

[(3*R*)-3-Methyl[1,4'-bipiperidine]-1'-yl](2-{[1-(4-methylpyridin-2-yl)ethyl]amino}-1,3-thiazol-5-yl)methanone

Yield: 53 mg

$R_t$ = 3.99 min; chemical purity > 99%; > 99% de

[Column: Daicel Chiralpak IE-3, 3 µm, 50 mm x 4.6 mm; eluent: n-heptane/ethanol + 0.2% diethylamine 50:50; flow rate: 1 ml/min; temperature: 30°C; UV detection: 220 nm].

LC-MS (Method 1): $R_t$ = 0.64 min; m/z = 426 $(M-H)^-$.

$^1$H-NMR (400 MHz, DMSO-$d_6$, δ/ppm): 0.73-0.88 (m, 4H, therein at 0.81 (d, 3H)), 1.27-1.47 (m, 6H, therein at 1.44 (d, 3H)), 1.47-1.67 (m, 3H), 1.68-1.79 (m, 3H), 1.98-2.10 (m, 1H), 2.30 (s, 3H), 2.43-2.56 (m, 1H, partly hidden by DMSO), 2.69-2.78 (m, 3H), 2.88 (br. t, 2H), 4.24 (br. d, 2H), 4.78-4.89 (m, 1H), 7.09 (dd, 1H), 7.20 (s, 1H), 7.35 (s, 1H), 8.37 (d, 1H), 8.58 (d, 1H).

$[\alpha]_D^{20}$ = +36.06° (c = 0.305, methanol).

Example 76 (*diastereomer 2*):

[(3*R*)-3-Methyl[1,4'-bipiperidine]-1'-yl](2-{[1-(4-methylpyridin-2-yl)ethyl]amino}-1,3-thiazol-5-yl)methanone

Yield: 53 mg

$R_t$ = 5.60 min; chemical purity > 99%; > 99% de

[Column: Daicel Chiralpak IE-3, 3 µm, 50 mm x 4.6 mm; eluent: n-heptane/ethanol + 0.2% diethylamine 50:50; flow rate: 1 ml/min; temperature: 30°C; UV detection: 220 nm].

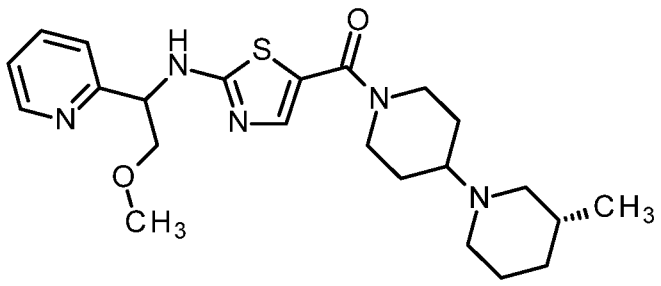
LC-MS (Method 1): $R_t$ = 0.63 min; m/z = 426 $(M-H)^-$.

$^1$H-NMR (400 MHz, DMSO-$d_6$, δ/ppm): 0.73-0.88 (m, 4H, therein at 0.81 (d, 3H)), 1.28-1.46 (m, 6H, therein at 1.44 (d, 3H)), 1.46-1.66 (m, 3H), 1.68-1.79 (m, 3H), 1.99-2.10 (m, 1H), 2.30 (s, 3H), 2.43-2.56 (m, 1H, partly hidden by DMSO), 2.69-2.78 (m, 3H), 2.88 (br. t, 2H), 4.24 (br. d, 2H), 4.79-4.89 (m, 1H), 7.09 (dd, 1H), 7.20 (s, 1H), 7.35 (s, 1H), 8.37 (d, 1H), 8.57 (d, 1H).

$[\alpha]_D^{20}$ = -48.52° (c = 0.270, methanol).

**Example 77 and Example 78**

(2-{[2-Methoxy-1-(pyridin-2-yl)ethyl]amino}-1,3-thiazol-5-yl)[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone (*diastereomers 1 and 2*)



68 mg (0.15 mmol) of the diastereomer mixture of (2-{[2-methoxy-1-(pyridin-2-yl)ethyl]amino}-1,3-thiazol-5-yl)[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone (Example 55) was separated into the diastereomers by preparative HPLC on a chiral phase [column: Daicel Chiralpak I5, 5 µm, 250 mm x 20 mm; eluent: ethanol + 0.2% diethylamine/n-heptane 50:50; flow rate: 18 ml/min; UV detection: 210 nm; temperature: 40°C]:

Example 77 (*diastereomer 1*):

(2-{[2-Methoxy-1-(pyridin-2-yl)ethyl]amino}-1,3-thiazol-5-yl)[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone

Yield: 15 mg

$R_t$ = 1.17 min; chemical purity > 99%; > 99% de

[Column: Daicel Chiralpak IB-3, 3 µm, 50 mm x 4.6 mm; eluent: n-heptane/ethanol + 0.2% diethylamine 50:50; flow rate: 1 ml/min; temperature: 30°C; UV detection: 220 nm].

LC-MS (Method 1): $R_t$ = 0.73 min; m/z = 442 $(M-H)^-$.

$^1$H-NMR (400 MHz, DMSO-$d_6$, δ/ppm): 0.73-0.88 (m, 4H, therein at 0.81 (d, 3H)), 1.27-1.45 (m, 3H), 1.46-1.67 (m, 3H), 1.67-1.80 (m, 3H), 1.99-2.11 (m, 1H), 2.43-2.56 (m, 1H, partly hidden by DMSO), 2.68-2.79 (m, 3H), 2.88 (br. t, 2H), 3.25 (s, 3H), 3.64-3.76 (m, 2H), 4.24 (br. d, 2H), 5.02-5.11 (m, 1H), 7.28 (ddd, 1H), 7.34 (s, 1H), 7.38 (d, 1H), 7.76 (td, 1H), 8.54 (d, 1H), 8.66 (d, 1H).

$[\alpha]_D^{20}$ = -34.69° (c = 0.270, methanol).

Example 78 (*diastereomer 2*):

(2-{[2-Methoxy-1-(pyridin-2-yl)ethyl]amino}-1,3-thiazol-5-yl)[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone

Yield: 19 mg

$R_t$ = 1.45 min; chemical purity > 99%; > 99% de

[Column: Daicel Chiralpak IB-3, 3 µm, 50 mm x 4.6 mm; eluent: n-heptane/ethanol + 0.2% diethylamine 50:50; flow rate: 1 ml/min; temperature: 30°C; UV detection: 220 nm].

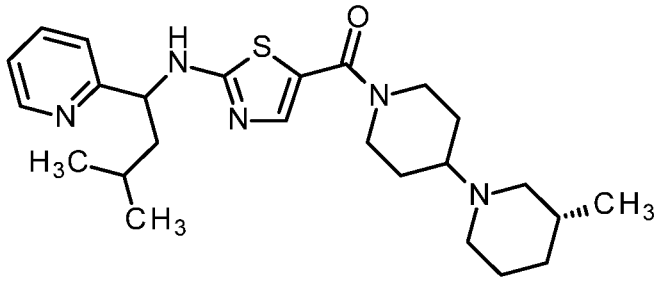
LC-MS (Method 1): $R_t$ = 0.72 min; m/z = 442 $(M-H)^-$.

$^1$H-NMR (400 MHz, DMSO-$d_6$, δ/ppm): 0.72-0.88 (m, 4H, therein at 0.81 (d, 3H)), 1.27-1.46 (m, 3H), 1.46-1.67 (m, 3H), 1.68-1.80 (m, 3H), 1.99-2.10 (m, 1H), 2.43-2.56 (m, 1H, partly hidden by DMSO), 2.69-2.79 (m, 3H), 2.88 (br. t, 2H), 3.25 (s, 3H), 3.65-3.75 (m, 2H), 4.24 (br. d, 2H), 5.02-5.11 (m, 1H), 7.28 (ddd, 1H), 7.34 (s, 1H), 7.38 (d, 1H), 7.76 (td, 1H), 8.54 (d, 1H), 8.66 (d, 1H).

$[\alpha]_D^{20}$ = +18.98° (c = 0.260, methanol).

**Example 79 and Example 80**

[(3*R*)-3-Methyl[1,4'-bipiperidine]-1'-yl](2-{[3-methyl-1-(pyridin-2-yl)butyl]amino}-1,3-thiazol-5-yl)methanone (*diastereomers 1 and 2*)




103 mg (0.23 mmol) of the diastereomer mixture of [(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl](2-{[3-methyl-1-(pyridin-2-yl)butyl]amino}-1,3-thiazol-5-yl)methanone (Example 52) was separated into the diastereomers by preparative HPLC on a chiral phase [column: Daicel Chiralpak IE, 5 µm, 250 mm x 20 mm; eluent: ethanol + 0.2% diethylamine/n-heptane 30:70; flow rate: 20 ml/min; UV detection: 220 nm; temperature: 50°C]:

Example 79 (*diastereomer 1*):

[(3*R*)-3-Methyl[1,4'-bipiperidine]-1'-yl](2-{[3-methyl-1-(pyridin-2-yl)butyl]amino}-1,3-thiazol-5-yl)methanone

Yield: 41 mg

$R_t$ = 2.07 min; chemical purity > 99%; > 99% de

[Column: Daicel Chiralpak ID-3, 3 µm, 50 mm x 4.6 mm; eluent: n-heptane/ethanol + 0.2% diethylamine 70:30; flow rate: 1 ml/min; temperature: 30°C; UV detection: 220 nm].

LC-MS (Method 1): $R_t$ = 1.00 min; m/z = 454 $(M-H)^-$.

$^1$H-NMR (400 MHz, DMSO-$d_6$, δ/ppm): 0.74-0.86 (m, 4H, therein at 0.81 (d, 3H)), 0.90 (d, 3H), 0.92 (d, 3H), 1.26-1.45 (m, 3H), 1.45-1.66 (m, 5H), 1.66-1.79 (m, 4H), 1.98-2.08 (m, 1H), 2.41-2.57 (m, 1H, partly hidden by DMSO), 2.68-2.78 (m, 2H), 2.87 (br. t, 2H), 4.23 (br. d, 2H), 4.78-4.87 (m, 1H), 7.25 (ddd, 1H), 7.33 (s, 1H), 7.37 (d, 1H), 7.75 (td, 1H), 8.52 (d, 1H), 8.60 (d, 1H).

$[\alpha]_D^{20}$ = +27.58° (c = 0.255, methanol).

Example 80 (*diastereomer 2*):

[(3*R*)-3-Methyl[1,4'-bipiperidine]-1'-yl](2-{[3-methyl-1-(pyridin-2-yl)butyl]amino}-1,3-thiazol-5-yl)methanone

Yield: 42 mg

$R_t$ = 3.19 min; chemical purity > 99%; > 99% de

[Column: Daicel Chiralpak ID-3, 3 µm, 50 mm x 4.6 mm; eluent: n-heptane/ethanol + 0.2% diethylamine 70:30; flow rate: 1 ml/min; temperature: 30°C; UV detection: 220 nm].

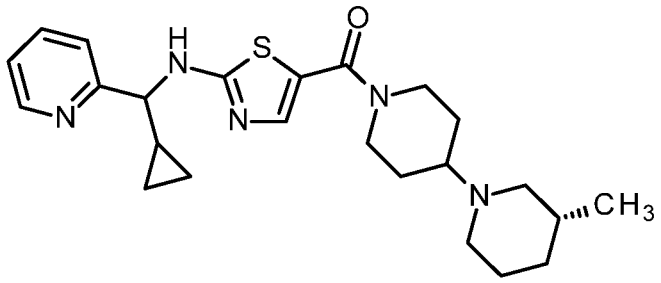
LC-MS (Method 1): $R_t$ = 1.01 min; m/z = 454 $(M-H)^-$.

$^1$H-NMR (400 MHz, DMSO-$d_6$, δ/ppm): 0.73-0.86 (m, 4H, therein at 0.81 (d, 3H)), 0.90 (d, 3H), 0.92 (d, 3H), 1.26-1.45 (m, 3H), 1.45-1.66 (m, 5H), 1.66-1.78 (m, 4H), 1.98-2.08 (m, 1H), 2.41-2.57 (m, 1H, partly hidden by DMSO), 2.68-2.78 (m, 2H), 2.87 (br. t, 2H), 4.23 (br. d, 2H), 4.78-4.87 (m, 1H), 7.25 (ddd, 1H), 7.34 (s, 1H), 7.36 (d, 1H), 7.75 (td, 1H), 8.52 (d, 1H), 8.60 (d, 1H).

$[\alpha]_D^{20}$ = -32.30° (c = 0.290, methanol).

**Example 81 and Example 82**

(2-{[Cyclopropyl(pyridin-2-yl)methyl]amino}-1,3-thiazol-5-yl)[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone (*diastereomer 1 and 2*)



174 mg (0.36 mmol) of the diastereomer mixture(2-{[cyclopropyl(pyridin-2-yl)methyl]amino}-1,3-thiazol-5-yl)[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone formate (Example 54) was separated into the diastereomers by preparative HPLC on a chiral phase [column: Daicel Chiralpak ID, 5 µm, 250 mm x 20 mm; eluent: ethanol + 0.2% diethylamine/n-heptane 50:50; flow rate: 15 ml/min; UV detection: 220 nm; temperature: 40°C]:

Example 81 (*diastereomer 1*):

(2-{[Cyclopropyl(pyridin-2-yl)methyl]amino}-1,3-thiazol-5-yl)[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone

Yield: 61 mg

$R_t$ = 1.91 min; chemical purity > 99%; > 99% de

[Column: Daicel Chiralpak ID-3, 3 µm, 50 mm x 4.6 mm; eluent: n-heptane/ethanol + 0.2% diethylamine 50:50; flow rate: 1 ml/min; temperature: 30°C; UV detection: 220 nm].

LC-MS (Method 1): $R_t$ = 0.80 min; m/z = 438 $(M-H)^-$.

$^1$H-NMR (400 MHz, DMSO-$d_6$, δ/ppm): 0.36-0.48 (m, 3H), 0.50-0.58 (m, 1H), 0.73-0.88 (m, 4H, therein at 0.81 (d, 3H)), 1.21-1.44 (m, 4H), 1.45-1.66 (m, 3H), 1.67-1.77 (m, 3H), 1.98-2.08 (m, 1H), 2.41-2.56 (m, 1H, partly hidden by DMSO), 2.68-2.77 (m, 2H), 2.86 (br. t, 2H), 4.18-4.29 (m, 3H), 7.26 (ddd, 1H), 7.30 (s, 1H), 7.40 (d, 1H), 7.76 (td, 1H), 8.52 (d, 1H), 8.75 (d, 1H).

Example 82 (*diastereomer 2*):

(2-{[Cyclopropyl(pyridin-2-yl)methyl]amino}-1,3-thiazol-5-yl)[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone

Yield: 61 mg

$R_t$ = 3.58 min; chemical purity > 99%; > 99% de

[Column: Daicel Chiralpak ID-3, 3 µm, 50 mm x 4.6 mm; eluent: n-heptane/ethanol + 0.2% diethylamine 50:50; flow rate: 1 ml/min; temperature: 30°C; UV detection: 220 nm].

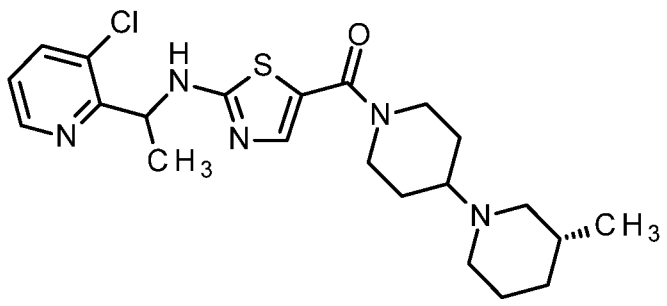
LC-MS (Method 1): $R_t$ = 0.80 min; m/z = 438 $(M-H)^-$.

$^1$H-NMR (400 MHz, DMSO-$d_6$, δ/ppm): 0.36-0.48 (m, 3H), 0.50-0.59 (m, 1H), 0.73-0.88 (m, 4H, therein at 0.81 (d, 3H)), 1.21-1.45 (m, 4H), 1.45-1.66 (m, 3H), 1.67-1.78 (m, 3H), 1.98-2.08 (m, 1H), 2.41-2.56 (m, 1H, partly hidden by DMSO), 2.68-2.77 (m, 2H), 2.87 (br. t, 2H), 4.18-4.30 (m, 3H), 7.26 (ddd, 1H), 7.30 (s, 1H), 7.40 (d, 1H), 7.76 (td, 1H), 8.52 (d, 1H), 8.75 (d, 1H).

$[\alpha]_D^{20}$ = -7.55° (c = 0.265, methanol).

**Example 83 (*diastereomer 1*)**

(2-{[1-(3-Chloropyridin-2-yl)ethyl]amino}-1,3-thiazol-5-yl)[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone




100 mg (0.27 mmol) of (5-bromo-1,3-thiazol-2-yl)[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone and 103 mg (0.54 mmol) of (1*S*)-1-(3-chloropyridin-2-yl)ethanamine hydrochloride (1:1) were dissolved in 1.2 ml of 1-methyl-2-pyrrolidone, and 0.14 ml of N,N-diisopropylethylamine was added. Thereafter, the reaction mixture (closed vessel) was stirred at 140°C overnight. After

cooling to room temperature, the solution was diluted with dichloromethane and washed with saturated sodium hydrogencarbonate solution. After the organic phase had been separated off, the solution was filtered through a hydrophobic filter and concentrated to dryness under reduced pressure. Partial epimerization was found, and therefore the resultant residue was purified by chiral prep. HPLC.

57 mg (0.13 mmol) of the diastereomer mixture of (2-{[(1*S*/*R*)-1-(3-chloropyridin-2-yl)ethyl]amino}-1,3-thiazol-5-yl)[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone was separated into the diastereomers by preparative HPLC on a chiral phase [column: Daicel Chiralpak AZ-H, 5 µm, 250 mm x 20 mm; eluent: ethanol/n-heptane 50:50; flow rate: 20 ml/min; UV detection: 220 nm; temperature: 50°C]:

This gave 32 mg of the title compound (2-{[1-(3-chloropyridin-2-yl)ethyl]amino}-1,3-thiazol-5-yl)[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone *(diastereomer 1)* and 5.4 mg of *diastereomer 2* (2-{[1-(3-chloropyridin-2-yl)ethyl]amino}-1,3-thiazol-5-yl)[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone.

Analysis of (2-{[1-(3-chloropyridin-2-yl)ethyl]amino}-1,3-thiazol-5-yl)[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone (*diastereomer 1)*:

$R_t$ = 3.16 min; chemical purity > 99%; > 99% ee

[Column: Chiralpak AZ-3, 3 µm, 50 mm x 4.6 mm; eluent: n-heptane/ethanol + 0.2% diethylamine 50:50; flow rate: 1 ml/min; temperature: 30°C; UV detection: 220 nm].

LC-MS (Method 1): $R_t$ = 1.00 min; m/z = 446/448 $(M-H)^-$.

$^1$H-NMR (400 MHz, DMSO-$d_6$, δ/ppm):, 0.73-0.87 (m, 4H, therein at 0.81 (d, 3H)), 1.27-1.46 (m, 6H) darin 1.43 (d, 3H)), 1.46-1.66 (m, 3H), 1.67-1.78 (m, 3H), 1.98-2.08 (m, 1H), 2.41-2.53 (m, 1H, partly hidden by DMSO), 2.68-2.78 (m, 2H), 2.87 (br. t, 2H), 4.23 (br. d, 2H), 5.37-5.47 (m, 1H), 7.33 (s, 1H), 7.34 (dd, 1H), 7.91 (dd, 1H), 8.52 (dd, 1H), 8.63 (d, 1H).

$[\alpha]_D^{20}$ = +9.63° (c = 0.270, methanol).

**Example 84 (*diastereomer 2*)**

(2-{[1-(3-Chloropyridin-2-yl)ethyl]amino}-1,3-thiazol-5-yl)[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone

Yield after separation and purification (see Example 83):

5.4 mg

Analysis of (2-{[1-(3-fluoropyridin-2-yl)ethyl]amino}-1,3-thiazol-5-yl)[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone (*diastereomer 2*):

$R_t$ = 2.64 min; chemical purity > 99%; > 99% ee

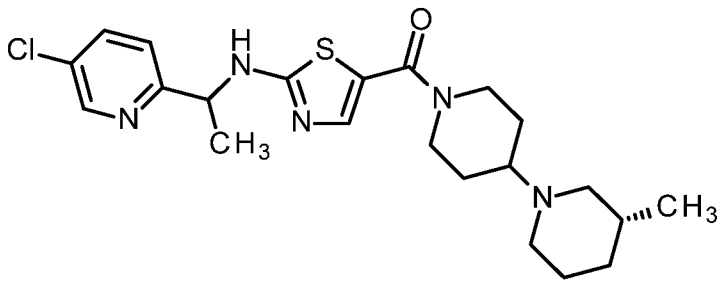
[Column: Chiralpak AZ-3, 3 µm, 50 mm x 4.6 mm; eluent: n-heptane/ethanol + 0.2% diethylamine 50:50; flow rate: 1 ml/min; temperature: 30°C; UV detection: 220 nm].

LC-MS (Method 1): $R_t$ = 0.99 min; m/z = 446/448 $(M-H)^-$.

$[\alpha]_D^{20}$ = -20.37° (c = 0.270, methanol).

**Example 85 and Example 86**

(2-{[1-(5-Chloropyridin-2-yl)ethyl]amino}-1,3-thiazol-5-yl)[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone (*diastereomers 1 and 2*)



91 mg (0.20 mmol) of the diastereomer mixture of (2-{[1-(5-chloropyridin-2-yl)ethyl]amino}-1,3-thiazol-5-yl)[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone (Example 56) was separated into the diastereomers by preparative HPLC on a chiral phase [column: Daicel Chiralpak IC, 5 µm, 250 mm x 20 mm; eluent: ethanol + 0.2% diethylamine/n-heptane 30:70; flow rate: 20 ml/min; UV detection: 220 nm; temperature: 40°C]:

Example 85 (*diastereomer 1*):

(2-{[1-(5-Chloropyridin-2-yl)ethyl]amino}-1,3-thiazol-5-yl)[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone

Yield: 28 mg

$R_t$ = 14.64 min; chemical purity > 99%; > 99% de

[Column: Daicel Chiralpak IC, 5 µm, 250 mm x 4.6 mm; eluent: n-heptane/ethanol + 0.2% diethylamine 70:30; flow rate: 1 ml/min; temperature: 40°C; UV detection: 235 nm].

LC-MS (Method 1): $R_t$ = 0.96 min; m/z = 446/448 $(M-H)^-$.

$^1$H-NMR (400 MHz, DMSO-$d_6$, δ/ppm): 0.73-0.88 (m, 4H, therein at 0.81 (d, 3H)), 1.21-1.43 (m, 3H), 1.43-1.66 (m, 6H, therein at 1.46 (d, 3H)), 1.67-1.78 (m, 3H), 1.98-2.08 (m, 1H), 2.41-2.56 (m, 1H, partly hidden by DMSO), 2.68-2.79 (m, 2H), 2.88 (br. t, 2H), 4.23 (br. d, 2H), 4.84-4.94 (m, 1H), 7.34 (s, 1H), 7.42 (d, 1H), 7.90 (dd, 1H), 8.57 (d, 1H), 8.64 (d, 1H).

$[\alpha]_D^{20}$ = -38.85° (c = 0.290, methanol).

Example 86 (*diastereomer 2*):

(2-{[1-(5-Chloropyridin-2-yl)ethyl]amino}-1,3-thiazol-5-yl)[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone

Yield: 31 mg

$R_t$ = 18.22 min; chemical purity > 99%; > 99% de

[Column: Daicel Chiralpak IC, 5 µm, 250 mm x 4.6 mm; eluent: n-heptane/ethanol + 0.2% diethylamine 70:30; flow rate: 1 ml/min; temperature: 40°C; UV detection: 235 nm].

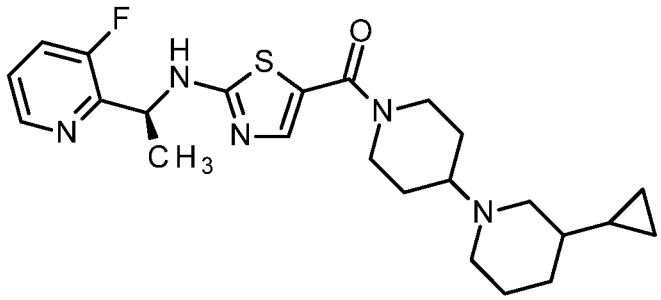
LC-MS (Method 1): $R_t$ = 0.94 min; m/z = 446/448 $(M-H)^-$.

$^1$H-NMR (400 MHz, DMSO-$d_6$, δ/ppm): 0.72-0.89 (m, 4H, therein at 0.81 (d, 3H)), 1.21-1.42 (m, 3H), 1.43-1.66 (m, 6H, therein at 1.46 (d, 3H)), 1.67-1.78 (m, 3H), 1.98-2.08 (m, 1H), 2.41-2.56 (m, 1H, partly hidden by DMSO), 2.69-2.78 (m, 2H), 2.88 (br. t, 2H), 4.23 (br. d, 2H), 4.84-4.94 (m, 1H), 7.34 (s, 1H), 7.42 (d, 1H), 7.89 (dd, 1H), 8.57 (d, 1H), 8.64 (d, 1H).

$[\alpha]_D^{20}$ = +32.24° (c = 0.305, methanol).

**Example 87**

(3-Cyclopropyl[1,4'-bipiperidine]-1'-yl)(2-{[(1*S*)-1-(3-fluoropyridin-2-yl)ethyl]amino}-1,3-thiazol-5-yl)methanone (*diastereomer mixture*)



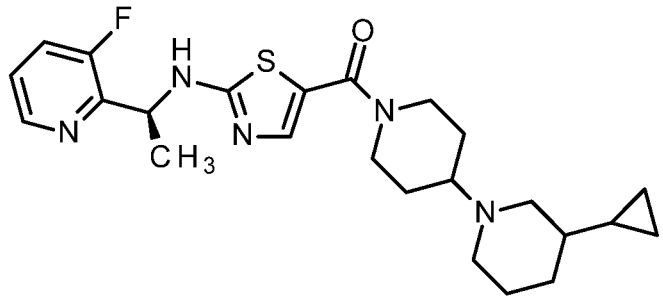
To a solution of 2-{[(1*S*)-1-(3-fluoropyridin-2-yl)ethyl]amino}-1,3-thiazole-5-carboxylic acid (80.0 mg, 299 µmol) and *rac*-3-cyclopropyl-1,4'-bipiperidine hydrochloride (73.3 mg, 299 µmol) in 3 ml of acetonitrile were successively added N,N-diisopropylethylamine (210 µl, 1.2 mmol) and propylphosphonic anhydride in ethyl acetate (230 µl, 50% purity, 390 µmol), and the mixture was stirred at room temperature overnight. The reaction mixture was diluted with acetonitrile, acidified with formic acid and purified by preparative HPLC (column: Chromatorex C18 10 µm, 250 x 30 mm, eluent A: water, B: acetonitrile; gradient: 0.0 min 15% B; 4.5 min 30% B; 11.5 min 50% B; 12 min 100% B; 18 min 100% B; flow rate: 50 ml/min; 0.1% formic acid). The product-containing fractions were combined and lyophilized. The residue was applied to Isolute® and purified using a Biotage cartridge (28 g Sfähr NH; DCM/MeOH gradient: 2-20% MeOH; flow rate: 25 ml/min). The product-containing fractions were combined and concentrated, and dried under high vacuum. This gave 59.0 mg (100% purity, 43% of theory) of the target compound.

LC-MS (Method 1): $R_t$ = 0.98 min; MS (ESIneg): m/z = 456 $[M-H]^-$

$^1$H-NMR (400 MHz, DMSO-d6) δ [ppm]: -0.012 (1.04), 0.029 (2.43), 0.039 (4.53), 0.045 (4.05), 0.305 (2.30), 0.312 (3.15), 0.323 (3.73), 0.332 (3.27), 0.341 (2.98), 0.469 (0.94), 0.481 (1.45), 0.490 (1.29), 0.502 (1.40), 0.640 (1.20), 0.666 (1.15), 0.940 (0.50), 0.960 (1.12), 0.970 (1.24), 0.991 (1.16), 0.999 (1.17), 1.020 (0.52), 1.312 (2.04), 1.340 (2.67), 1.450 (14.17), 1.467 (14.14), 1.572 (1.52), 1.604 (1.29), 1.706 (3.61), 1.736 (2.28), 1.938 (1.55), 1.963 (2.85), 1.990 (1.58), 2.041 (1.02), 2.063 (1.81), 2.091 (1.12), 2.327 (0.42), 2.366 (0.51), 2.459 (1.01), 2.669 (0.54), 2.694 (1.54), 2.710 (1.43), 2.722 (1.45), 2.783 (1.58), 2.804 (1.64), 2.839 (1.28), 2.869 (2.05), 2.899 (1.18), 3.258 (0.48), 3.269 (0.53), 3.275 (0.48), 3.289 (0.89), 3.306 (1.05), 3.381 (1.77), 3.410 (0.42), 4.218 (2.74), 4.251 (2.61), 5.250 (0.48), 5.267 (1.64), 5.285 (2.51), 5.302 (1.64), 5.319 (0.45), 5.749 (1.61), 7.331 (16.00), 7.368 (1.80), 7.379 (3.04), 7.390 (3.52), 7.400 (3.60), 7.411 (2.16), 7.661 (2.31), 7.664 (2.45), 7.681 (2.22), 7.686 (3.07), 7.690 (2.57), 7.707 (2.05), 7.710 (2.04), 7.969 (0.92), 7.982 (0.43), 8.387 (2.26), 8.390 (3.87), 8.394 (2.54), 8.399 (2.48), 8.402 (3.82), 8.598 (4.10), 8.617 (4.01).

**Example 88 and Example 89**

(3-Cyclopropyl[1,4'-bipiperidine]-1'-yl)(2-{[(1*S*)-1-(3-fluoropyridin-2-yl)ethyl]amino}-1,3-thiazol-5-yl)methanone (*diastereomers 1 and 2*)



52 mg of the diastereomer mixture of (3-cyclopropyl[1,4'-bipiperidine]-1'-yl)(2-{[(1*S*)-1-(3-fluoropyridin-2-yl)ethyl]amino}-1,3-thiazol-5-yl)methanone (Example 87) was separated into the diastereomers by preparative HPLC on a chiral phase [Daicel® Chiralpak ID column, 5 µm, 20 x 250 mm; eluent: 60% n-heptane & 40% ethanol + 0.2% diethylamine; flow rate: 20 ml/min; temperature: 50°C, detection: 220 nm]: The two diastereomers were separately collected and lyophilized.

Example 88 (*diastereomer 1*):

(3-Cyclopropyl[1,4'-bipiperidine]-1'-yl)(2-{[(1*S*)-1-(3-fluoropyridin-2-yl)ethyl]amino}-1,3-thiazol-5-yl)methanone

Yield: 16 mg

$R_t$ = 2,899 min; chemical purity > 99%; > 99% de

[Column: Chiralpak ID-3 3 µm 4.6 mm x 50 mm, flow rate: 1 ml/min, UV: 220 nm, temp.: 30°C, eluent: 50% n-heptane & 50% ethanol + 0.2% DEA].

LC-MS (Method 1): $R_t$ = 1.00 min; MS (ESIpos): m/z = 458 $[M+H]^+$.

$^1$H-NMR (400 MHz, DMSO-d6) δ [ppm]: -0.010 (0.75), 0.006 (0.90), 0.031 (2.56), 0.041 (4.79), 0.047 (4.00), 0.306 (2.44), 0.314 (3.16), 0.325 (3.84), 0.334 (3.22), 0.343 (2.89), 0.472 (0.99), 0.483 (1.47), 0.492 (1.26), 0.503 (1.38), 0.642 (1.23), 0.666 (1.18), 0.942 (0.48), 0.963 (1.23), 0.972 (1.22), 0.994 (1.21), 1.022 (0.57), 1.315 (2.29), 1.345 (2.98), 1.364 (1.94), 1.373 (1.89), 1.451 (14.85), 1.468 (14.85), 1.573 (1.59), 1.605 (1.28), 1.707 (3.61), 1.942 (1.51), 1.968 (2.74), 1.994 (1.50), 2.046 (1.02), 2.067 (1.81), 2.094 (1.04), 2.326 (0.47), 2.698 (1.56), 2.709 (1.42), 2.724 (1.45), 2.785 (1.69),

2.809 (1.62), 2.838 (1.29), 2.870 (2.20), 3.380 (0.75), 4.220 (2.96), 4.251 (2.85), 5.250 (0.48), 5.269 (1.78), 5.287 (2.70), 5.304 (1.76), 5.323 (0.48), 7.333 (16.00), 7.369 (1.83), 7.380 (3.13), 7.391 (3.63), 7.401 (3.78), 7.412 (2.23), 7.662 (2.35), 7.666 (2.56), 7.683 (2.29), 7.688 (3.23), 7.691 (2.66), 7.709 (2.12), 7.712 (2.16), 8.392 (4.03), 8.395 (2.70), 8.403 (3.98), 8.599 (4.35), 8.618 (4.24).

$[\alpha]_D^{20}$ = -20.82° (c = 0.255, methanol).

Example 89 (*diastereomer 2*):

(3-Cyclopropyl[1,4'-bipiperidine]-1'-yl)(2-{[(1*S*)-1-(3-fluoropyridin-2-yl)ethyl]amino}-1,3-thiazol-5-yl)methanone

Yield: 15 mg

$R_t$ = 3,525 min; chemical purity > 99%; > 99% de

[Column: Chiralpak ID-3 3 µm 4.6 mm x 50 mm, flow rate: 1 ml/min, UV: 220 nm, temp.: 30°C, eluent: 50% n-heptane & 50% ethanol + 0.2% DEA].

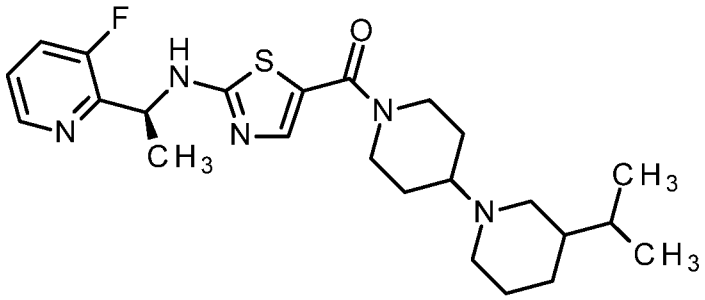
LC-MS (Method 1): $R_t$ = 1.01 min; MS (ESIpos): m/z = 458 $[M+H]^+$.

$^1$H-NMR (400 MHz, DMSO-d6) δ [ppm]: 0.043 (5.64), 0.316 (3.67), 0.326 (4.56), 0.336 (3.72), 0.344 (3.18), 0.474 (1.18), 0.485 (1.72), 0.495 (1.51), 0.506 (1.63), 0.516 (1.01), 0.619 (0.62), 0.643 (1.50), 0.668 (1.41), 0.944 (0.64), 0.965 (1.41), 0.974 (1.46), 0.995 (1.46), 1.025 (0.64), 1.318 (2.56), 1.347 (3.28), 1.361 (2.57), 1.454 (16.00), 1.471 (15.98), 1.575 (1.92), 1.607 (1.52), 1.708 (4.84), 1.738 (2.97), 1.944 (1.75), 1.970 (3.28), 1.996 (1.73), 2.048 (1.23), 2.071 (2.22), 2.099 (1.24), 2.465 (1.19), 2.699 (1.93), 2.725 (1.75), 2.789 (2.06), 2.812 (1.99), 2.842 (1.60), 2.871 (2.77), 2.904 (1.54), 4.222 (3.58), 4.255 (3.45), 5.255 (0.50), 5.272 (2.06), 5.290 (3.15), 5.307 (2.07), 5.324 (0.51), 7.336 (15.92), 7.372 (1.90), 7.383 (3.33), 7.393 (3.73), 7.404 (3.88), 7.415 (2.23), 7.665 (2.81), 7.668 (2.51), 7.686 (2.91), 7.690 (3.75), 7.694 (2.72), 7.712 (2.47), 7.715 (2.14), 8.395 (4.52), 8.406 (4.37), 8.602 (4.77), 8.621 (4.67).

$[\alpha]_D^{20}$ = -51.92° (c = 0.251, methanol).

**Example 90**

(2-{[(1*S*)-1-(3-Fluoropyridin-2-yl)ethyl]amino}-1,3-thiazol-5-yl)(3-isopropyl[1,4'-bipiperidine]-1'-yl)methanone (*diastereomer mixture*)



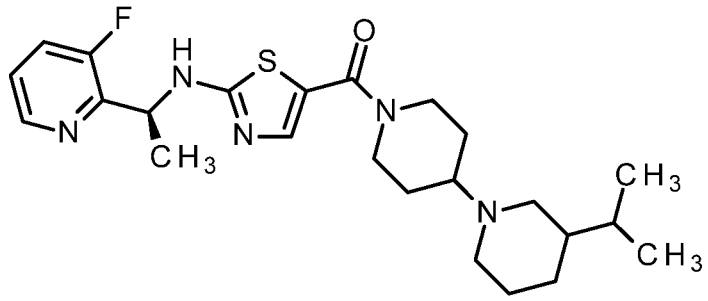
To a solution of 2-{[(1*S*)-1-(3-fluoropyridin-2-yl)ethyl]amino}-1,3-thiazole-5-carboxylic acid (80.0 mg, 299 µmol) and *rac*-3-isopropyl-1,4'-bipiperidine hydrochloride (73.9 mg, 299 µmol) in 3 ml of acetonitrile were successively added N,N-diisopropylethylamine (210 µl, 1.2 mmol) and propylphosphonic anhydride in ethyl acetate (230 µl, 50% purity, 390 µmol), and the mixture was stirred at room temperature overnight. The reaction mixture was diluted with acetonitrile, acidified with formic acid and purified by preparative HPLC (column: Chromatorex C18 10 µm, 250 x 30 mm, eluent A: water, B: acetonitrile; gradient: 0.0 min 15% B; 4.5 min 30% B; 11.5 min 50% B; 12 min 100% B; 18 min 100% B; flow rate: 50 ml/min; 0.1% formic acid). The product-containing fractions were combined and lyophilized. The residue was applied to Isolute® and purified using a Biotage cartridge (28 g Sfähr NH; DCM/MeOH gradient: 2-20% MeOH; flow rate: 25 ml/min). The product-containing fractions were combined and concentrated, and dried under high vacuum. This gave 41.0 mg (100% purity, 30% of theory) of the target compound.

LC-MS (Method 1): $R_t$ = 1.04 min; MS (ESIpos): m/z = 460 $[M+H]^+$

$^1$H-NMR (400 MHz, DMSO-d6) δ [ppm]: 0.828 (14.65), 0.834 (15.31), 0.844 (15.86), 0.851 (16.00), 0.883 (1.16), 0.891 (1.12), 0.913 (0.50), 0.923 (0.44), 1.134 (0.47), 1.151 (0.84), 1.160 (1.02), 1.169 (0.92), 1.177 (1.01), 1.316 (1.48), 1.337 (2.22), 1.347 (2.69), 1.366 (3.40), 1.376 (2.35), 1.383 (2.80), 1.399 (2.47), 1.416 (1.16), 1.433 (0.49), 1.454 (13.04), 1.471 (13.03), 1.585 (1.37), 1.626 (1.58), 1.665 (1.13), 1.705 (2.36), 1.737 (2.02), 1.832 (1.41), 1.859 (2.64), 1.885 (1.36), 2.002 (0.94), 2.025 (1.67), 2.052 (0.92), 2.461 (0.84), 2.470 (0.66), 2.715 (1.42), 2.752 (1.94), 2.781 (1.36), 2.838 (1.02), 2.866 (1.78), 2.896 (1.01), 4.229 (2.43), 4.262 (2.32), 5.272 (1.53), 5.290 (2.31), 5.307 (1.50), 7.334 (14.51), 7.371 (1.63), 7.382 (2.78), 7.392 (3.22), 7.403 (3.30), 7.414 (1.99), 7.663 (2.12), 7.667 (2.20), 7.684 (2.08), 7.689 (2.80), 7.692 (2.30), 7.710 (1.90), 7.713 (1.84), 8.390 (2.11), 8.394 (3.57), 8.397 (2.25), 8.402 (2.23), 8.405 (3.48), 8.409 (2.01), 8.602 (3.82), 8.621 (3.70).

**Example 91 and Example 92**

(2-{[(1*S*)-1-(3-Fluoropyridin-2-yl)ethyl]amino}-1,3-thiazol-5-yl)(3-isopropyl[1,4'-bipiperidine]-1'-yl)methanone (*diastereomers 1 and 2*)



41 mg of the diastereomer mixture of (2-{[(1*S*)-1-(3-fluoropyridin-2-yl)ethyl]amino}-1,3-thiazol-5-yl)(3-isopropyl[1,4'-bipiperidine]-1'-yl)methanone (Example 90) was separated into the diastereomers by preparative HPLC on a chiral phase [Chiralpak AZ-H column, 250 x 20 mm; eluent: 70% n-heptane & 30% ethanol + 0.2% diethylamine; flow rate: 20 ml/min; temperature: 50°C, detection: 220 nm]. The two diastereomers were separately collected and lyophilized.

Example 91 (*diastereomer 1*):

(2-{[(1*S*)-1-(3-Fluoropyridin-2-yl)ethyl]amino}-1,3-thiazol-5-yl)(3-isopropyl[1,4'-bipiperidine]-1'-yl)methanone

Yield: 12 mg

$R_t$ = 4.894 min; chemical purity > 99%; > 99% de

[Column: Chiralpak AZ-3 3 µm 4.6 mm x 50 mm, flow rate: 1 ml/min, UV: 220 nm, temp.: 30°C, eluent: 70% n-heptane & 30% ethanol + 0.2% DEA].

LC-MS (Method 1): $R_t$ = 1.03 min; MS (ESIneg): m/z = 458 $[M-H]^-$.

$^1$H-NMR (400 MHz, DMSO-d6) δ [ppm]: 0.828 (14.82), 0.834 (15.57), 0.845 (16.00), 0.851 (15.94), 0.884 (1.18), 1.178 (1.18), 1.316 (1.58), 1.347 (2.70), 1.367 (3.35), 1.384 (2.82), 1.401 (2.40), 1.417 (1.18), 1.452 (13.14), 1.470 (13.05), 1.587 (1.37), 1.627 (1.73), 1.666 (1.18), 1.707 (2.28), 1.738 (1.92), 1.836 (1.06), 1.863 (1.96), 1.889 (1.01), 2.001 (0.79), 2.031 (1.42), 2.056 (0.77), 2.368 (0.52), 2.712 (1.40), 2.754 (1.97), 2.783 (1.33), 2.865 (1.63), 3.284 (0.52), 3.389 (0.65), 4.228 (2.39), 4.260 (2.28), 5.270 (1.52), 5.287 (2.32), 5.305 (1.56), 7.333 (14.79), 7.371 (1.65), 7.382 (2.78), 7.392 (3.30), 7.403 (3.35), 7.414 (2.06), 7.664 (2.15), 7.667 (2.28), 7.684 (2.07), 7.689 (2.85), 7.693 (2.42),

7.710 (1.93), 7.714 (1.88), 8.390 (2.08), 8.393 (3.57), 8.397 (2.33), 8.401 (2.22), 8.405 (3.49), 8.408 (2.09), 8.601 (3.78), 8.620 (3.67).

$[\alpha]_D^{20}$ = -32.40° (c = 0.250, methanol).

Example 92 (*diastereomer 2*):

(2-{[(1*S*)-1-(3-Fluoropyridin-2-yl)ethyl]amino}-1,3-thiazol-5-yl)(3-isopropyl[1,4'-bipiperidine]-1'-yl)methanone

Yield: 12 mg

$R_t$ = 5.972 min; chemical purity > 99%; > 99% de

[Column: Chiralpak AZ-3 3 µm 4.6 mm x 50 mm, flow rate: 1 ml/min, UV: 220 nm, temp.: 30°C, eluent: 70% n-heptane & 30% ethanol + 0.2% DEA].

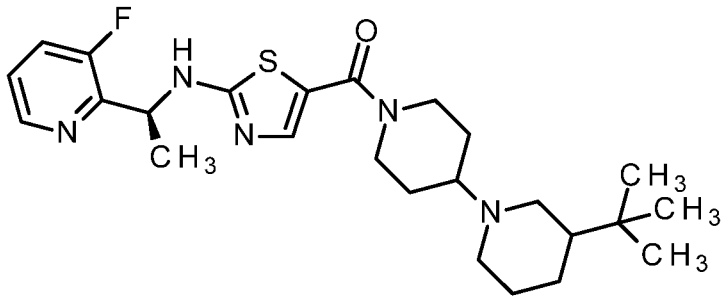
LC-MS (Method 1): $R_t$ = 1.04 min; MS (ESIneg): m/z = 458 $[M-H]^-$.

$^1$H-NMR (400 MHz, DMSO-d6) δ [ppm]: 0.828 (14.90), 0.834 (15.44), 0.845 (16.00), 0.851 (15.71), 0.885 (1.14), 0.894 (1.07), 0.916 (0.53), 1.179 (1.21), 1.318 (1.45), 1.349 (2.60), 1.368 (3.32), 1.384 (2.75), 1.401 (2.44), 1.418 (1.17), 1.453 (13.12), 1.470 (13.04), 1.588 (1.33), 1.629 (1.71), 1.666 (1.12), 1.709 (2.40), 1.737 (2.03), 1.838 (0.97), 1.863 (1.80), 1.890 (0.94), 2.006 (0.77), 2.032 (1.34), 2.059 (0.72), 2.720 (1.24), 2.756 (1.76), 2.785 (1.29), 2.835 (1.10), 2.866 (1.93), 2.896 (1.09), 4.229 (2.46), 4.261 (2.33), 5.270 (1.52), 5.288 (2.31), 5.305 (1.50), 5.323 (0.41), 7.334 (14.83), 7.371 (1.71), 7.382 (2.80), 7.392 (3.27), 7.403 (3.37), 7.414 (2.04), 7.664 (2.18), 7.667 (2.24), 7.684 (2.11), 7.690 (2.80), 7.693 (2.34), 7.710 (1.96), 7.714 (1.91), 8.390 (2.11), 8.393 (3.60), 8.397 (2.28), 8.402 (2.26), 8.405 (3.52), 8.409 (2.04), 8.602 (3.76), 8.621 (3.68).

$[\alpha]_D^{20}$ = -39.47° (c = 0.250, methanol).

**Example 93**

(3-*tert*-Butyl[1,4'-bipiperidine]-1'-yl)(2-{[(1*S*)-1-(3-fluoropyridin-2-yl)ethyl]amino}-1,3-thiazol-5-yl)methanone (*diastereomer mixture*)



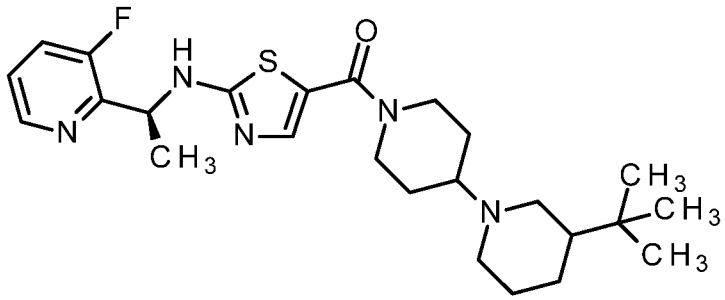
To a solution of 2-{[(1*S*)-1-(3-fluoropyridin-2-yl)ethyl]amino}-1,3-thiazole-5-carboxylic acid (80.0 mg, 299 µmol) and *rac*-3-*tert*-butyl-1,4'-bipiperidine hydrochloride (78.1 mg, 299 µmol) in 3 ml of acetonitrile were successively added N,N-diisopropylethylamine (210 µl, 1.2 mmol) and propylphosphonic anhydride in ethyl acetate (230 µl, 50% purity, 390 µmol), and the mixture was stirred at room temperature overnight. The reaction mixture was diluted with acetonitrile, acidified with formic acid and purified by preparative HPLC (column: Chromatorex C18 10 µm, 250 x 30 mm, eluent A: water, B: acetonitrile; gradient: 0.0 min 15% B; 4.5 min 30% B; 11.5 min 50% B; 12 min 100% B; 18 min 100% B; flow rate: 50 ml/min; 0.1% formic acid). The product-containing fractions were combined and lyophilized. The residue was applied to Isolute® and purified using a Biotage cartridge (28 g Sfähr NH; DCM/MeOH gradient: 2-20% MeOH; flow rate: 25 ml/min). The product-containing fractions were combined and concentrated, and dried under high vacuum. This gave 39.0 mg (100% purity, 28% of theory) of the target compound.

LC-MS (Method 1): $R_t$ = 1.10 min; MS (ESIpos): m/z = 474 $[M+H]^+$

$^1$H-NMR (400 MHz, DMSO-d6) δ [ppm]: 0.826 (16.00), 1.324 (0.46), 1.348 (0.58), 1.369 (0.44), 1.449 (2.94), 1.466 (2.94), 1.705 (0.82), 1.735 (0.52), 1.834 (0.67), 2.837 (0.57), 2.863 (0.74), 4.228 (0.56), 4.260 (0.53), 5.283 (0.54), 5.749 (0.81), 7.331 (3.17), 7.378 (0.63), 7.388 (0.72), 7.399 (0.74), 7.409 (0.43), 7.659 (0.47), 7.662 (0.49), 7.679 (0.47), 7.684 (0.64), 7.687 (0.52), 7.705 (0.41), 7.708 (0.41), 8.389 (0.81), 8.393 (0.53), 8.397 (0.52), 8.401 (0.78), 8.596 (0.87), 8.616 (0.85).

**Example 94 and Example 95**

(3-*tert*-Butyl[1,4'-bipiperidine]-1'-yl)(2-{[(1*S*)-1-(3-fluoropyridin-2-yl)ethyl]amino}-1,3-thiazol-5-yl)methanone (*diastereomers 1 and 2*)



32 mg of the diastereomer mixture of (3-*tert*-butyl[1,4'-bipiperidine]-1'-yl)(2-{[(1*S*)-1-(3-fluoropyridin-2-yl)ethyl]amino}-1,3-thiazol-5-yl)methanone (Example 93) was separated into the diastereomers by preparative HPLC on a chiral phase [Chiralpak ID column, 250 x 20 mm; eluent: 80% n-heptane & 20% ethanol + 0.2% diethylamine; flow rate: 20 ml/min; temperature: 50°C, detection: 220 nm]: The two diastereomers were separately collected and lyophilized.

Example 94 (*diastereomer 1*):

(3-*tert*-Butyl[1,4'-bipiperidine]-1'-yl)(2-{[(1*S*)-1-(3-fluoropyridin-2-yl)ethyl]amino}-1,3-thiazol-5-yl)methanone

Yield: 10 mg

$R_t$ = 3.921 min; chemical purity > 99%; > 99% de

[Column: DAICEL Chiralpak ID-3 3 µm 4.6 mm x 50 mm, flow rate: 1 ml/min, UV: 220 nm, temp.: 30°C, eluent: 70% n-heptane & 30% ethanol + 0.2% DEA].

LC-MS (Method 1): $R_t$ = 1.12 min; MS (ESIneg): m/z = 472 $[M-H]^-$

$^1$H-NMR (400 MHz, DMSO-d6) δ [ppm]: 0.831 (16.00), 1.330 (0.44), 1.355 (0.55), 1.452 (2.96), 1.469 (2.95), 1.709 (0.73), 1.740 (0.44), 1.844 (0.42), 2.845 (0.52), 2.870 (0.62), 4.230 (0.51), 4.265 (0.49), 5.287 (0.53), 7.335 (3.30), 7.382 (0.65), 7.392 (0.73), 7.403 (0.76), 7.413 (0.46), 7.663 (0.48), 7.666 (0.51), 7.684 (0.48), 7.689 (0.63), 7.692 (0.54), 7.710 (0.45), 7.713 (0.41), 8.393 (0.81), 8.397 (0.50), 8.401 (0.50), 8.404 (0.80), 8.600 (0.86), 8.619 (0.82).

$[\alpha]_D^{20}$ = -30.13° (c = 0.250, methanol).

Example 95 (*diastereomer 2*):

(3-*tert*-Butyl[1,4'-bipiperidine]-1'-yl)(2-{[(1*S*)-1-(3-fluoropyridin-2-yl)ethyl]amino}-1,3-thiazol-5-yl)methanone

Yield: 10 mg

$R_t$ = 4.691 min; chemical purity > 99%; > 96% de

[Column: DAICEL Chiralpak ID-3 3 µm 4.6 mm x 50 mm, flow rate: 1 ml/min, UV: 220 nm, temp.: 30°C, eluent: 70% n-heptane & 30% ethanol + 0.2% DEA].

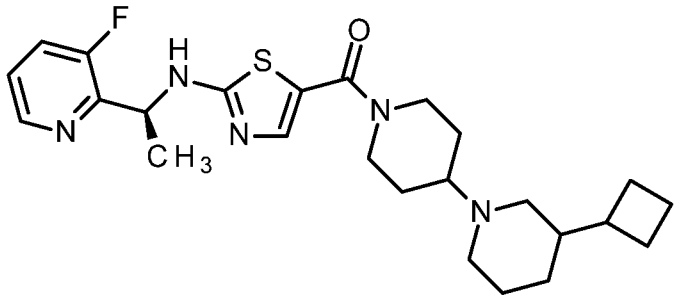
LC-MS (Method 1): $R_t$ = 1.12 min; MS (ESIneg): m/z = 472 $[M-H]^-$

$^1$H-NMR (400 MHz, DMSO-d6) δ [ppm]: 0.831 (16.00), 1.330 (0.49), 1.353 (0.59), 1.373 (0.42), 1.453 (2.95), 1.470 (2.94), 1.708 (0.81), 1.740 (0.49), 1.842 (0.52), 2.843 (0.52), 2.868 (0.74), 4.230 (0.57), 4.264 (0.56), 5.287 (0.54), 7.335 (3.18), 7.382 (0.63), 7.392 (0.72), 7.402 (0.74), 7.413 (0.44), 7.663 (0.48), 7.666 (0.49), 7.684 (0.47), 7.689 (0.64), 7.692 (0.52), 7.710 (0.43), 7.713 (0.41), 8.393 (0.80), 8.397 (0.51), 8.401 (0.51), 8.404 (0.79), 8.600 (0.87), 8.620 (0.84).

$[\alpha]_D^{20}$ = -41.47° (c = 0.250, methanol).

**Example 96**

(3-Cyclobutyl[1,4'-bipiperidine]-1'-yl)(2-{[(1*S*)-1-(3-fluoropyridin-2-yl)ethyl]amino}-1,3-thiazol-5-yl)methanone (*diastereomer mixture*)




To a solution of 2-{[(1S)-1-(3-fluoropyridin-2-yl)ethyl]amino}-1,3-thiazole-5-carboxylic acid (80.0 mg, 299 µmol) and *rac*-3-cyclobutyl-1,4'-bipiperidine hydrochloride (77.5 mg, 299 µmol) in 3 ml of acetonitrile were successively added N,N-diisopropylethylamine (210 µl, 1.2 mmol) and propylphosphonic anhydride in ethyl acetate (230 µl, 50% purity, 390 µmol), and the mixture was stirred at room temperature for 2.5 h. The reaction mixture was diluted with acetonitrile, acidified with formic acid and purified by preparative HPLC (column: Chromatorex C18 10 µm, 250 x 30

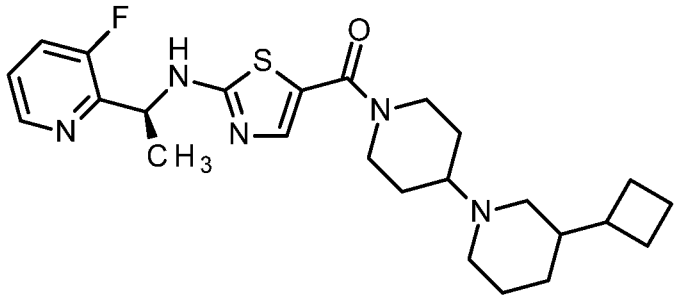
mm, eluent A: water, B: acetonitrile; gradient: 0.0 min 15% B; 4.5 min 30% B; 11.5 min 50% B; 12 min 100% B; 18 min 100% B; flow rate: 50 ml/min; 0.1% formic acid). The product-containing fractions were combined and lyophilized. The residue was applied to Isolute® and purified using a Biotage cartridge (28 g Sfähr NH; DCM/MeOH gradient: 2-20% MeOH; flow rate: 25 ml/min). The product-containing fractions were combined and concentrated, and dried under high vacuum. This gave 44.0 mg (100% purity, 31% of theory) of the target compound.

LC-MS (Method 1): $R_t$ = 1.13 min; MS (ESIpos): m/z = 472 $[M+H]^+$

$^1$H-NMR (400 MHz, DMSO-d6) δ [ppm]: 0.646 (0.52), 0.668 (1.25), 0.698 (1.69), 0.724 (0.64), 0.825 (0.44), 1.048 (0.41), 1.064 (0.43), 1.317 (4.29), 1.347 (4.03), 1.378 (1.55), 1.447 (15.89), 1.465 (16.00), 1.547 (1.82), 1.555 (1.72), 1.584 (4.05), 1.612 (4.30), 1.634 (2.92), 1.653 (3.11), 1.678 (4.31), 1.694 (6.70), 1.719 (4.76), 1.760 (2.03), 1.781 (1.75), 1.804 (1.08), 1.828 (0.44), 1.876 (1.44), 1.894 (3.12), 1.916 (3.30), 1.935 (1.96), 1.960 (1.30), 1.981 (2.02), 1.988 (1.74), 2.003 (2.04), 2.040 (2.31), 2.062 (1.22), 2.439 (1.09), 2.467 (2.00), 2.644 (1.90), 2.674 (2.90), 2.709 (1.80), 2.857 (2.45), 3.302 (0.85), 3.310 (1.37), 3.320 (1.35), 3.397 (1.68), 3.406 (1.26), 3.415 (0.76), 3.574 (1.38), 4.213 (3.30), 4.245 (3.10), 5.245 (0.53), 5.263 (2.00), 5.281 (2.98), 5.298 (1.99), 5.317 (0.51), 5.746 (0.88), 7.324 (15.64), 7.366 (1.81), 7.377 (3.32), 7.387 (3.80), 7.398 (3.93), 7.409 (2.15), 7.657 (2.44), 7.660 (2.46), 7.682 (3.60), 7.704 (2.15), 8.388 (4.36), 8.399 (4.17), 8.596 (4.77), 8.615 (4.63).

**Example 97 and Example 98**

(3-Cyclobutyl[1,4'-bipiperidine]-1'-yl)(2-{[(1*S*)-1-(3-fluoropyridin-2-yl)ethyl]amino}-1,3-thiazol-5-yl)methanone (*diastereomers 1 and 2*)




44 mg of the diastereomer mixture of (3-cyclobutyl[1,4'-bipiperidine]-1'-yl)(2-{[(1*S*)-1-(3-fluoropyridin-2-yl)ethyl]amino}-1,3-thiazol-5-yl)methanone (Example 96) was separated into the diastereomers by preparative HPLC on a chiral phase [column: Daicel Chiralpak IG, 250 x 20 mm; eluent: 40% n-heptane & 60% ethanol + 0.2% diethylamine; flow rate: 15 ml/min; detection: 220 nm]: The two diastereomers were separately collected and lyophilized.

Example 97 (*diastereomer 1*):

(3-Cyclobutyl[1,4'-bipiperidine]-1'-yl)(2-{[(1*S*)-1-(3-fluoropyridin-2-yl)ethyl]amino}-1,3-thiazol-5-yl)methanone

Yield: 17 mg

$R_t$ = 10.763 min; chemical purity > 99%; > 99% de

[Column: 250 x 4.6 mm filled with Daicel Chiralcel IG, 5 µm, flow rate: 1.0 ml/min, temperature: 60°C, eluent: 50% n-heptane & 50% ethanol + 0.2% DEA].

LC-MS (Method 1): $R_t$ = 1.09 min; MS (ESIneg): m/z = 470 $[M-H]^-$

$^1$H-NMR (400 MHz, DMSO-d6) δ [ppm]: 0.671 (1.20), 0.700 (1.31), 0.728 (0.63), 1.319 (4.25), 1.350 (4.05), 1.448 (15.31), 1.466 (15.32), 1.549 (1.71), 1.587 (3.78), 1.614 (4.05), 1.637 (2.80), 1.656 (3.06), 1.674 (4.49), 1.699 (6.67), 1.723 (4.02), 1.762 (1.91), 1.784 (1.64), 1.806 (0.96), 1.831 (0.41), 1.879 (1.42), 1.897 (2.98), 1.919 (3.10), 1.938 (1.79), 1.963 (1.22), 1.984 (1.84), 2.006 (1.91), 2.038 (2.18), 2.066 (1.20), 2.327 (0.66), 2.366 (0.61), 2.441 (0.96), 2.469 (2.16), 2.645 (1.85), 2.674 (2.85), 2.709 (2.13), 2.858 (1.99), 3.279 (0.42), 3.386 (1.59), 3.437 (0.44), 4.212 (3.05), 4.246 (2.89), 5.247 (0.51), 5.265 (1.94), 5.282 (2.85), 5.300 (1.84), 7.326 (16.00), 7.368 (1.89), 7.379 (3.27), 7.389 (3.73), 7.400 (3.80), 7.411 (2.21), 7.660 (2.56), 7.663 (2.56), 7.681 (2.62), 7.686 (3.37), 7.689 (2.61), 7.707 (2.21), 7.710 (2.05), 8.390 (4.22), 8.401 (4.06), 8.597 (4.55), 8.616 (4.37).

$[\alpha]_D^{20}$ = -24.37° (c = 0.290, methanol).

Example 98 (*diastereomer 2*):

(3-*tert*-Butyl[1,4'-bipiperidine]-1'-yl)(2-{[(1*S*)-1-(3-fluoropyridin-2-yl)ethyl]amino}-1,3-thiazol-5-yl)methanone

Yield: 17 mg

$R_t$ = 13,475 min; chemical purity > 99%; > 99% de

[Column: 250 x 4.6 mm filled with Daicel Chiralcel IG, 5 µm, flow rate: 1.0 ml/min, temperature: 60°C, eluent: 50% n-heptane & 50% ethanol + 0.2% DEA].

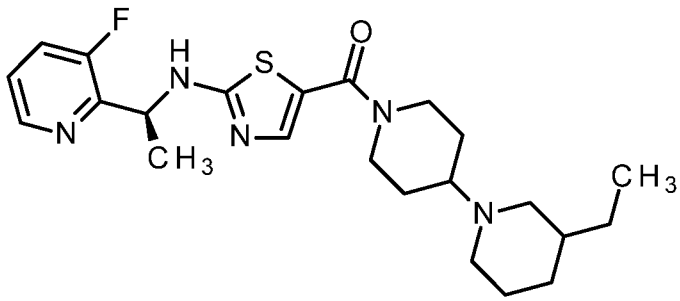
LC-MS (Method 1): $R_t$ = 1.09 min; MS (ESIneg): m/z = 470 $[M-H]^-$

$^1$H-NMR (400 MHz, DMSO-d6) δ [ppm]: 0.676 (1.20), 0.698 (1.35), 0.727 (0.62), 1.319 (4.20), 1.349 (3.95), 1.448 (15.24), 1.466 (15.35), 1.550 (1.75), 1.586 (3.76), 1.615 (4.01), 1.636 (2.71), 1.656 (2.93), 1.698 (6.17), 1.722 (4.28), 1.762 (1.98), 1.784 (1.63), 1.806 (1.01), 1.879 (1.43), 1.896 (2.94), 1.919 (3.09), 1.937 (1.81), 1.963 (1.25), 1.984 (1.86), 2.006 (1.90), 2.045 (2.16), 2.066 (1.17), 2.326 (0.70), 2.365 (0.88), 2.470 (2.09), 2.648 (1.80), 2.674 (2.96), 2.710 (2.32), 2.830 (1.39), 2.858 (2.52), 2.887 (1.37), 3.253 (0.47), 3.282 (1.24), 3.296 (1.60), 3.372 (2.02), 3.400 (1.20), 4.214 (3.18), 4.246 (3.04), 5.265 (1.94), 5.283 (2.81), 5.300 (1.92), 7.326 (16.00), 7.368 (1.86), 7.379 (3.25), 7.389 (3.78), 7.399 (3.81), 7.411 (2.18), 7.660 (2.50), 7.663 (2.47), 7.685 (3.40), 7.707 (2.19), 7.710 (2.13), 8.389 (4.20), 8.401 (4.09), 8.597 (4.52), 8.617 (4.45).

$[\alpha]_D^{20}$ = -45.20° (c = 0.250, methanol).

**Example 99**

(3-Ethyl[1,4'-bipiperidine]-1'-yl)(2-{[(1*S*)-1-(3-fluoropyridin-2-yl)ethyl]amino}-1,3-thiazol-5-yl)methanone (*diastereomer mixture*)




To a solution of 2-{[(1*S*)-1-(3-fluoropyridin-2-yl)ethyl]amino}-1,3-thiazole-5-carboxylic acid (80.0 mg, 299 µmol) and *rac*-3-ethyl-1,4'-bipiperidine hydrochloride (69.7 mg, 299 µmol) in 3 ml of acetonitrile were successively added N,N-diisopropylethylamine (210 µl, 1.2 mmol) and propylphosphonic anhydride in ethyl acetate (230 µl, 50% purity, 390 µmol), and the mixture was stirred at room temperature for 2.5 h. The reaction mixture was diluted with acetonitrile, acidified with formic acid and purified by preparative HPLC (column: Chromatorex C18 10 µm, 250 x 30 mm, eluent A: water, B: acetonitrile; gradient: 0.0 min 15% B; 4.5 min 30% B; 11.5 min 50% B; 12 min 100% B; 18 min 100% B; flow rate: 50 ml/min; 0.1% formic acid). The product-containing fractions were combined and lyophilized. The residue was applied to Isolute® and purified using a Biotage cartridge (28 g Sfähr NH; DCM/MeOH gradient: 2-20% MeOH; flow rate: 25 ml/min). The

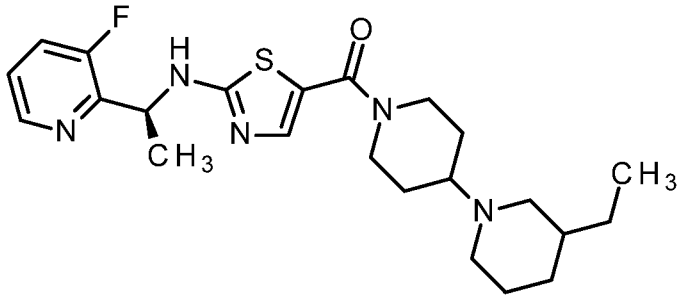
product-containing fractions were combined and concentrated, and dried under high vacuum. This gave 84.0 mg (100% purity, 63% of theory) of the target compound.

LC-MS (Method 1): $R_t$ = 0.98 min; MS (ESIpos): m/z = 446 $[M+H]^+$

$^1$H-NMR (400 MHz, DMSO-d6) δ [ppm]: 0.740 (0.46), 0.770 (1.12), 0.799 (1.31), 0.817 (6.42), 0.836 (16.00), 0.854 (7.79), 1.088 (0.61), 1.106 (1.12), 1.122 (1.81), 1.140 (2.63), 1.158 (2.76), 1.176 (2.27), 1.194 (1.79), 1.211 (0.96), 1.228 (0.79), 1.246 (0.65), 1.289 (1.80), 1.316 (2.68), 1.350 (3.09), 1.380 (1.96), 1.411 (0.61), 1.448 (13.29), 1.466 (13.12), 1.558 (1.55), 1.589 (1.19), 1.658 (1.33), 1.698 (3.78), 1.737 (3.59), 1.764 (2.73), 1.789 (1.45), 2.028 (1.03), 2.050 (1.82), 2.055 (1.81), 2.077 (1.00), 2.447 (0.92), 2.475 (1.89), 2.709 (1.85), 2.738 (2.83), 2.770 (1.53), 2.833 (1.20), 2.864 (2.06), 2.894 (1.16), 3.281 (0.52), 3.292 (0.47), 3.310 (0.95), 3.410 (0.93), 3.420 (1.03), 3.435 (0.48), 4.218 (2.79), 4.251 (2.65), 5.246 (0.43), 5.264 (1.67), 5.282 (2.50), 5.300 (1.66), 5.317 (0.42), 5.746 (0.56), 7.327 (12.85), 7.367 (1.51), 7.378 (2.74), 7.388 (3.11), 7.399 (3.20), 7.409 (1.78), 7.661 (2.13), 7.683 (3.00), 7.707 (1.81), 8.389 (3.54), 8.400 (3.49), 8.597 (3.87), 8.616 (3.79).

**Example 100 and Example 101**

(3-Ethyl[1,4'-bipiperidine]-1'-yl)(2-{[(1*S*)-1-(3-fluoropyridin-2-yl)ethyl]amino}-1,3-thiazol-5-yl)methanone (*diastereomers 1 and 2*)




70 mg of the diastereomer mixture of (3-ethyl[1,4'-bipiperidine]-1'-yl)(2-{[(1*S*)-1-(3-fluoropyridin-2-yl)ethyl]amino}-1,3-thiazol-5-yl)methanone (Example 99) was separated into the diastereomers by preparative HPLC on a chiral phase [column: Chiralcel OD-H, 250 x 20 mm; eluent: 85% n-heptane & 15% ethanol + 0.2% diethylamine; flow rate: 20 ml/min; temperature: 30°C, detection: 220 nm]: The two diastereomers were separately collected and lyophilized.

Example 100 (*diastereomer 1*):

(3-Ethyl[1,4'-bipiperidine]-1'-yl)(2-{[(1*S*)-1-(3-fluoropyridin-2-yl)ethyl]amino}-1,3-thiazol-5-yl)methanone

Yield: 28 mg

$R_t$ = 1.716 min; chemical purity > 99%; > 99% de

[Column: DAICEL Chiralcel OD-3, 3 µm 4.6 mm x 50 mm, flow rate: 1 ml/min, UV: 220 nm, temp.: 30°C, eluent: 80% n-heptane & 20% ethanol + 0.2% diethylamine].

LC-MS (Method 1): $R_t$ = 0.97 min; MS (ESIneg): m/z = 444 $[M-H]^-$

$^1$H-NMR (500 MHz, DMSO-d6) δ [ppm]: -0.120 (0.64), 0.117 (0.62), 0.839 (5.01), 0.854 (10.75), 0.869 (5.86), 1.159 (1.15), 1.173 (1.27), 1.212 (1.16), 1.456 (16.00), 1.471 (15.84), 1.584 (0.54), 1.597 (0.57), 1.702 (1.45), 1.722 (1.46), 2.889 (1.87), 4.276 (1.43), 5.263 (0.45), 5.277 (1.72), 5.291 (2.59), 5.306 (1.70), 5.320 (0.44), 7.356 (3.35), 7.379 (1.91), 7.387 (3.13), 7.395 (3.54), 7.404 (3.57), 7.413 (2.07), 7.672 (2.22), 7.675 (2.28), 7.689 (2.27), 7.693 (3.11), 7.695 (2.43), 7.710 (2.04), 7.712 (1.97), 8.394 (2.36), 8.396 (3.88), 8.399 (2.53), 8.403 (2.56), 8.406 (3.83), 8.409 (2.26), 8.636 (1.52), 8.650 (1.50).

$[\alpha]_D^{20}$ = -31.85° (c = 0.270, methanol).

Example 101 (*diastereomer 2*):

(3-Ethyl[1,4'-bipiperidine]-1'-yl)(2-{[(1*S*)-1-(3-fluoropyridin-2-yl)ethyl]amino}-1,3-thiazol-5-yl)methanone

Yield: 28 mg

$R_t$ = 2.04 min; chemical purity > 99%; > 99% de

[Column: DAICEL Chiralcel OD-3, 3 µm 4.6 mm x 50 mm, flow rate: 1 ml/min, UV: 220 nm, temp.: 30°C, eluent: 80% n-heptane & 20% ethanol + 0.2% diethylamine].

LC-MS (Method 1): $R_t$ = 0.96 min; MS (ESIneg): m/z = 444 $[M-H]^-$

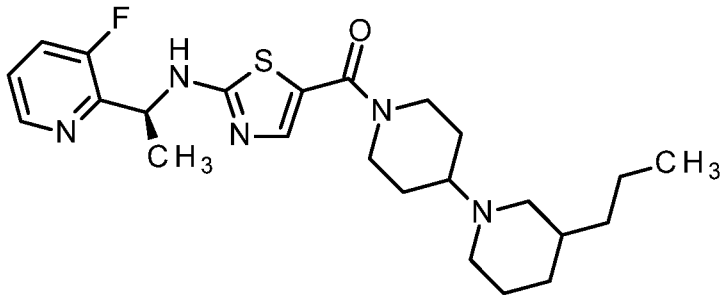
$^1$H-NMR (500 MHz, DMSO-d6) δ [ppm]: -0.120 (0.53), 0.117 (0.54), 0.841 (4.91), 0.856 (10.82), 0.871 (5.76), 1.160 (1.01), 1.179 (1.28), 1.193 (1.15), 1.207 (1.09), 1.218 (1.11), 1.233 (1.09), 1.327 (0.49), 1.341 (0.55), 1.457 (16.00), 1.471 (15.88), 1.584 (0.49), 1.598 (0.49), 1.707 (1.36), 1.729 (1.31), 1.802 (0.67), 2.892 (1.77), 4.283 (1.35), 5.264 (0.42), 5.278 (1.64), 5.292 (2.47), 5.307 (1.62), 5.320 (0.41), 7.361 (3.40), 7.379 (2.02), 7.388 (3.12), 7.396 (3.57), 7.404 (3.56), 7.413 (2.16), 7.673

(2.27), 7.675 (2.31), 7.690 (2.27), 7.693 (3.00), 7.696 (2.44), 7.710 (2.04), 7.713 (1.98), 8.394 (2.26), 8.397 (3.83), 8.400 (2.42), 8.403 (2.43), 8.406 (3.78), 8.409 (2.19), 8.641 (1.48), 8.656 (1.47).

$[\alpha]_D^{20}$ = -35.92° (c = 0.270, methanol).

**Example 102**

(2-{[(1*S*)-1-(3-Fluoropyridin-2-yl)ethyl]amino}-1,3-thiazol-5-yl)(3-propyl[1,4'-bipiperidine]-1'-yl)methanone (*diastereomer mixture*)



To a solution of 2-{[(1*S*)-1-(3-fluoropyridin-2-yl)ethyl]amino}-1,3-thiazole-5-carboxylic acid (80.0 mg, 299 µmol) and *rac*-3-propyl-1,4'-bipiperidine hydrochloride (73.9 mg, 299 µmol) in 3 ml of acetonitrile were successively added N,N-diisopropylethylamine (210 µl, 1.2 mmol) and propylphosphonic anhydride in ethyl acetate (230 µl, 50% purity, 390 µmol), and the mixture was stirred at room temperature for 2.5 h. The reaction mixture was diluted with acetonitrile, acidified with formic acid and purified by preparative HPLC (column: Chromatorex C18 10 µm, 250 x 30 mm, eluent A: water, B: acetonitrile; gradient: 0.0 min 15% B; 4.5 min 30% B; 11.5 min 50% B; 12 min 100% B; 18 min 100% B; flow rate: 50 ml/min; 0.1% formic acid). The product-containing fractions were combined and lyophilized. The residue was applied to Isolute® and purified using a Biotage cartridge (28 g Sfähr NH; DCM/MeOH gradient: 2-20% MeOH; flow rate: 25 ml/min). The product-containing fractions were combined and concentrated, and dried under high vacuum. This gave 31.0 mg (100% purity, 23% of theory) of the target compound.

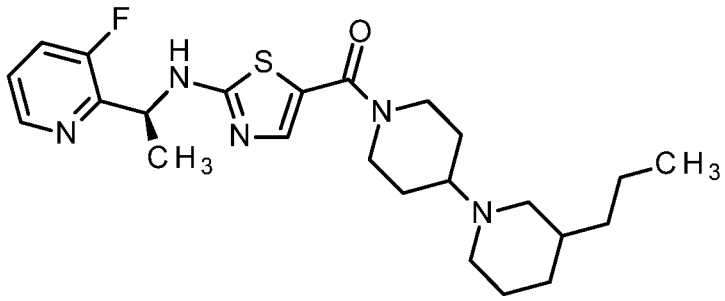
LC-MS (Method 1): $R_t$ = 1.07 min; MS (ESIpos): m/z = 460 $[M+H]^+$

$^1$H-NMR (400 MHz, DMSO-d6) δ [ppm]: 0.768 (0.99), 0.806 (1.20), 0.820 (6.80), 0.838 (16.00), 0.856 (7.94), 1.054 (0.55), 1.069 (0.83), 1.088 (1.84), 1.107 (2.18), 1.134 (1.95), 1.152 (1.31), 1.168 (0.68), 1.226 (0.97), 1.244 (2.75), 1.262 (4.16), 1.281 (3.84), 1.301 (1.96), 1.320 (2.26), 1.350 (2.88), 1.383 (2.54), 1.448 (12.33), 1.466 (12.25), 1.551 (1.37), 1.584 (1.07), 1.638 (1.20), 1.699 (2.68),

1.738 (2.74), 1.765 (2.41), 1.791 (1.24), 2.027 (0.98), 2.054 (1.65), 2.078 (0.96), 2.365 (0.82), 2.709 (2.30), 2.730 (2.42), 2.748 (1.85), 2.863 (1.95), 3.225 (0.56), 3.255 (0.60), 3.282 (0.84), 3.288 (0.82), 3.297 (0.88), 3.311 (4.93), 3.321 (3.08), 3.403 (1.64), 3.416 (2.38), 3.447 (0.90), 3.472 (0.87), 3.503 (0.49), 3.538 (0.41), 3.595 (0.74), 4.214 (2.51), 4.248 (2.41), 5.263 (1.55), 5.282 (2.32), 5.299 (1.53), 7.326 (12.52), 7.368 (1.43), 7.379 (2.59), 7.389 (2.92), 7.399 (2.98), 7.410 (1.73), 7.662 (1.98), 7.684 (2.79), 7.706 (1.67), 8.389 (3.35), 8.401 (3.27), 8.596 (3.70), 8.616 (3.58).

**Example 103 and Example 104**

(2-{[(1*S*)-1-(3-Fluoropyridin-2-yl)ethyl]amino}-1,3-thiazol-5-yl)(3-propyl[1,4'-bipiperidine]-1'-yl)methanone (*diastereomers 1 and 2*)



30 mg of the diastereomer mixture of (2-{[(1*S*)-1-(3-fluoropyridin-2-yl)ethyl]amino}-1,3-thiazol-5-yl)(3-propyl[1,4'-bipiperidine]-1'-yl)methanone (Example 102) was separated into the diastereomers by preparative HPLC on a chiral phase [column: Daicel Chiralpak IG 5 µm, 250 x 20 mm; eluent: 50% n-heptane & 50% ethanol + 0.2% diethylamine; flow rate: 15 ml/min, temperature: 60°C, detection: 220 nm]. The two diastereomers were separately collected and lyophilized.

Example 103 (*diastereomer 1*):

(2-{[(1*S*)-1-(3-Fluoropyridin-2-yl)ethyl]amino}-1,3-thiazol-5-yl)(3-propyl[1,4'-bipiperidine]-1'-yl)methanone

Yield: 13 mg

$R_t$ = 10.468 min; chemical purity > 99%; > 99% de

[Column: 250 x 4.6 mm filled with Daicel Chiralcel IG, 5 µm, flow rate: 1.0 ml/min, temperature: 60°C, eluent: 50% n-heptane & 50% ethanol + 0.2% DEA].

LC-MS (Method 1): $R_t$ = 1.05 min; MS (ESIneg): m/z = 458 $[M-H]^-$

$^1$H-NMR (400 MHz, DMSO-d6) δ [ppm]: 0.748 (0.41), 0.769 (0.92), 0.778 (0.93), 0.799 (1.03), 0.807 (1.12), 0.820 (6.72), 0.838 (16.00), 0.856 (7.86), 1.055 (0.54), 1.073 (0.79), 1.089 (1.74), 1.107 (1.98), 1.115 (1.58), 1.127 (1.34), 1.135 (1.81), 1.152 (1.22), 1.169 (0.67), 1.184 (0.46), 1.226 (0.90), 1.244 (2.64), 1.263 (3.86), 1.282 (3.48), 1.299 (1.78), 1.319 (2.11), 1.350 (2.71), 1.382 (2.36), 1.450 (11.95), 1.467 (11.91), 1.551 (1.30), 1.584 (0.98), 1.638 (1.08), 1.697 (2.41), 1.728 (2.10), 1.740 (2.05), 1.767 (2.22), 1.792 (1.20), 2.028 (0.85), 2.049 (1.49), 2.056 (1.48), 2.078 (0.82), 2.442 (0.79), 2.470 (1.50), 2.709 (1.60), 2.729 (2.13), 2.746 (1.66), 2.833 (0.96), 2.862 (1.69), 2.893 (0.96), 3.297 (0.48), 3.303 (0.57), 3.376 (0.46), 4.216 (2.30), 4.249 (2.21), 5.267 (1.40), 5.284 (2.17), 5.302 (1.40), 7.328 (13.21), 7.368 (1.49), 7.379 (2.54), 7.389 (2.93), 7.399 (3.01), 7.410 (1.81), 7.660 (1.94), 7.663 (2.04), 7.681 (1.89), 7.686 (2.59), 7.689 (2.19), 7.707 (1.74), 7.710 (1.74), 8.387 (1.91), 8.390 (3.27), 8.394 (2.16), 8.398 (2.06), 8.402 (3.21), 8.405 (1.95), 8.597 (3.48), 8.617 (3.40).

$[\alpha]_D^{20}$ = -34.67° (c = 0.250, methanol).

Example 104 (*diastereomer 2*):

(2-{[(1*S*)-1-(3-Fluoropyridin-2-yl)ethyl]amino}-1,3-thiazol-5-yl)(3-propyl[1,4'-bipiperidine]-1'-yl)methanone

Yield: 13 mg

$R_t$ = 12.178 min; chemical purity > 99%; > 99% de

[Column: 250 x 4.6 mm filled with Daicel Chiralcel IG, 5 µm, flow rate: 1.0 ml/min, temperature: 60°C, eluent: 50% n-heptane & 50% ethanol + 0.2% DEA].

LC-MS (Method 1): $R_t$ = 1.05 min; MS (ESIneg): m/z = 458 $[M-H]^-$

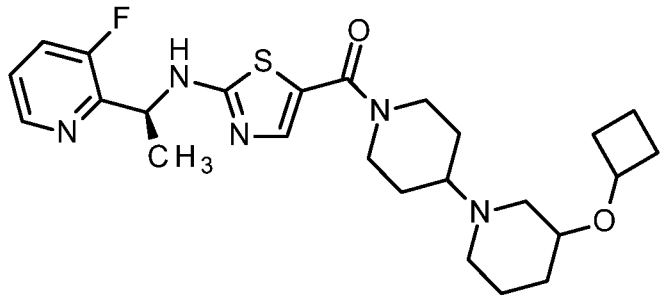
$^1$H-NMR (400 MHz, DMSO-d6) δ [ppm]: 0.779 (0.87), 0.807 (1.04), 0.821 (6.66), 0.839 (16.00), 0.857 (7.88), 1.056 (0.51), 1.073 (0.73), 1.090 (1.66), 1.108 (1.90), 1.116 (1.52), 1.127 (1.29), 1.136 (1.75), 1.153 (1.20), 1.170 (0.65), 1.185 (0.44), 1.227 (0.84), 1.245 (2.53), 1.264 (3.75), 1.283 (3.48), 1.300 (1.62), 1.323 (2.08), 1.354 (2.67), 1.375 (2.03), 1.383 (2.27), 1.450 (11.80), 1.467 (11.77), 1.553 (1.25), 1.584 (0.92), 1.638 (1.02), 1.699 (2.35), 1.739 (2.06), 1.766 (2.11), 1.792 (1.15), 2.029 (0.84), 2.052 (1.41), 2.079 (0.79), 2.443 (0.71), 2.472 (1.44), 2.709 (1.56), 2.732 (2.18), 2.747 (1.46), 2.834 (0.97), 2.865 (1.70), 2.894 (0.96), 3.370 (0.91), 3.380 (0.76), 4.216 (2.20), 4.248 (2.12), 5.267 (1.37), 5.284 (2.08), 5.302 (1.34), 7.328 (13.29), 7.368 (1.51), 7.379 (2.54), 7.389 (2.92), 7.400 (2.96), 7.411 (1.76), 7.661 (1.93), 7.664 (1.96), 7.681 (1.88), 7.686 (2.51), 7.690 (2.06), 7.707 (1.71),

7.711 (1.64), 8.387 (1.94), 8.390 (3.24), 8.394 (2.00), 8.399 (2.02), 8.402 (3.12), 8.406 (1.75), 8.598 (3.41), 8.617 (3.33).

$[\alpha]_D^{20}$ = -36.54° (c = 0.260, methanol).

**Example 105**

[3-(Cyclobutyloxy)[1,4'-bipiperidine]-1'-yl](2-{[(1*S*)-1-(3-fluoropyridin-2-yl)ethyl]amino}-1,3-thiazol-5-yl)methanone (*diastereomer mixture*)



To a solution of 2-{[(1*S*)-1-(3-fluoropyridin-2-yl)ethyl]amino}-1,3-thiazole-5-carboxylic acid (80.0 mg, 299 µmol) and *rac*-3-(cyclobutyloxy)-1,4'-bipiperidine hydrochloride (82.3 mg, 299 µmol) in 3 ml of acetonitrile were successively added N,N-diisopropylethylamine (210 µl, 1.2 mmol) and propylphosphonic anhydride in ethyl acetate (230 µl, 50% purity, 390 µmol), and the mixture was stirred at room temperature for 2.5 h. The reaction mixture was diluted with acetonitrile, acidified with formic acid and purified by preparative HPLC (column: Chromatorex C18 10 µm, 250 x 30 mm, eluent A: water, B: acetonitrile; gradient: 0.0 min 15% B; 4.5 min 30% B; 11.5 min 50% B; 12 min 100% B; 18 min 100% B; flow rate: 50 ml/min; 0.1% formic acid). The product-containing fractions were combined and lyophilized. The residue was applied to Isolute® and purified using a Biotage cartridge (28 g Sfähr NH; DCM/MeOH gradient: 2-20% MeOH; flow rate: 25 ml/min). The product-containing fractions were combined and concentrated, and dried under high vacuum. This gave 67.0 mg (100% purity, 46% of theory) of the target compound.

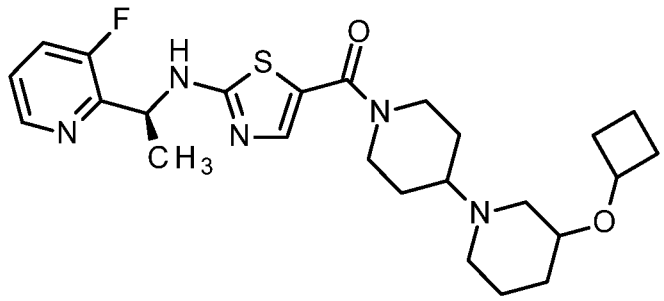
LC-MS (Method 1): $R_t$ = 1.03 min; MS (ESIpos): m/z = 488 $[M+H]^+$

$^1$H-NMR (400 MHz, DMSO-d6) δ [ppm]: 0.999 (0.55), 1.020 (1.28), 1.055 (1.42), 1.076 (0.69), 1.231 (0.40), 1.281 (1.36), 1.311 (3.45), 1.341 (3.95), 1.362 (2.13), 1.368 (2.57), 1.388 (2.68), 1.395 (1.69), 1.408 (1.60), 1.414 (2.95), 1.434 (1.96), 1.449 (16.00), 1.466 (15.89), 1.529 (0.85), 1.553 (2.27), 1.578 (3.76), 1.604 (2.01), 1.692 (3.40), 1.721 (3.05), 1.759 (2.67), 1.779 (3.38), 1.784 (3.55),

1.805 (3.63), 1.830 (2.01), 1.897 (1.78), 1.921 (3.06), 1.946 (1.88), 2.015 (1.20), 2.038 (2.17), 2.082 (1.73), 2.101 (3.32), 2.113 (2.68), 2.118 (2.97), 2.142 (1.29), 2.327 (0.41), 2.619 (1.86), 2.647 (1.69), 2.709 (0.41), 2.853 (3.80), 3.199 (0.79), 3.210 (1.26), 3.233 (2.40), 3.245 (1.89), 3.257 (1.54), 3.302 (1.32), 3.319 (1.37), 3.399 (1.73), 3.410 (1.30), 3.946 (0.66), 3.964 (2.30), 3.982 (3.24), 4.001 (2.21), 4.018 (0.62), 4.216 (3.27), 4.249 (3.18), 5.246 (0.52), 5.265 (2.01), 5.282 (3.01), 5.300 (1.96), 5.317 (0.49), 5.747 (0.53), 7.329 (15.59), 7.367 (1.84), 7.378 (3.37), 7.388 (3.77), 7.399 (3.89), 7.409 (2.15), 7.658 (2.46), 7.661 (2.54), 7.683 (3.63), 7.705 (2.18), 7.708 (2.10), 8.389 (4.38), 8.400 (4.20), 8.598 (4.78), 8.617 (4.65).

**Example 106 and Example 107**

[3-(Cyclobutyloxy)[1,4'-bipiperidine]-1'-yl](2-{[(1*S*)-1-(3-fluoropyridin-2-yl)ethyl]amino}-1,3-thiazol-5-yl)methanone (*diastereomers 1 and 2*)



67 mg of the diastereomer mixture of [3-(cyclobutyloxy)[1,4'-bipiperidine]-1'-yl](2-{[(1*S*)-1-(3-fluoropyridin-2-yl)ethyl]amino}-1,3-thiazol-5-yl)methanone (Example 105) was separated into the diastereomers by preparative HPLC on a chiral phase [column: Daicel Chiralpak IG, 5 µm, 250 x 20 mm; eluent: 50% n-heptane & 50% ethanol + 0.2% diethylamine; flow rate: 15 ml/min; temperature: 60°C, detection: 220 nm]. The two diastereomers were separately collected and lyophilized.

Example 106 (*diastereomer 1*):

[3-(Cyclobutyloxy)[1,4'-bipiperidine]-1'-yl](2-{[(1*S*)-1-(3-fluoropyridin-2-yl)ethyl]amino}-1,3-thiazol-5-yl)methanone

Yield: 27 mg

$R_t$ = 13.954 min; chemical purity > 99%; > 99% de

[Column: 250 x 4.6 mm filled with Daicel Chiralcel IG, 5 µm, flow rate: 1.0 ml/min, temperature: 60°C, eluent: 50% n-heptane & 50% ethanol + 0.2% DEA].

LC-MS (Method 1): $R_t$ = 0.99 min; MS (ESIneg): m/z = 486 $[M-H]^-$

$^1$H-NMR (500 MHz, DMSO-d6) δ [ppm]: 0.117 (0.44), 1.011 (0.49), 1.028 (1.22), 1.036 (1.16), 1.048 (1.18), 1.056 (1.33), 1.072 (0.64), 1.081 (0.55), 1.293 (1.12), 1.298 (1.17), 1.315 (3.21), 1.340 (3.55), 1.358 (1.38), 1.364 (1.45), 1.373 (1.59), 1.379 (1.43), 1.390 (0.66), 1.395 (2.47), 1.400 (1.54), 1.411 (1.50), 1.416 (2.84), 1.421 (0.84), 1.432 (1.57), 1.437 (1.31), 1.453 (16.00), 1.467 (15.69), 1.541 (0.73), 1.560 (2.06), 1.580 (3.16), 1.594 (1.65), 1.601 (1.62), 1.613 (1.40), 1.695 (3.18), 1.719 (2.82), 1.744 (0.73), 1.749 (0.83), 1.753 (0.61), 1.765 (1.98), 1.768 (2.24), 1.784 (3.08), 1.788 (3.12), 1.804 (3.01), 1.808 (3.22), 1.823 (1.73), 1.828 (1.57), 1.906 (1.72), 1.926 (2.87), 1.945 (1.81), 2.024 (1.15), 2.041 (2.06), 2.046 (2.05), 2.063 (1.16), 2.091 (1.36), 2.095 (1.29), 2.104 (2.62), 2.107 (2.95), 2.116 (2.67), 2.125 (2.76), 2.137 (1.17), 2.141 (1.21), 2.628 (1.81), 2.649 (1.64), 2.859 (3.57), 2.871 (2.88), 3.208 (0.58), 3.217 (1.11), 3.226 (1.40), 3.236 (1.93), 3.245 (1.37), 3.255 (1.09), 3.263 (0.58), 3.958 (0.62), 3.972 (2.26), 3.986 (3.03), 4.002 (2.20), 4.016 (0.60), 4.223 (3.03), 4.249 (2.93), 5.259 (0.47), 5.273 (1.81), 5.287 (2.74), 5.302 (1.80), 5.316 (0.46), 7.333 (15.78), 7.376 (1.76), 7.385 (3.12), 7.393 (3.53), 7.401 (3.54), 7.410 (2.02), 7.670 (2.30), 7.672 (2.30), 7.687 (2.38), 7.690 (3.23), 7.693 (2.47), 7.708 (2.07), 7.710 (1.98), 8.395 (3.98), 8.397 (2.58), 8.404 (3.86), 8.609 (4.59), 8.624 (4.40).

$[\alpha]_D^{20}$ = -26.67° (c = 0.285, methanol).

Example 107 (*diastereomer 2*):

[3-(Cyclobutyloxy)[1,4'-bipiperidine]-1'-yl](2-{[(1*S*)-1-(3-fluoropyridin-2-yl)ethyl]amino}-1,3-thiazol-5-yl)methanone

Yield: 28 mg

$R_t$ = 15.616 min; chemical purity > 99%; > 98.5% de

[Column: 250 x 4.6 mm filled with Daicel Chiralcel IG, 5 µm, flow rate: 1.0 ml/min, temperature: 60°C, eluent: 50% n-heptane & 50% ethanol + 0.2% DEA].

LC-MS (Method 1): $R_t$ = 1.00 min; MS (ESIneg): m/z = 486 $[M-H]^-$

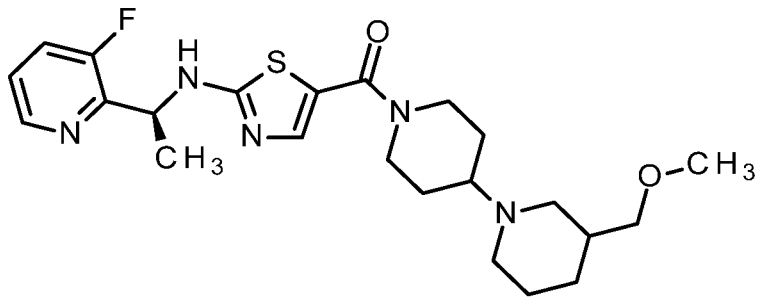
$^1$H-NMR (500 MHz, DMSO-d6) δ [ppm]: 0.117 (0.55), 1.011 (0.42), 1.027 (0.98), 1.036 (0.93), 1.048 (0.95), 1.056 (1.08), 1.072 (0.53), 1.080 (0.43), 1.293 (0.99), 1.318 (2.67), 1.342 (2.83), 1.358

(1.31), 1.366 (1.20), 1.373 (1.39), 1.379 (1.38), 1.389 (0.58), 1.395 (2.29), 1.400 (1.39), 1.410 (1.36), 1.416 (2.61), 1.421 (0.70), 1.431 (1.43), 1.437 (1.18), 1.453 (14.60), 1.467 (14.21), 1.541 (0.58), 1.558 (1.53), 1.560 (1.65), 1.562 (1.25), 1.564 (0.99), 1.579 (2.52), 1.581 (2.28), 1.584 (1.92), 1.594 (1.32), 1.599 (1.28), 1.605 (1.14), 1.613 (1.09), 1.695 (2.45), 1.717 (2.16), 1.744 (0.61), 1.749 (0.68), 1.753 (0.49), 1.760 (0.85), 1.765 (1.55), 1.768 (1.73), 1.772 (1.36), 1.779 (1.47), 1.784 (2.44), 1.788 (2.51), 1.792 (1.62), 1.800 (1.56), 1.804 (2.26), 1.807 (2.43), 1.819 (1.19), 1.823 (1.33), 1.828 (1.19), 1.840 (0.96), 1.905 (1.42), 1.924 (2.20), 1.944 (1.44), 2.025 (0.88), 2.042 (1.62), 2.047 (1.62), 2.064 (0.96), 2.091 (1.10), 2.095 (1.03), 2.104 (1.99), 2.107 (2.28), 2.111 (1.90), 2.114 (1.72), 2.116 (2.10), 2.121 (1.99), 2.125 (2.15), 2.127 (1.84), 2.129 (1.68), 2.137 (0.90), 2.141 (0.95), 2.144 (0.69), 2.520 (1.10), 2.523 (1.02), 2.627 (1.35), 2.633 (1.18), 2.636 (1.21), 2.640 (1.13), 2.648 (1.28), 2.860 (2.61), 2.873 (2.24), 3.216 (0.91), 3.226 (1.13), 3.235 (2.11), 3.248 (1.22), 3.254 (0.97), 3.958 (0.53), 3.972 (1.93), 3.986 (2.55), 3.988 (2.51), 4.002 (1.87), 4.016 (0.52), 4.223 (2.32), 4.249 (2.25), 5.273 (1.49), 5.288 (2.28), 5.301 (1.49), 7.333 (16.00), 7.376 (1.78), 7.385 (2.90), 7.393 (3.40), 7.401 (3.37), 7.410 (2.10), 7.670 (2.21), 7.672 (2.26), 7.686 (2.17), 7.690 (2.77), 7.693 (2.34), 7.707 (2.01), 7.710 (1.94), 8.392 (2.12), 8.395 (3.58), 8.398 (2.19), 8.401 (2.22), 8.404 (3.51), 8.407 (1.95), 8.609 (4.03), 8.624 (3.87).

$[\alpha]_D^{20}$ = -41.15° (c = 0.260, methanol).

**Example 108**

(2-{[(1*S*)-1-(3-Fluoropyridin-2-yl)ethyl]amino}-1,3-thiazol-5-yl)[3-(methoxymethyl)[1,4'-bipiperidine]-1'-yl]methanone (*diastereomer mixture*)




92 mg (229 µmol) of (2-bromo-1,3-thiazol-5-yl)[3-(methoxymethyl)[1,4'-bipiperidine]-1'-yl]methanone (*racemic*) and 97 mg (457 µmol) of (1*S*)-1-(3-fluoropyridin-2-yl)ethanamine dihydrochloride were dissolved in 2.2 ml of 1-methyl-2-pyrrolidone, and 0.2 ml of *N*,*N*-diisopropylethylamine was added. Thereafter, the reaction mixture (closed vessel) was stirred at 140°C overnight. After cooling to room temperature, the reaction mixture was purified by prep. HPLC.

Method:

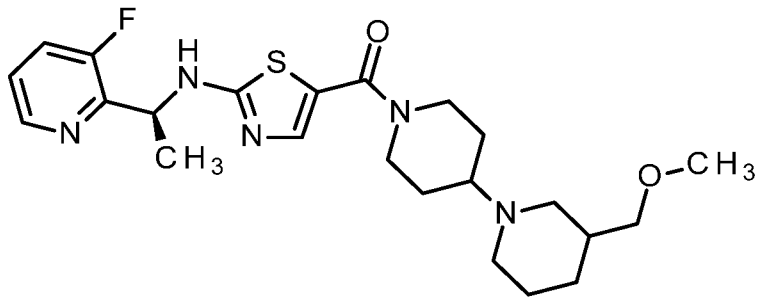
Instrument: Waters Prep LC/MS system, column: XBridge C18 5 µm 100 x 30 mm. Eluent A: water, eluent B: acetonitrile, eluent C: 2% ammonia in water, eluent D: acetonitrile/water (80% by vol./20% by vol.), total flow rate: 80 ml/min, room temperature, wavelength: 200-400 nm, at-column injection (complete injection); gradient profile: eluent A 0 to 2 min 55 ml, eluent B 0 to 2 min 15 ml, eluent A 2 to 10 min from 55 ml to 31 ml and eluent B from 15 ml to 39 ml, 10 to 12 min 0 ml eluent A and 70 ml eluent B. Constant flow rate of eluent C and eluent D of 5 ml/min each over the entire run time.

36 mg (34% of theory, 77 µmol) of the title compound was obtained.

LC-MS (Method 1): $R_t$ = 0.83 min; m/z = 462 $(M+H)^+$.

**Example 109 and Example 110**

(2-{[(1*S*)-1-(3-Fluoropyridin-2-yl)ethyl]amino}-1,3-thiazol-5-yl)[3-(methoxymethyl)[1,4'-bipiperidine]-1'-yl]methanone (*diastereomers 1 and 2*)



60 mg of the diastereomer mixture of (2-{[(1*S*)-1-(3-fluoropyridin-2-yl)ethyl]amino}-1,3-thiazol-5-yl)[3-(methoxymethyl)[1,4'-bipiperidine]-1'-yl]methanone (Example 108) was separated into the diastereomers by preparative HPLC on a chiral phase [column: Daicel Chiralpak IB 5 µm, 250 x 20 mm; eluent: 50% n-heptane & 50% ethanol + 0.2% diethylamine; flow rate: 15 ml/min, temperature: 40°C, detection: 210 nm]: The two diastereomers were separately collected and lyophilized.

Example 109 (*diastereomer 1*):

(2-{[(1*S*)-1-(3-Fluoropyridin-2-yl)ethyl]amino}-1,3-thiazol-5-yl)[3-(methoxymethyl)[1,4'-bipiperidine]-1'-yl]methanone

Yield: 19 mg

$R_t$ = 1.32 min; chemical purity > 99%; > 99% de

[Column: DAICEL Chiralpak IB-3 3 µm 4.6 mm x 50 mm, flow rate: 1 ml/min, UV: 220 nm, temp.: 30°C, eluent: 50% n-heptane & 50% ethanol + 0.2% DEA].

LC-MS (Method 1): $R_t$ = 0.83 min; MS (ESIneg): m/z = 460 $[M-H]^-$.

$^1$H-NMR (400 MHz, DMSO-$d_6$, δ/ppm): 0.82-0.97 (m, 1H), 1.21-1.50 (m, 6H, therein at 1.46 (d, 3H)), 1.52-1.64 (m, 2H), 1.65-1.78 (m, 3H), 1.88 (br. t, 1H), 2.09 (br. t, 1H), 2.42-2.57 (m, 1H, partly hidden by DMSO), 2.66-2.75 (m, 1H), 2.75-2.95 (m, 3H), 3.09-3.18 (m, 2H), 3.20 (s, 3H), 4.23 (br. d, 2H), 5.24-5.34 (m, 1H), 7.33 (s, 1H), 7.36-7.43 (m, 1H), 7.64-7.73 (m, 1H), 8.40 (d, 1H), 8.61 (d, 1H).

$[\alpha]_D^{20}$ = -26.67° (c = 0.315, methanol).

Example 110 (*diastereomer 2*):

(2-{[(1*S*)-1-(3-Fluoropyridin-2-yl)ethyl]amino}-1,3-thiazol-5-yl)[3-(methoxymethyl)[1,4'-bipiperidine]-1'-yl]methanone

Yield: 19 mg

$R_t$ = 3.27 min; chemical purity > 99%; > 99% de

[Column: DAICEL Chiralpak IB-3 3 µm 4.6 mm x 50 mm, flow rate: 1 ml/min, UV: 220 nm, temp.: 30°C, eluent: 50% n-heptane & 50% ethanol + 0.2% DEA].

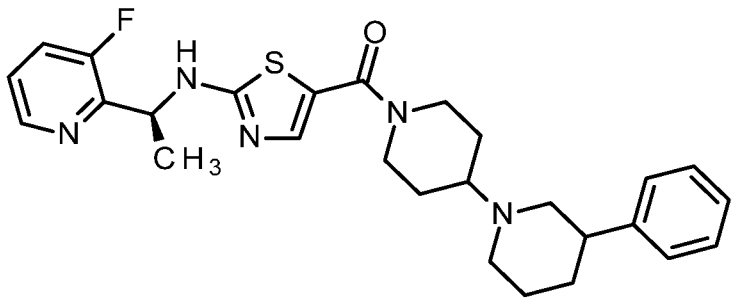
LC-MS (Method 1): $R_t$ = 0.82 min; MS (ESIneg): m/z = 460 $[M-H]^-$.

$^1$H-NMR (400 MHz, DMSO-$d_6$, δ/ppm): 0.82-0.97 (m, 1H), 1.21-1.50 (m, 6H, therein at 1.46 (d, 3H)), 1.53-1.64 (m, 2H), 1.66-1.77 (m, 3H), 1.88 (br. t, 1H), 2.09 (br. t, 1H), 2.42-2.57 (m, 1H, partly hidden by DMSO), 2.66-2.75 (m, 1H), 2.76-2.93 (m, 3H), 3.10-3.18 (m, 2H), 3.20 (s, 3H), 4.23 (br. d, 2H), 5.24-5.34 (m, 1H), 7.33 (s, 1H), 7.36-7.42 (m, 1H), 7.69 (t, 1H), 8.40 (d, 1H), 8.61 (d, 1H).

$[\alpha]_D^{20}$ = -29.40° (c = 0.305, methanol).

**Example 111**

(2-{[(1*S*)-1-(3-Fluoropyridin-2-yl)ethyl]amino}-1,3-thiazol-5-yl)[3-phenyl[1,4'-bipiperidine]-1'-yl]methanone (*diastereomer mixture*)



186 mg (0.43 mmol) of (2-bromo-1,3-thiazol-5-yl)[3-phenyl[1,4'-bipiperidine]-1'-yl]methanone (*racemic*) and 182 mg (0.86 mmol) of (1*S*)-1-(3-fluoropyridin-2-yl)ethanamine dihydrochloride were dissolved in 1.2 ml of 1-methyl-2-pyrrolidone, and 0.37 ml of *N*,*N*-diisopropylethylamine was added. Thereafter, the reaction mixture (closed vessel) was stirred at 140°C overnight. After cooling to room temperature, the reaction mixture was purified by prep. HPLC.

Method:

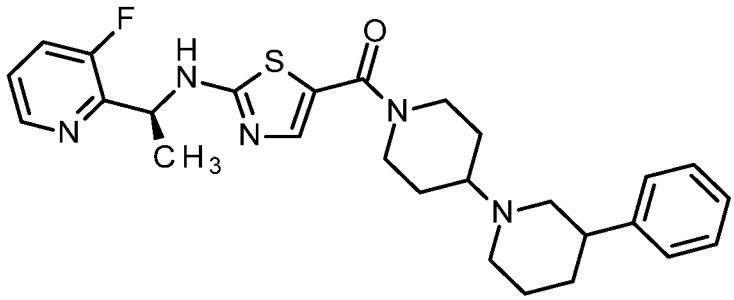
Instrument: Waters Prep LC/MS system, column: XBridge C18 5 µm 100 x 30 mm. Eluent A: water, eluent B: acetonitrile, eluent C: 2% ammonia in water, eluent D: acetonitrile/water (80% by vol./20% by vol.), total flow rate: 80 ml/min, room temperature, wavelength: 200-400 nm, at-column injection (complete injection); gradient profile: eluent A 0 to 2 min 47 ml, eluent B 0 to 2 min 23 ml, eluent A 2 to 10 min from 47 ml to 23 ml and eluent B from 23 ml to 47 ml, 10 to 12 min 0 ml eluent A and 70 ml eluent B. Constant flow rate of eluent C and eluent D of 5 ml/min each over the entire run time.

In this way, 99 mg (47% of theory, 0.20 mmol) of the title compound was obtained.

LC-MS (Method 1): $R_t$ = 1.11 min; m/z = 494 $(M+H)^+$.

**Example 112 and Example 113**

(2-{[(1*S*)-1-(3-Fluoropyridin-2-yl)ethyl]amino}-1,3-thiazol-5-yl)[3-phenyl[1,4'-bipiperidine]-1'-yl]methanone (*diastereomers 1 and 2*)



95 mg of the diastereomer mixture of (2-{[(1*S*)-1-(3-fluoropyridin-2-yl)ethyl]amino}-1,3-thiazol-5-yl)[3-phenyl[1,4'-bipiperidine]-1'-yl]methanone (Example 111) was separated into the diastereomers by preparative HPLC on a chiral phase [column: Daicel Chiralpak IF 5 µm, 250 x 20 mm; eluent: 50% n-heptane & 50% ethanol + 0.2% diethylamine; flow rate: 20 ml/min, temperature: 50°C, detection: 220 nm]: The two diastereomers were separately collected and lyophilized.

Example 112 (*diastereomer 1*):

(2-{[(1*S*)-1-(3-Fluoropyridin-2-yl)ethyl]amino}-1,3-thiazol-5-yl)[3-phenyl[1,4'-bipiperidine]-1'-yl]methanone

Yield: 34 mg

$R_t$ = 3.96 min; chemical purity > 99%; > 99% de

[Column: DAICEL Chiralpak IF-3 3 µm 4.6 mm x 50 mm, flow rate: 1 ml/min, UV: 220 nm, temp.: 30°C, eluent: 50% n-heptane & 50% ethanol + 0.2% DEA].

LC-MS (Method 1): $R_t$ = 1.12 min; MS (ESIneg): m/z = 492 $[M-H]^-$.

$^1$H-NMR (400 MHz, DMSO-$d_6$, δ/ppm): 1.30-1.48 (m, 6H, therein at 1.46 (d, 3H)), 1.49-1.61 (m, 1H), 1.66-1.84 (m, 4H), 2.12-2.25 (m, 2H), 2.47-2.60 (m, 1H, partly hidden by DMSO), 2.62-2.73 (m, 1H), 2.80-2.94 (m, 4H), 4.24 (br. d, 2H), 5.23-5.33 (m, 1H), 7.15-7.22 (m, 1H), 7.22-7.31 (m, 4H), 7.33 (s, 1H), 7.36-7.42 (m, 1H), 7.64-7.73 (m, 1H), 8.37-8.42 (m, 1H), 8.60 (d, 1H).

$[\alpha]_D^{20}$ = -47.41° (c = 0.270, methanol).

Example 113 (*diastereomer 2*):

(2-{[(1*S*)-1-(3-Fluoropyridin-2-yl)ethyl]amino}-1,3-thiazol-5-yl)[3-phenyl[1,4'-bipiperidine]-1'-yl]methanone

Yield: 33 mg

$R_t$ = 5.41 min; chemical purity > 99%; > 99% de

[Column: DAICEL Chiralpak IF-3 3 µm 4.6 mm x 50 mm, flow rate: 1 ml/min, UV: 220 nm, temp.: 30°C, eluent: 50% n-heptane & 50% ethanol + 0.2% DEA].

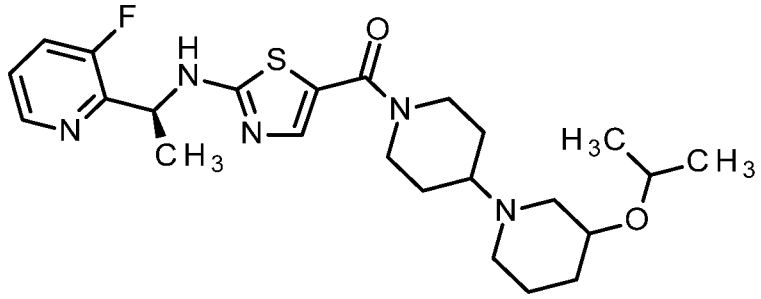
LC-MS (Method 1): $R_t$ = 1.12 min; MS (ESIneg): m/z = 492 $[M-H]^-$.

$^1$H-NMR (400 MHz, DMSO-$d_6$, δ/ppm): 1.30-1.48 (m, 6H, therein at 1.46 (d, 3H)), 1.48-1.62 (m, 1H), 1.66-1.84 (m, 4H), 2.12-2.25 (m, 2H), 2.47-2.61 (m, 1H, partly hidden by DMSO), 2.62-2.73 (m, 1H), 2.80-2.94 (m, 4H), 4.24 (br. d, 2H), 5.23-5.33 (m, 1H), 7.14-7.22 (m, 1H), 7.22-7.31 (m, 4H), 7.33 (s, 1H), 7.36-7.42 (m, 1H), 7.64-7.72 (m, 1H), 8.37-8.43 (m, 1H), 8.60 (d, 1H).

$[\alpha]_D^{20}$ = -28.93° (c = 0.265, methanol).

**Example 114**

(2-{[(1*S*)-1-(3-Fluoropyridin-2-yl)ethyl]amino}-1,3-thiazol-5-yl)[3-isopropoxy[1,4'-bipiperidine]-1'-yl]methanone (*diastereomer mixture*)



145 mg (348 µmol) of (2-bromo-1,3-thiazol-5-yl)[3-isopropoxy[1,4'-bipiperidine]-1'-yl]methanone (*racemic*) and 148 mg (696 µmol) of (1*S*)-1-(3-fluoropyridin-2-yl)ethanamine dihydrochloride were dissolved in 1.2 ml of 1-methyl-2-pyrrolidone, and 0.3 ml of *N*,*N*-diisopropylethylamine was added. Thereafter, the reaction mixture (closed vessel) was stirred at 140°C overnight. After cooling to room temperature, the reaction mixture was purified by prep. HPLC.

Method:

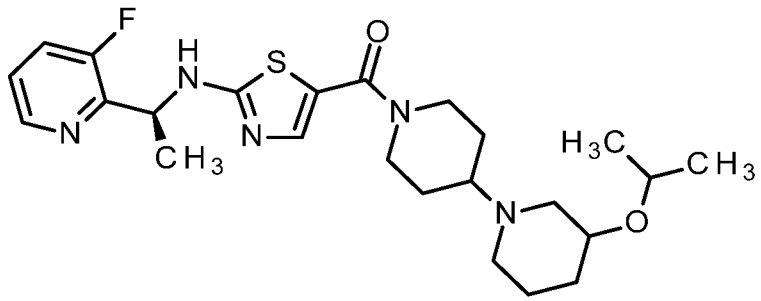
Instrument: Waters Prep LC/MS system, column: Phenomenex Kinetex C18 5µm 100 x 30 mm. Eluent A: water, eluent B: acetonitrile, eluent C: 2% formic acid in water, eluent D: acetonitrile/water (80% by vol./20% by vol.), total flow rate: 80 ml/min, room temperature, wavelength: 200-400 nm, at-column injection (complete injection); gradient profile: eluent A 0 to 2 min 70 ml, eluent B 0 to 2 min 0 ml, eluent A 2 to 10 min from 70 ml to 0 ml and eluent B from 0 ml to 70 ml, 10 to 12 min 0 ml eluent A and 70 ml eluent B. Constant flow rate of eluent C and eluent D of 5 ml/min each over the entire run time.

77 mg (44% of theory) of the title compound was obtained.

LC-MS (Method 1): $R_t$ = 0.95 min; m/z = 476 $(M+H)^+$.

**Example 115 and Example 116**

(2-{[(1*S*)-1-(3-Fluoropyridin-2-yl)ethyl]amino}-1,3-thiazol-5-yl)[3-isopropoxy[1,4'-bipiperidine]-1'-yl]methanone (*diastereomers 1 and 2*)



70 mg of the diastereomer mixture of (2-{[(1*S*)-1-(3-fluoropyridin-2-yl)ethyl]amino}-1,3-thiazol-5-yl)[3-isopropoxy[1,4'-bipiperidine]-1'-yl]methanone (Example 114) was separated into the diastereomers by preparative HPLC on a chiral phase [column: Daicel Chiralpak AD-H 5 µm, 250 x 20 mm; eluent: 70% n-heptane & 30% ethanol + 0.2% diethylamine; flow rate: 15 ml/min, temperature: 30°C, detection: 300 nm]: The two diastereomers were separately collected and lyophilized.

Example 115 (*diastereomer 1*):

(2-{[(1*S*)-1-(3-Fluoropyridin-2-yl)ethyl]amino}-1,3-thiazol-5-yl)[3-isopropoxy[1,4'-bipiperidine]-1'-yl]methanone

Yield: 16 mg

$R_t$ = 12.68 min; chemical purity > 99%; > 99% de

[Column: DAICEL Chiralpak AD-H, 5 µm 4.6 mm x 250 mm, flow rate: 1 ml/min, UV: 300 nm, temp.: 30°C, eluent: 70% n-heptane & 30% ethanol + 0.2% DEA].

LC-MS (Method 1): $R_t$ = 0.92 min; MS (ESIneg): m/z = 474 $[M-H]^-$.

$^1$H-NMR (400 MHz, DMSO-$d_6$, δ/ppm): 0.96-1.10 (m, 7H, therein at 1.04 (d, 6H)), 1.16-1.42 (m, 4H), 1.46 (d, 3H), 1.61 (br. d, 1H), 1.72 (br. d, 2H), 1.79-1.95 (m, 2H), 2.03 (br. t, 1H), 2.66 (br. d, 1H), 2.80-2.97 (m, 3H), 3.24-3.43 (m, 1H, partly hidden by $H_2O$), 3.61-3.72 (m, 1H), 4.24 (br. d, 2H), 5.29 (quin., 1H), 7.34 (s, 1H), 7.36-7.44 (m, 1H), 7.69 (t, 1H), 8.40 (d, 1H), 8.61 (d, 1H).

Example 116 (*diastereomer 2*):

(2-{[(1*S*)-1-(3-Fluoropyridin-2-yl)ethyl]amino}-1,3-thiazol-5-yl)[3-isopropoxy[1,4'-bipiperidine]-1'-yl]methanone

Yield: 9 mg

$R_t$ = 16.91 min; chemical purity > 99%; > 98% de

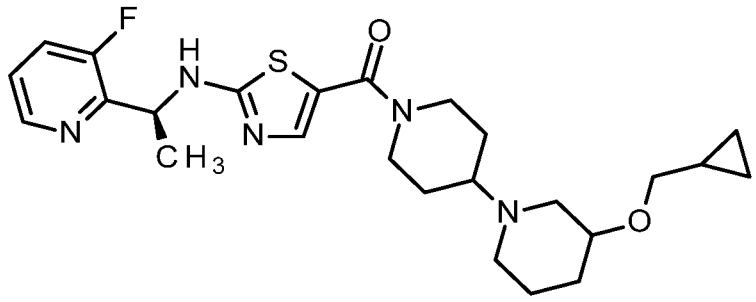
[Column: DAICEL Chiralpak AD-H, 5 µm 4.6 mm x 250 mm, flow rate: 1 ml/min, UV: 300 nm, temp.: 30°C, eluent: 70% n-heptane & 30% ethanol + 0.2% DEA].

LC-MS (Method 1): $R_t$ = 0.92 min; MS (ESIneg): m/z = 474 $[M-H]^-$.

$^1$H-NMR (400 MHz, DMSO-$d_6$, δ/ppm): 0.96-1.09 (m, 7H, therein at 1.04 (d, 6H)), 1.14-1.41 (m, 4H), 1.46 (d, 3H), 1.55-1.65 (m, 1H), 1.72 (br. d, 2H), 1.78-1.94 (m, 2H), 2.03 (br. t, 1H), 2.66 (br. d, 1H), 2.79-2.95 (m, 3H), 3.24-3.43 (m, 1H, partly hidden by $H_2O$), 3.61-3.74 (m, 1H), 4.24 (br. d, 2H), 5.23-5.34 (m, 1H), 7.34 (s, 1H), 7.36-7.43 (m, 1H), 7.69 (ddd, 1H), 8.40 (d, 1H), 8.61 (d, 1H).

**Example 117**

[3-(Cyclopropylmethoxy)[1,4'-bipiperidine]-1'-yl](2-{[(1*S*)-1-(3-fluoropyridin-2-yl)ethyl]amino}-1,3-thiazol-5-yl)methanone (*diastereomer mixture*)



109 mg (254 µmol) of (2-bromo-1,3-thiazol-5-yl)[3-(cyclopropylmethoxy)[1,4'-bipiperidine]-1'-yl]methanone (*racemic*) and 108 mg (509 µmol) of (1*S*)-1-(3-fluoropyridin-2-yl)ethanamine dihydrochloride were dissolved in 2.3 ml of 1-methyl-2-pyrrolidone, and 0.2 ml of *N*,*N*-diisopropylethylamine was added. Thereafter, the reaction mixture (closed vessel) was stirred at 140°C overnight. After cooling to room temperature, the reaction mixture was purified by prep. HPLC.

Method:

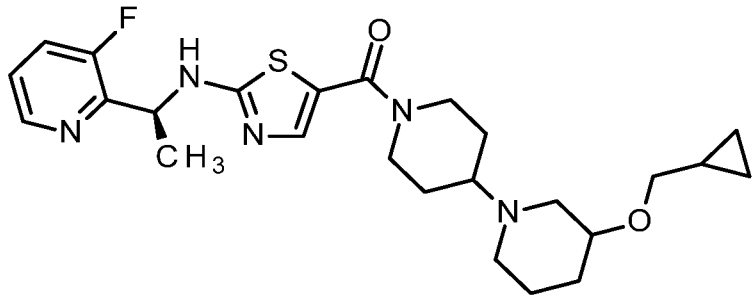
Instrument: Waters Prep LC/MS system, column: Phenomenex Kinetex C18 5µm 100 x 30 mm. Eluent A: water, eluent B: acetonitrile, eluent C: 2% formic acid in water, eluent D: acetonitrile/water (80% by vol./20% by vol.), total flow rate: 80 ml/min, room temperature, wavelength: 200-400 nm, at-column injection (complete injection); gradient profile: eluent A 0 to 2 min 63 ml, eluent B 0 to 2 min 7 ml, eluent A 2 to 10 min from 63 ml to 39 ml and eluent B from 7 ml to 31 ml, 10 to 12 min 0 ml eluent A and 70 ml eluent B. Constant flow rate of eluent C and eluent D of 5 ml/min each over the entire run time.

52 mg (42% of theory) of the title compound was obtained.

LC-MS (Method 1): $R_t$ = 0.98 min; m/z = 488 $(M+H)^+$.

**Example 118 and Example 119**

[3-(Cyclopropylmethoxy)[1,4'-bipiperidine]-1'-yl](2-{[(1*S*)-1-(3-fluoropyridin-2-yl)ethyl]amino}-1,3-thiazol-5-yl)methanone (*diastereomers 1 and 2*)



60 mg of the diastereomer mixture of [3-(cyclopropylmethoxy)[1,4'-bipiperidine]-1'-yl](2-{[(1*S*)-1-(3-fluoropyridin-2-yl)ethyl]amino}-1,3-thiazol-5-yl)methanone (Example 117) was separated into the diastereomers by preparative HPLC on a chiral phase [column: Daicel Chiralpak IB 5 µm, 250 x 20 mm; eluent: 50% n-heptane & 50% ethanol + 0.2% diethylamine; flow rate: 20 ml/min; temperature: 50°C, detection: 220 nm]: The two diastereomers were separately collected and lyophilized.

Example 118 (*diastereomer 1*):

[3-(Cyclopropylmethoxy)[1,4'-bipiperidine]-1'-yl](2-{[(1*S*)-1-(3-fluoropyridin-2-yl)ethyl]amino}-1,3-thiazol-5-yl)methanone

Yield: 16 mg

$R_t$ = 1.48 min; chemical purity > 99%; > 99% de

[Column: DAICEL Chiralpak IB-3 3 µm 4.6 mm x 50 mm, flow rate: 1 ml/min, UV: 220 nm, temp.: 30°C, eluent: 50% n-heptane & 50% ethanol + 0.2% DEA].

LC-MS (Method 1): $R_t$ = 0.97 min; MS (ESIneg): m/z = 486 $[M-H]^-$.

$^1$H-NMR (400 MHz, DMSO-$d_6$, δ/ppm): 0.08-0.16 (m, 2H), 0.38-0.47 (m, 2H), 0.86-0.98 (m, 1H), 0.98-1.11 (m, 1H), 1.27-1.42 (m, 3H), 1.46 (d, 3H), 1.56-1.66 (m, 1H), 1.71 (br. d, 2H), 1.84-1.97 (m, 2H), 2.07 (br. t, 1H), 2.45-2.58 (m, 1H, partly hidden by DMSO), 2.65 (br. d, 1H), 2.86 (br. t, 2H), 2.95 (br. d, 1H), 3.24 (d, 3H), 4.24 (br. d, 2H), 5.24-5.34 (m, 1H), 7.34 (s, 1H), 7.36-7.43 (m, 1H), 7.65-7.73 (m, 1H), 8.37-8.43 (m, 1H), 8.61 (d, 1H).

$[\alpha]_D^{20}$ = -27.84° (c = 0.255, methanol).

Example 119 (*diastereomer 2*):

[3-(Cyclopropylmethoxy)[1,4'-bipiperidine]-1'-yl](2-{[(1*S*)-1-(3-fluoropyridin-2-yl)ethyl]amino}-1,3-thiazol-5-yl)methanone

Yield: 16 mg

$R_t$ = 4.25 min; chemical purity > 99%; > 99% de

[Column: DAICEL Chiralpak IB-3 3 µm 4.6 mm x 50 mm, flow rate: 1 ml/min, UV: 220 nm, temp.: 30°C, eluent: 50% n-heptane & 50% ethanol + 0.2% DEA].

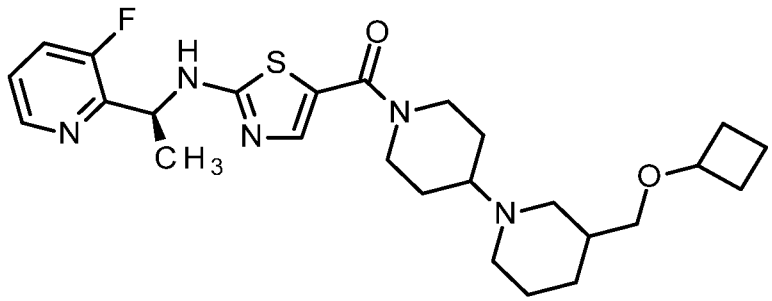
LC-MS (Method 1): $R_t$ = 0.96 min; MS (ESIneg): m/z = 486 $[M-H]^-$.

$^1$H-NMR (400 MHz, DMSO-$d_6$, δ/ppm): 0.08-0.16 (m, 2H), 0.38-0.46 (m, 2H), 0.87-0.98 (m, 1H), 0.98-1.11 (m, 1H), 1.26-1.42 (m, 3H), 1.46 (d, 3H), 1.57-1.66 (m, 1H), 1.71 (br. d, 2H), 1.83-1.97 (m, 2H), 2.07 (br. t, 1H), 2.45-2.58 (m, 1H, partly hidden by DMSO), 2.65 (br. d, 1H), 2.86 (br. t, 2H), 2.95 (br. d, 1H), 3.24 (d, 3H), 4.24 (br. d, 2H), 5.24-5.34 (m, 1H), 7.33 (s, 1H), 7.36-7.43 (m, 1H), 7.64-7.73 (m, 1H), 8.40 (d, 1H), 8.61 (d, 1H).

$[\alpha]_D^{20}$ = -43.21° (c = 0.270, methanol).

**Example 120**

{3-[(Cyclobutyloxy)methyl][1,4'-bipiperidine]-1'-yl}(2-{[(1S)-1-(3-fluoropyridin-2-yl)ethyl]amino}-1,3-thiazol-5-yl)methanone (*diastereomer mixture*)




50 mg (113 µmol) of (2-bromo-1,3-thiazol-5-yl){3-[(cyclobutyloxy)methyl][1,4'-bipiperidine]-1'-yl}methanone (*racemic*) and 48 mg (226 µmol) of (1*S*)-1-(3-fluoropyridin-2-yl)ethanamine dihydrochloride were dissolved in 1.6 ml of 1-methyl-2-pyrrolidone, and 0.1 ml of *N*,*N*-diisopropylethylamine was added. Thereafter, the reaction mixture (closed vessel) was stirred at 140°C for 2 days. After cooling to room temperature, the reaction mixture was purified by prep. HPLC.

Method:
Instrument: Waters Prep LC/MS system, column: Phenomenex Kinetex C18 5µm 100 x 30 mm. Eluent A: water, eluent B: acetonitrile, eluent C: 2% formic acid in water, eluent D: acetonitrile/water (80% by vol./20% by vol.), total flow rate: 80 ml/min, room temperature, wavelength: 200-400 nm,

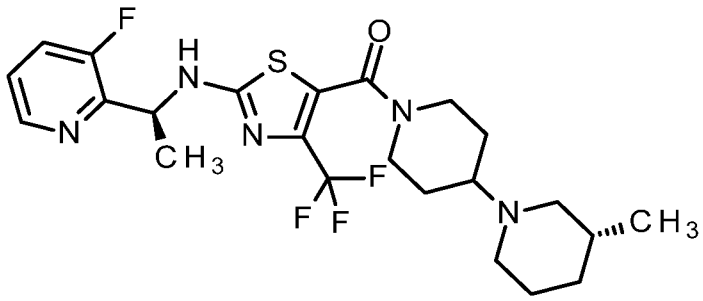
at-column injection (complete injection); gradient profile: eluent A 0 to 2 min 70 ml, eluent B 0 to 2 min 0 ml, eluent A 2 to 10 min from 70 ml to 0 ml and eluent B from 0 ml to 70 ml, 10 to 12 min 0 ml eluent A and 70 ml eluent B. Constant flow rate of eluent C and eluent D of 5 ml/min each over the entire run time.

15 mg (26% of theory) of the title compound was obtained.

LC-MS (Method 3): $R_t$ = 1.67 min; m/z = 502 $(M+H)^+$.

**Example 121**

[2-{[(1*S*)-1-(3-Fluoropyridin-2-yl)ethyl]amino}-4-(trifluoromethyl)-1,3-thiazol-5-yl][(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone



142 mg (0.32 mmol) of [2-bromo-4-(trifluoromethyl)-1,3-thiazol-5-yl][(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone and 137 mg (0.65 mmol) of (1*S*)-1-(3-fluoropyridin-2-yl)ethanamine dihydrochloride were dissolved in 1.9 ml of 1-methyl-2-pyrrolidone, and 0.23 ml of *N*,*N*-diisopropylethylamine was added. Thereafter, the reaction mixture (closed vessel) was stirred at 140°C overnight. After cooling to room temperature, the reaction mixture was purified by prep. HPLC.

Method:

Instrument: Waters Prep LC/MS system, column: XBridge C18 5 µm 100 x 30 mm. Eluent A: water, eluent B: acetonitrile, eluent C: 2% ammonia in water, eluent D: acetonitrile/water (80% by vol. / 20% by vol.), total flow rate: 80 ml/min, room temperature, wavelength: 200-400 nm, at-column injection (complete injection); gradient profile: eluent A 0 to 2 min 47 ml, eluent B 0 to 2 min 23 ml, eluent A 2 to 10 min from 47 ml to 23 ml and eluent B from 23 ml to 47 ml, 10 to 12 min 0 ml eluent A and 70 ml eluent B. Constant flow rate of eluent C and eluent D of 5 ml/min each over the entire run time.

71 mg (0.13 mmol, 20% of theory) of the title compound was obtained.

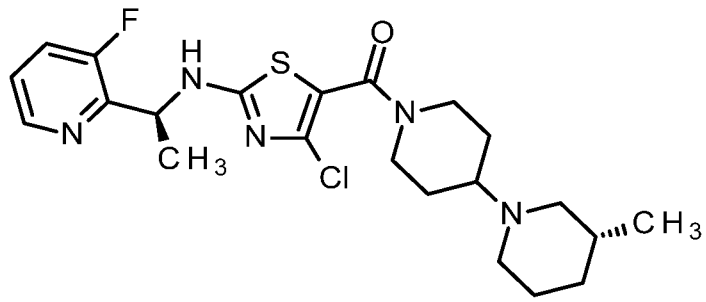
LC-MS (Method 1): $R_t$ = 1.11 min; m/z = 500 $(M+H)^+$.

$^1$H-NMR (400 MHz, DMSO-$d_6$, δ/ppm): 0.73-0.87 (m, 4H, therein at 0.81 (d, 3H)), 1.20-1.44 (m, 3H), 1.44-1.66 (m, 6H, therein at 1.48 (d, 3H)), 1.66-1.80 (m, 3H), 2.02 (br. t, 1H), 2.41-2.53 (m, 1H, partly hidden by DMSO), 2.64-2.78 (m, 3H), 2.90-3.08 (m, 1H), 3.46-3.68 (m, 1H), 4.24-4.47 (m, 1H), 5.27 (quin., 1H), 7.39-7.47 (m, 1H), 7.68-7.76 (m, 1H), 8.40-8.45 (m, 1H), 8.83 (d, 1H).

$[\alpha]_D^{20}$ = -7.10° (c = 0.310, methanol).

**Example 122**

(4-Chloro-2-{[(1*S*)-1-(3-fluoropyridin-2-yl)ethyl]amino}-1,3-thiazol-5-yl)[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone



200 mg (0.49 mmol) of (2-bromo-4-chloro-1,3-thiazol-5-yl)[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone and 210 mg (0.98 mmol) of (1*S*)-1-(3-fluoropyridin-2-yl)ethanamine dihydrochloride were dissolved in 2.5 ml of 1-methyl-2-pyrrolidone, and 0.26 ml of *N*,*N*-diisopropylethylamine was added. Thereafter, the reaction mixture (closed vessel) was stirred at 140°C overnight. After cooling to room temperature, the reaction mixture was purified by prep. HPLC.

Method:
Instrument: Waters Prep LC/MS system, column: XBridge C18 5 µm 100 x 30 mm. Eluent A: water, eluent B: acetonitrile, eluent C: 2% ammonia in water, eluent D: acetonitrile/water (80% by vol. / 20% by vol.), total flow rate: 80 ml/min, room temperature, wavelength: 200-400 nm, at-column injection (complete injection); gradient profile: eluent A 0 to 2 min 47 ml, eluent B 0 to 2 min 23 ml, eluent A 2 to 10 min from 47 ml to 23 ml and eluent B from 23 ml to 47 ml, 10 to 12 min 0 ml eluent A and 70 ml eluent B. Constant flow rate of eluent C and eluent D of 5 ml/min each over the entire run time.

75 mg (0.16 mmol, 33% of theory) of the title compound was obtained.

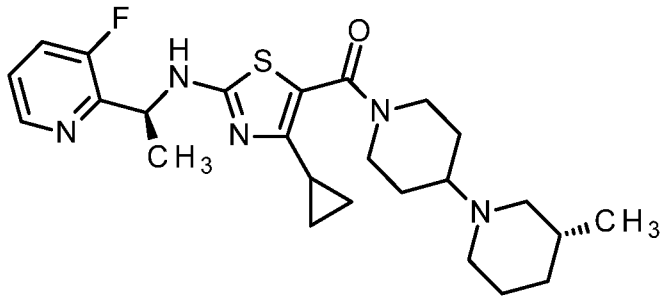
LC-MS (Method 1): $R_t$ = 0.99 min; m/z = 466/468 $(M+H)^+$.

$^1$H-NMR (400 MHz, DMSO-$d_6$, δ/ppm): 0.74-0.87 (m, 4H, therein at 0.81 (d, 3H)), 1.26-1.42 (m, 3H), 1.42-1.66 (m, 6H, therein at 1.46 (d, 3H)), 1.68-1.78 (m, 3H), 2.02 (br. t, 1H), 2.41-2.52 (m, 1H, partly hidden by DMSO), 2.65-2.77 (m, 2H), 2.81-2.98 (m, 2H), 3.93-4.12 (m, 2H), 5.24 (quin., 1H), 7.39-7.47 (m, 1H), 7.68-7.77 (m, 1H), 8.39-8.46 (m, 1H), 8.73 (d, 1H).

$[\alpha]_D^{20}$ = -39.64° (c = 0.280, methanol).

**Example 123**

(4-Cyclopropyl-2-{[(1*S*)-1-(3-fluoropyridin-2-yl)ethyl]amino}-1,3-thiazol-5-yl)[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone



194 mg (0.47 mmol) of (2-bromo-4-cyclopropyl-1,3-thiazol-5-yl)[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone and 200 mg (0.94 mmol) of (1*S*)-1-(3-fluoropyridin-2-yl)ethanamine dihydrochloride were dissolved in 3 ml of 1-methyl-2-pyrrolidone, and 0.33 ml of N,N-diisopropylethylamine was added. Thereafter, the reaction mixture (closed vessel) was stirred at 140°C overnight. After cooling to room temperature, the solution was concentrated to dryness under reduced pressure. Partial epimerization was found, and therefore the resultant residue was purified by chiral prep. HPLC.

95 mg (0.20 mmol) of the diastereomer mixture of (4-cyclopropyl-2-{[(1*SR*)-1-(3-fluoropyridin-2-yl)ethyl]amino}-1,3-thiazol-5-yl)[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone (88% de) was separated into the diastereomers by preparative HPLC on a chiral phase [column: Daicel Chiralcel OX-H, 5 µm, 250 mm x 20 mm; eluent: n-heptane/(isopropanol + 0.2% diethylamine) 70:30; flow rate: 25 ml/min; UV detection: 210 nm; temperature: 40°C]:

This gave 67 mg (43% of theory, purity > 99%) of the title compound (4-cyclopropyl-2-{[(1*S*)-1-(3-fluoropyridin-2-yl)ethyl]amino}-1,3-thiazol-5-yl)[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone).

$R_t$ = 2.39 min; chemical purity > 99%; > 99% de

[Column: Chiralpak OX-3, 3 µm, 50 mm x 4.6 mm; eluent: n-heptane/isopropanol + 0.2% diethylamine 70:30; flow rate: 1 ml/min; temperature: 30°C; UV detection: 220 nm].

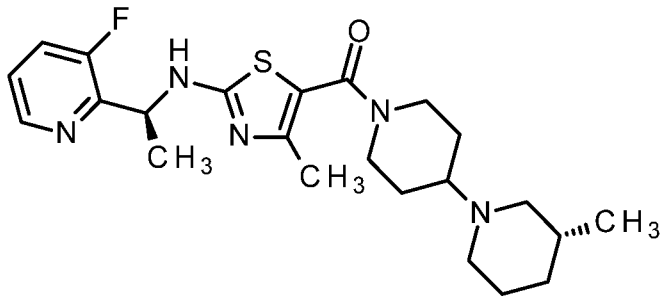
LC-MS (Method 1): $R_t$ = 1.11 min; m/z = 472 $(M+H)^+$.

$^1$H-NMR (400 MHz, DMSO-$d_6$, δ/ppm): 0.53-0.63 (m, 1H), 0.68-0.90 (m, 7H, therein at 0.81 (d, 3H)), 1.21-1.46 (m, 6H, therein at 1.43 (d, 3H)), 1.46-1.66 (m, 3H), 1.68-1.82. (m, 4H), 1.97-2.08 (m, 1H), 2.39-2.49 (m, 1H), 2.69-2.78 (m, 2H), 2.85 (br. t, 2H), 4.10 (br. d, 2H), 5.06-5.16 (m, 1H), 7.33-7.41 (m, 1H), 7.62-7.71 (m, 1H), 8.35-8.41 (m, 2H).

$[\alpha]_D^{20}$ = -30.48° (c = 0.280, methanol).

**Example 124**

(2-{[(1*S*)-1-(3-Fluoropyridin-2-yl)ethyl]amino}-4-methyl-1,3-thiazol-5-yl)[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone



200 mg (0.52 mmol) of (2-bromo-4-methyl-1,3-thiazol-5-yl)[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone and 183 mg (1.04 mmol) of (1*S*)-1-(3-fluoropyridin-2-yl)ethanamine hydrochloride (1:1) were dissolved in 3 ml of 1-methyl-2-pyrrolidone, and 0.27 ml of N,N-diisopropylethylamine was added. Thereafter, the reaction mixture (closed vessel) was stirred at 140°C overnight. After cooling to room temperature, the solution was concentrated to dryness under reduced pressure. Partial epimerization was found, and therefore the resultant residue was purified by chiral prep. HPLC.

56 mg (0.13 mmol) of the diastereomer mixture of (2-{[(1*SR*)-1-(3-fluoropyridin-2-yl)ethyl]amino}-4-methyl-1,3-thiazol-5-yl)[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone (87.6% de) was separated into the diastereomers by preparative HPLC on a chiral phase [column: Daicel Chiralcel OX-H, 5 µm, 250 mm x 20 mm; eluent: n-heptane/(isopropanol + 0.2% diethylamine) 70:30; flow rate: 25 ml/min; UV detection: 210 nm; temperature: 40°C]:

This gave 41 mg (25% of theory) of the title compound ((2-{[(1*S*)-1-(3-fluoropyridin-2-yl)ethyl]amino}-4-methyl-1,3-thiazol-5-yl)[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone).

$R_t$ = 2,497 min; chemical purity > 99%; > 99% de

[Column: Chiralpak OX-3, 3 µm, 50 mm x 4.6 mm; eluent: n-heptane/isopropanol + 0.2% diethylamine 70:30; flow rate: 1 ml/min; temperature: 30°C; UV detection: 220 nm].

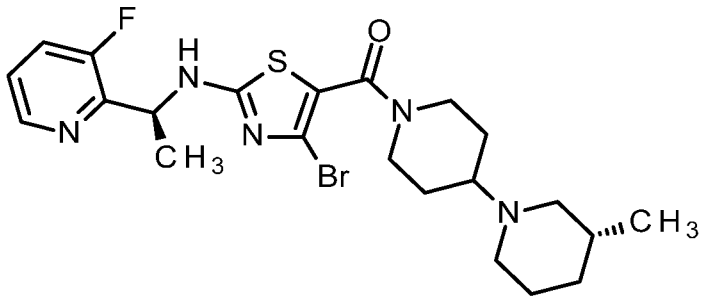
LC-MS (Method 1): $R_t$ = 0.85 min; m/z = 446 $(M+H)^+$.

$^1$H-NMR (400 MHz, DMSO-$d_6$, δ/ppm): 0.75-0.87 (m, 4H, therein at 0.81 (d, 3H)), 1.22-1.48 (m, 6H, therein at 1.45 (d, 3H)), 1.48-1.66 (m, 3H), 1.68-1.81. (m, 3H), 2.00-2.10 (m, 4H, therein at 2.06 (s, 3H)), 2.43-2.53 (m, 1H, partly hidden by DMSO), 2.70-2.78 (m, 2H), 2.83 (br. t, 2H), 4.05 (br. d, 2H), 5.21-5.31 (m, 1H), 7.37-7.44 (m, 1H), 7.66-7.74 (m, 1H), 8.37 (d, 1H), 8.39-8.44 (m, 1H).

$[\alpha]_D^{20}$ = -43.93° (c = 0.280, methanol).

**Example 125**

(4-Bromo-2-{[(1*S*)-1-(3-fluoropyridin-2-yl)ethyl]amino}-1,3-thiazol-5-yl)[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone




200 mg (0.44 mmol) of (2,4-dibromo-1,3-thiazol-5-yl)[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone and 189 mg (0.87 mmol) of (1*S*)-1-(3-fluoropyridin-2-yl)ethanamine dihydrochloride were dissolved in 2 ml of 1-methyl-2-pyrrolidone, and 0.23 ml of *N*,*N*-diisopropylethylamine was added. Thereafter, the reaction mixture (closed vessel) was stirred at 140°C overnight. After cooling to room temperature, the reaction mixture was purified by prep. HPLC.

Method:

Instrument: Waters Prep LC/MS System, column: XBridge C18 5µm 100x30 mm. Eluent A: water, eluent B: acetonitrile, eluent C: 2% ammonia in water, eluent D: acetonitrile/water (80% by volume/20% by volume) total flow rate: 80 ml/min, room temperature, wavelength 200-400 nm, At-Column Injection (complete injection). Gradient profile: eluent A 0 to 2 min 47 ml, eluent B 0 to 2 min 23 ml, eluent A 2 to 10 min from 47 ml to 23 ml and eluent B from 23 ml to 47 ml, 10 to 12 min 0 ml of eluent A and 70 ml of eluent B. eluent C and eluent D constant flow rate of 5 ml/min each over the entire running time.

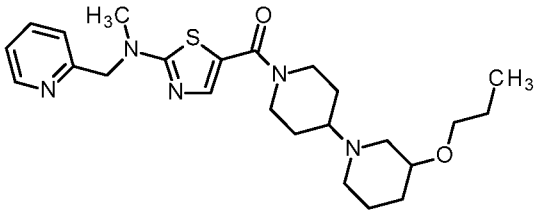
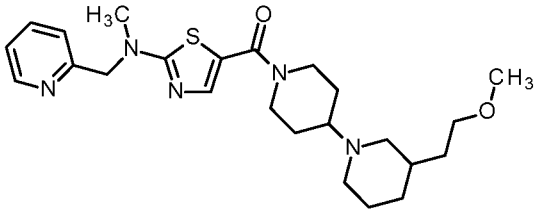
95 mg (0.19 mmol, 42% of theory) of the title compound was obtained.

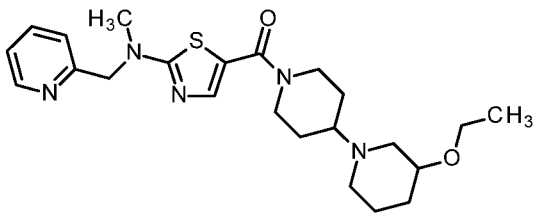
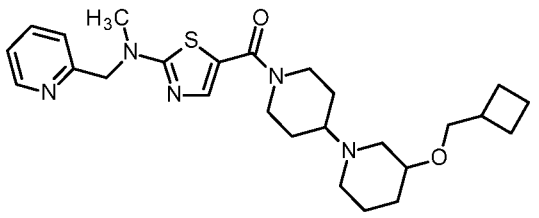
LC-MS (Method 1): $R_t$ = 0.97 min; m/z = 510/512 $(M+H)^+$.

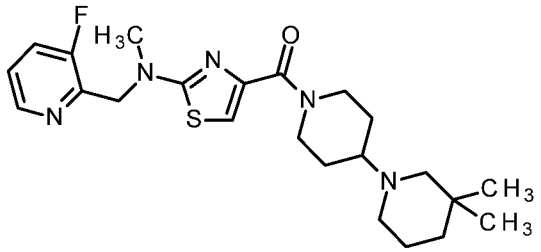
$^1$H-NMR (400 MHz, DMSO-$d_6$, δ/ppm): 0.73-0.88 (m, 4H, therein at 0.81 (d, 3H)), 1.27-1.67 (m, 9H, therein at 1.46 (d, 3H)), 1.68-1.80 (m, 3H), 2.02 (br. t, 1H), 2.40-2.53 (m, 1H, partly hidden by DMSO), 2.65-2.77 (m, 2H), 2.79-2.96 (m, 2H), 3.90-4.16 (m, 2H), 5.24 (quin., 1H), 7.38-7.46 (m, 1H), 7.67-7.77 (m, 1H), 8.38-8.46 (m, 1H), 8.83 (d, 1H).

$[\alpha]_D^{20}$ = -45.08° (c = 0.295, methanol).

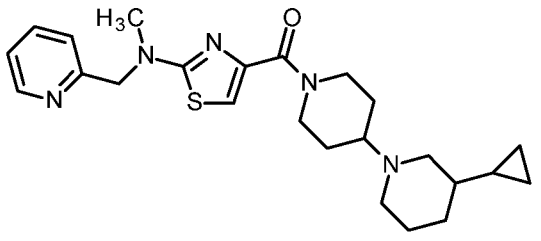
Analogously to Examples 1, 2 and 25 to 27, the following compounds of Examples 126 to 130 were prepared from the respectively specified starting materials:

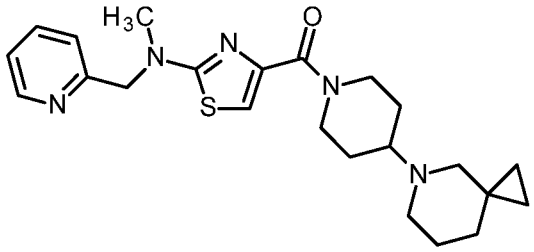
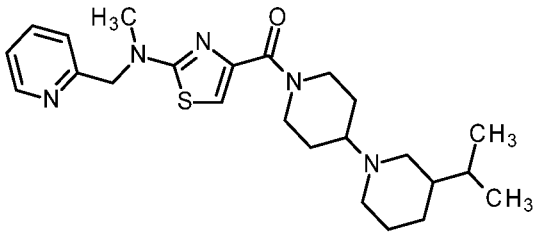
| Example | Name / Structure / Starting material | Analytical data |
|---|---|---|
| **126** | {2-[methyl(pyridin-2-ylmethyl)amino]-1,3-thiazol-5-yl}[3-propoxy[1,4'-bipiperidine]-1'-yl]methanone (*racemic*)<br>  <br>from (2-bromo-1,3-thiazol-5-yl)[3-propoxy[1,4'-bipiperidine]-1'-yl]methanone (*racemic*) and *N*-methyl-1-(pyridin-2-yl)methanamine | $^1$H-NMR (400 MHz, DMSO-$d_6$, δ/ppm): 0.84 (t, 3H), 0.97-1.11 (m, 1H), 1.28-1.52 (m, 5H), 1.57-1.66 (m, 1H), 1.74 (br. d, 2H), 1.85-1.98 (m, 2H), 2.08 (br. t, 1H), 2.47-2.60 (m, 1H, partly hidden by DMSO), 2.66 (br. d, 1H), 2.83-3.01 (m, 3H), 3.17 (s, 3H), 3.18-3.26 (m, 1H), 3.30-3.42 (m, 2H, partly hidden by $H_2O$), 4.28 (br. d, 2H), 4.81 (s, 2H), 7.24-7.33 (m, 2H), 7.50 (s , 1H), 7.77 (td, 1H), 8.53 (d, 1H).<br>LC-MS (Method 4):<br>$R_t$ = 0.92 min; m/z = 458 $(M+H)^+$. |
| **127** | [3-(2-methoxyethyl)[1,4'-bipiperidine]-1'-yl]{2-[methyl(pyridin-2-ylmethyl)amino]-1,3-thiazol-5-yl}methanone (*racemic*)<br>  <br>from (2-bromo-1,3-thiazol-5-yl)[3-(2-methoxyethyl)[1,4'-bipiperidine]-1'-yl]methanone (*racemic*) and *N*-methyl-1-(pyridin-2-yl)methanamine | $^1$H-NMR (400 MHz, DMSO-$d_6$, δ/ppm): 0.77-0.92 (m, 1H), 1.28-1.45 (m, 5H), 1.45-1.62 (m, 2H), 1.61-1.69 (m, 1H), 1.74 (br. d, 2H), 1.83 (t, 1H), 2.08 (br. t, 1H), 2.43-2.54 (m, 1H, partly hidden by DMSO), 2.66 (br. d, 1H), 2.73 (br. t, 2H), 2.91 (br. t, 2H), 3.17 (s, 3H), 3.20 (s, 3H), 3.18-3.26 (m, 1H), 3.32 (t, 2H, partly hidden by $H_2O$), 4.28 (br. d, 2H), 4.80 (s, 2H), 7.24-7.32 (m, 2H), 7.50 (s , 1H), 7.77 (td, 1H), 8.53 (d, 1H).<br>LC-MS (Method 1):<br>$R_t$ = 0.80 min; m/z = 458 $(M+H)^+$. |

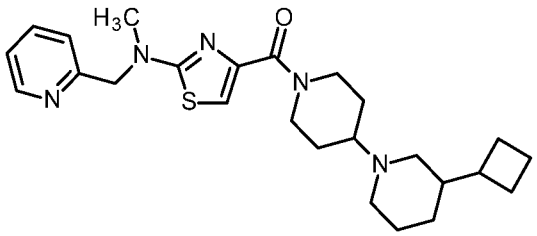
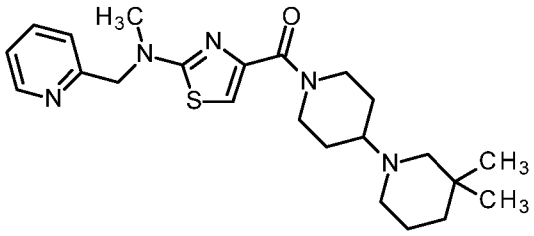
| Example | Name / Structure / Starting material | Analytical data |
|---|---|---|
| **128** | [3-ethoxy[1,4'-bipiperidine]-1'-yl]{2-[methyl(pyridin-2-ylmethyl)amino]-1,3-thiazol-5-yl}methanone (*racemic*)<br>  <br>from (2-bromo-1,3-thiazol-5-yl)[3-ethoxy[1,4'-bipiperidine]-1'-yl]methanone (*racemic*) and *N*-methyl-1-(pyridin-2-yl)methanamine | $^1$H-NMR (400 MHz, DMSO-$d_6$, δ/ppm): 0.98-1.11 (m, 4H, therein at 1.07 (t, 3H)), 1.27-1.45 (m, 3H), 1.57-1.67 (m, 1H), 1.74 (br. d, 2H), 1.85-1.99 (m, 2H), 2.08 (br. t, 1H), 2.47-2.59 (m, 1H, partly hidden by DMSO), 2.66 (br. d, 1H), 2.84-3.00 (m, 3H), 3.17 (s, 3H), 3.20-3.29 (m, 1H), 3.40-3.51 (m, 2H), 4.28 (br. d, 2H), 4.81 (s, 2H), 7.24-7.33 (m, 2H), 7.50 (s , 1H), 7.77 (td, 1H), 8.53 (d, 1H).<br>LC-MS (Method 1):<br>$R_t$ = 0.74 min; m/z = 444 $(M+H)^+$. |
| **129** | [3-(cyclobutylmethoxy)[1,4'-bipiperidine]-1'-yl]{2-[methyl(pyridin-2-ylmethyl)amino]-1,3-thiazol-5-yl}methanone (*racemic*)<br>  <br>from (2-bromo-1,3-thiazol-5-yl)[3-(cyclobutylmethoxy)[1,4'-bipiperidine]-1'-yl]methanone (*racemic*) and *N*-methyl-1-(pyridin-2-yl)methanamine | LC-MS (Method 1):<br>$R_t$ = 1.03 min; m/z = 484 $(M+H)^+$. |

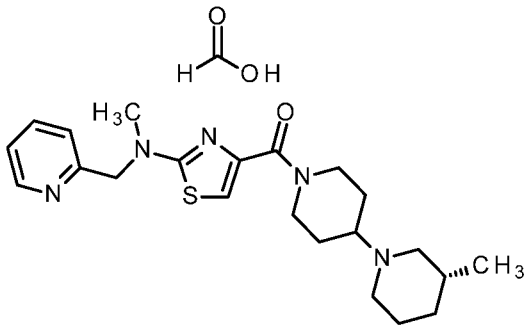
| Example | Name / Structure / Starting material | Analytical data |
|---|---|---|
| **130** | (3,3-dimethyl[1,4'-bipiperidine]-1'-yl)(2-{[(3-fluoropyridin-2-yl)methyl](methyl)amino}-1,3-thiazol-4-yl)methanone<br>  <br>from (2-bromo-1,3-thiazol-4-yl)(3,3-dimethyl[1,4'-bipiperidine]-1'-yl)methanone and 1-(3-fluoropyridin-2-yl)-*N*-methylmethanamine | LC-MS (Method 1):<br>$R_t$ = 0.97 min; m/z = 446 $(M+H)^+$. |

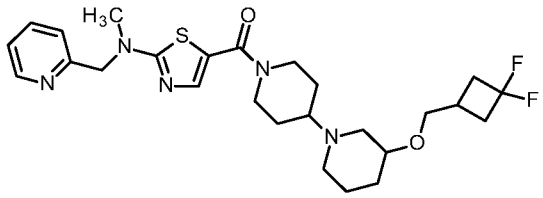
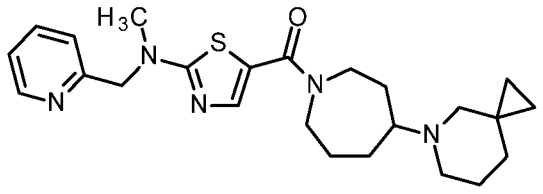
Analogously to Examples 87, 90 and 93, the following compounds of Examples 131 to 148 were prepared from the respectively specified starting materials:

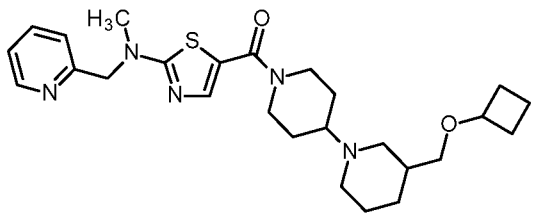
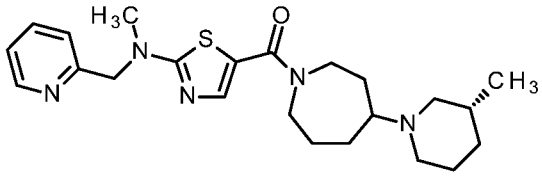
| Example | Name / Structure / Starting material | Analytical data |
|---|---|---|
| **131** | [3-cyclopropyl[1,4'-bipiperidine]-1'-yl]{2-[methyl(pyridin-2-ylmethyl)amino]-1,3-thiazol-4-yl}methanone (*racemic*)<br>  <br>from 2-[methyl(pyridin-2-ylmethyl)amino]-1,3-thiazole-4-carboxylic acid and 3-cyclopropyl-1,4'-bipiperidine dihydrochloride (*racemic*) | LC-MS (Method 1):<br>$R_t$ = 0.90 min; m/z = 440 $(M+H)^+$. |

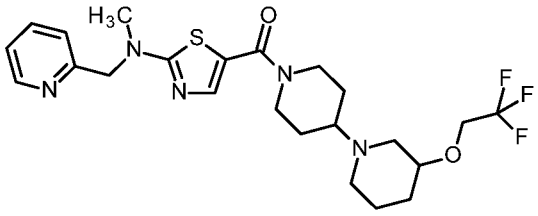
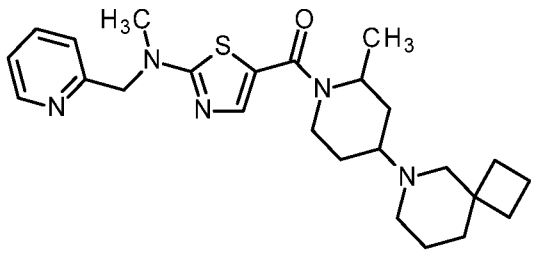
| Example | Name / Structure / Starting material | Analytical data |
|---|---|---|
| **132** | [4-(5-azaspiro[2.5]octan-5-yl)piperidin-1-yl]{2-[methyl(pyridin-2-ylmethyl)amino]-1,3-thiazol-4-yl}methanone<br>  <br>from 2-[methyl(pyridin-2-ylmethyl)amino]-1,3-thiazole-4-carboxylic acid and 5-(piperidin-4-yl)-5-azaspiro[2.5]octane dihydrochloride (WO2021089683 Example 49A; CAS Registry Number 2642237-14-5) | $^1$H-NMR (400 MHz, DMSO-$d_6$, δ/ppm): 0.18-0.29 (m, 4H), 1.12-1.31 (m, 4H), 1.42-1.60 (m, 3H), 1.65-1.79 (m, 1H), 2.14 (s, 2H), 2.31-2.47 (m, 3H), 2.57-2.70 (m, 1H), 2.74-2.89 (m, 1H), 3.17 (s, 3H), 4.02-4.17 (m, 1H), 4.25-4.41 (m, 1H), 4.76 (br. d, 2H), 7.07 (s, 1H), 7.24 (d , 1H), 7.26-7.30 (m, 1H), 7.75 (td, 1H), 8.49-8.54 (m, 1H).<br>LC-MS (Method 1):<br>$R_t$ = 0.75 min; m/z = 426 $(M+H)^+$. |
| **133** | [3-isopropyl[1,4'-bipiperidine]-1'-yl]{2-[methyl(pyridin-2-ylmethyl)amino]-1,3-thiazol-4-yl}methanone (*racemic*)<br>  <br>from 2-[methyl(pyridin-2-ylmethyl)amino]-1,3-thiazole-4-carboxylic acid and 3-isopropyl-1,4'-bipiperidine hydrochloride (1:1) (*racemic*) | LC-MS (Method 1):<br>$R_t$ = 0.99 min; m/z = 442 $(M+H)^+$. |

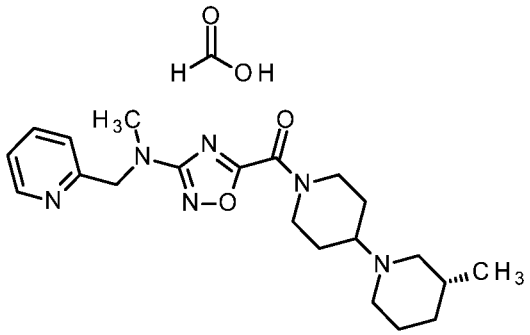
| Example | Name / Structure / Starting material | Analytical data |
|---|---|---|
| **134** | [3-cyclobutyl[1,4'-bipiperidine]-1'-yl]{2-[methyl(pyridin-2-ylmethyl)amino]-1,3-thiazol-4-yl}methanone (*racemic*)<br>  <br>from 2-[methyl(pyridin-2-ylmethyl)amino]-1,3-thiazole-4-carboxylic acid and 3-cyclobutyl-1,4'-bipiperidine hydrochloride (1:1) (*racemic*) | LC-MS (Method 1):<br>$R_t$ = 1.03 min; m/z = 454 $(M+H)^+$. |
| **135** | [3-cyclobutyl[1,4'-bipiperidine]-1'-yl]{2-[methyl(pyridin-2-ylmethyl)amino]-1,3-thiazol-4-yl}methanone<br>  <br>from 2-[methyl(pyridin-2-ylmethyl)amino]-1,3-thiazole-4-carboxylic acid and 3,3-dimethyl-1,4'-bipiperidine dihydrochloride (WO2021089683 Example 48A; CAS Registry Number 2642237-13-4) | LC-MS (Method 1):<br>$R_t$ = 0.82 min; m/z = 428 $(M+H)^+$. |

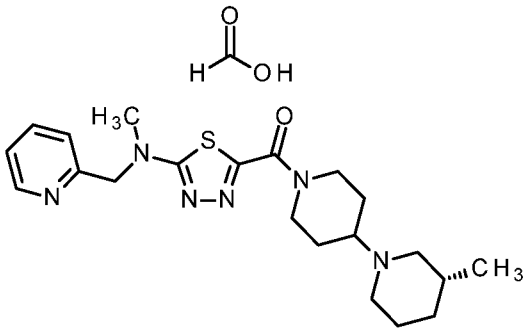
| Example | Name / Structure / Starting material | Analytical data |
|---|---|---|
| **136** | [(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]{2-[methyl(pyridin-2-ylmethyl)amino]-1,3-thiazol-4-yl}methanone formate (1:1)<br>  <br>from 2-[methyl(pyridin-2-ylmethyl)amino]-1,3-thiazole-4-carboxylic acid and (3*R*)-3-methyl-1,4'-bipiperidine dihydrochloride | $^1$H-NMR (400 MHz, DMSO-$d_6$, δ/ppm): 0.79-0.92 (m, 4H, therein at 0.83 (d, 3H)), 1.21-1.38 (m, 2H), 1.39-1.51 (m, 1H), 1.52-1.69 (m, 4H), 1.71-1.83 (m, 1H), 1.88 (br. t, 1H), 2.17 (br. t, 1H), 2.58-2.71 (m, 2H), 2.81 (br. t, 3H), 3.17 (s, 3H), 4.10-4.30 (m, 2H), 4.33-4.48 (m, 1H), 4.77 (br. d, 2H), 7.10 (s, 1H), 7.22-7.32 (m, 2H), 7.76 (td, 1H), 8.19 (s, 1H), 8.52 (dd, 1H).<br>LC-MS (Method 1):<br>$R_t$ = 0.82 min; m/z = 414 $(M+H-HCO_2H)^+$.<br>Purification method: preparative HPLC (column: Chromatorex C18 10 µm, 125 x 40 mm; wavelength 210 nm; eluent A = water, B = acetonitrile; gradient: 5 min 10% B; 20 min 95% B; flow rate: 100 ml/min; 0.05% formic acid). |

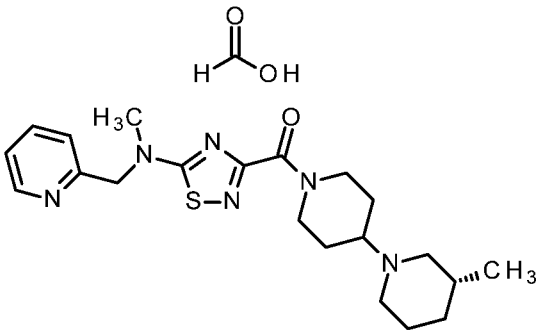
| Example | Name / Structure / Starting material | Analytical data |
|---|---|---|
| **137** | {3-[(3,3-difluorocyclobutyl)methoxy][1,4'-bipiperidine]-1'-yl}{2-[methyl(pyridin-2-ylmethyl)amino]-1,3-thiazol-5-yl}methanone (*racemic*)<br>  <br>from 2-[methyl(pyridin-2-ylmethyl)amino]-1,3-thiazole-5-carboxylic acid and 3-[(3,3-difluorocyclobutyl)methoxy]-1,4'-bipiperidine dihydrochloride (*racemic*) | LC-MS (Method 1):<br>$R_t$ = 0.98 min; m/z = 520 $(M+H)^+$. |
| **138** | [4-(5-azaspiro[2.5]octan-5-yl)azepan-1-yl]{2-[methyl(pyridin-2-ylmethyl)amino]-1,3-thiazol-5-yl}methanone (*racemic*)<br>  <br>from 2-[methyl(pyridin-2-ylmethyl)amino]-1,3-thiazole-5-carboxylic acid and 5-[azepan-4-yl]-5-azaspiro[2.5]octane dihydrochloride (*racemic*) (WO2021089683 Example 85A; CAS Registry Number 2642237-60-1) | LC-MS (Method 1):<br>$R_t$ = 0.73 min; m/z = 440 $(M+H)^+$. |

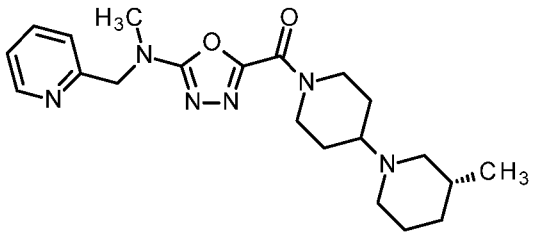
| Example | Name / Structure / Starting material | Analytical data |
|---|---|---|
| **139** | {3-[(cyclobutyloxy)methyl][1,4'-bipiperidine]-1'-yl}{2-[methyl(pyridin-2-ylmethyl)amino]-1,3-thiazol-5-yl}methanone (*racemic*)<br>  <br>from 2-[methyl(pyridin-2-ylmethyl)amino]-1,3-thiazole-5-carboxylic acid and 3-[(cyclobutyloxy)methyl]-1,4'-bipiperidine dihydrochloride (*racemic*) (WO2021089683 Example 52A; CAS Registry Number 2642237-19-0) | LC-MS (Method 1):<br>$R_t$ = 0.96 min; m/z = 484 $(M+H)^+$. |
| **140** | {4-[(3*R*)-3-methylpiperidin-1-yl]azepan-1-yl}{2-[methyl(pyridin-2-ylmethyl)amino]-1,3-thiazol-5-yl}methanone (diastereomer mixture)<br>  <br>from 2-[methyl(pyridin-2-ylmethyl)amino]-1,3-thiazole-5-carboxylic acid and 4-[(3*R*)-3-methylpiperidin-1-yl]azepane dihydrochloride (diastereomer mixture) (WO2021089683 Example 54A; CAS Registry Number 2642237-23-6) | LC-MS (Method 1):<br>$R_t$ = 0.74 min; m/z = 428 $(M+H)^+$. |

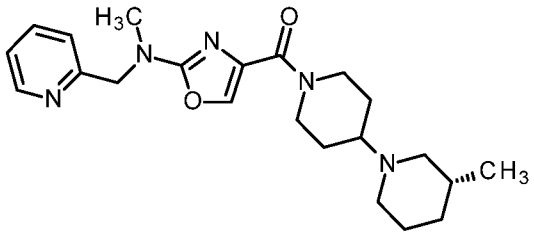
| Example | Name / Structure / Starting material | Analytical data |
|---|---|---|
| **141** | {2-[methyl(pyridin-2-ylmethyl)amino]-1,3-thiazol-5-yl}[3-(2,2,2-trifluoroethoxy)[1,4'-bipiperidine]-1'-yl]methanone (*racemic*)<br>  <br>from 2-[methyl(pyridin-2-ylmethyl)amino]-1,3-thiazole-5-carboxylic acid and 3-(2,2,2-trifluoroethoxy)-1,4'-bipiperidine dihydrochloride (*racemic*) | LC-MS (Method 1):<br>$R_t$ = 0.85 min; m/z = 498 $(M+H)^+$. |
| **142** | [4-(6-azaspiro[3.5]nonan-6-yl)-2-methylpiperidin-1-yl]{2-[methyl(pyridin-2-ylmethyl)amino]-1,3-thiazol-5-yl}methanone (diastereomer mixture)<br>  <br>from 2-[methyl(pyridin-2-ylmethyl)amino]-1,3-thiazole-5-carboxylic acid and 6-[2-methylpiperidin-4-yl]-6-azaspiro[3.5]nonane dihydrochloride (diastereomer mixture) | LC-MS (Method 1):<br>$R_t$ = 0.89/0.91 min; m/z = 454 $(M+H)^+$. |

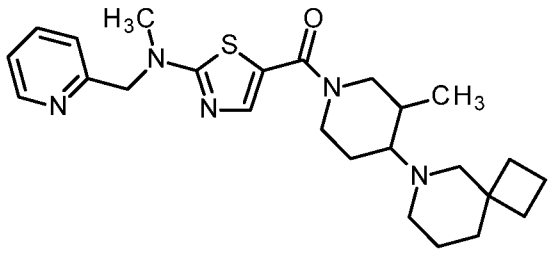
| Example | Name / Structure / Starting material | Analytical data |
|---|---|---|
| **143** | [(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]{3-[methyl(pyridin-2-ylmethyl)amino]-1,2,4-oxadiazol-5-yl}methanone formate (1:1)<br>  <br>from 3-[methyl(pyridin-2-ylmethyl)amino]-1,2,4-oxadiazole-5-carboxylic acid and (3*R*)-3-methyl[1,4'-bipiperidine] dihydrochloride | LC-MS (Method 1):<br>$R_t$ = 0.73 min; m/z = 399 $(M+H-HCO_2H)^+$.<br>Purification method: prep. HPLC:<br>Instrument: Waters Prep LC/MS system, column: Phenomenex Kinetex C18 5µm 100 x 30 mm. Eluent A: water, eluent B: acetonitrile, eluent C: 2% formic acid in water, eluent D: acetonitrile/water (80% by vol./20% by vol.), total flow rate: 80 ml/min, room temperature, wavelength: 200-400 nm, at-column injection (complete injection); gradient profile: eluent A 0 to 2 min 70 ml, eluent B 0 to 2 min 0 ml, eluent A 2 to 10 min from 70 ml to 55 ml and eluent B from 0 ml to 15 ml, 10 to 12 min 0 ml eluent A and 70 ml eluent B. Constant flow rate of eluent C and eluent D of 5 ml/min each over the entire run time. |

| Example | Name / Structure / Starting material | Analytical data |
|---|---|---|
| **144** | [(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]{5-[methyl(pyridin-2-ylmethyl)amino]-1,3,4-thiadiazol-2-yl}methanone formate (1:1)<br>  <br>from 5-[methyl(pyridin-2-ylmethyl)amino]-1,3,4-thiadiazole-2-carboxylic acid and (3*R*)-3-methyl[1,4'-bipiperidine] dihydrochloride | LC-MS (Method 1):<br>$R_t$ = 0.76 min; m/z = 415 $(M+H-HCO_2H)^+$.<br>Purification method: prep. HPLC:<br>Instrument: Waters Prep LC/MS system, column: Phenomenex Kinetex C18 5µm 100 x 30 mm. Eluent A: water, eluent B: acetonitrile, eluent C: 2% formic acid in water, eluent D: acetonitrile/water (80% by vol./20% by vol.), total flow rate: 80 ml/min, room temperature, wavelength: 200-400 nm, at-column injection (complete injection); gradient profile: eluent A 0 to 2 min 70 ml, eluent B 0 to 2 min 0 ml, eluent A 2 to 10 min from 70 ml to 55 ml and eluent B from 0 ml to 15 ml, 10 to 12 min 0 ml eluent A and 70 ml eluent B. Constant flow rate of eluent C and eluent D of 5 ml/min each over the entire run time. |

| Example | Name / Structure / Starting material | Analytical data |
|---|---|---|
| **145** | [(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]{5-[methyl(pyridin-2-ylmethyl)amino]-1,2,4-thiadiazol-3-yl}methanone formate (1:1)<br>  <br>from 5-[methyl(pyridin-2-ylmethyl)amino]-1,2,4-thiadiazole-3-carboxylic acid and (3*R*)-3-methyl[1,4'-bipiperidine] dihydrochloride | LC-MS (Method 1):<br>$R_t$ = 0.75 min; m/z = 415 $(M+H-HCO_2H)^+$.<br>Purification method: prep. HPLC:<br>Instrument: Waters Prep LC/MS system, column: Phenomenex Kinetex C18 5µm 100 x 30 mm. Eluent A: water, eluent B: acetonitrile, eluent C: 2% formic acid in water, eluent D: acetonitrile/water (80% by vol./20% by vol.), total flow rate: 80 ml/min, room temperature, wavelength: 200-400 nm, at-column injection (complete injection); gradient profile: eluent A 0 to 2 min 70 ml, eluent B 0 to 2 min 0 ml, eluent A 2 to 10 min from 70 ml to 55 ml and eluent B from 0 ml to 15 ml, 10 to 12 min 0 ml eluent A and 70 ml eluent B. Constant flow rate of eluent C and eluent D of 5 ml/min each over the entire run time.<br>$[\alpha]_D^{20}$ = -5.57° (c = 0.305, methanol). |

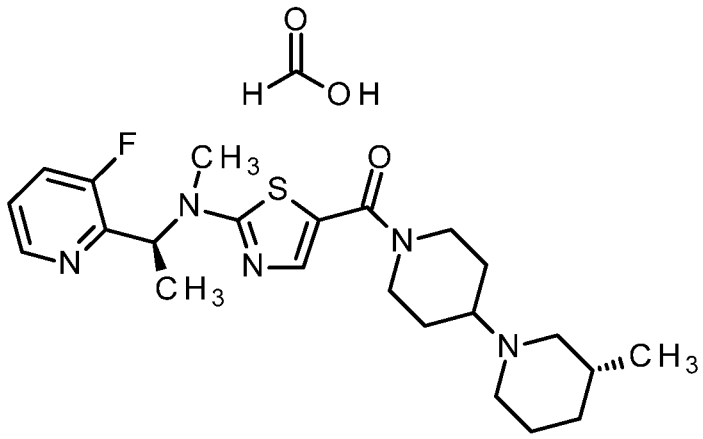
| Example | Name / Structure / Starting material | Analytical data |
|---|---|---|
| 146 | [(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]{5-[methyl(pyridin-2-ylmethyl)amino]-1,3,4-oxadiazol-2-yl}methanone<br>  <br>from 5-[methyl(pyridin-2-ylmethyl)amino]-1,3,4-oxadiazole-2-carboxylic acid and (3*R*)-3-methyl[1,4'-bipiperidine] dihydrochloride | $^1$H-NMR (400 MHz, DMSO-$d_6$, δ/ppm): 0.79-0.88 (m, 4H, therein at 0.81 (d, 3H)), 1.28-1.68 (m, 6H), 1.70-1.84 (m, 3H), 2.05 (br. t, 1H), 2.46-2.60 (m, 1H, hidden by DMSO), 2.65-2.84 (m, 3H), 3.08-3.18 (m, 4H, therein at 3.12 (s, 3H)), 4.41 (br. d, 1H), 4.69 (br. d, 1H), 4.77 (br. d, 2H), 4.72 (s, 2H), 7.28-7.34 (m, 1H), 7.36 (d, 1H), 7.80 (td, 1H), 8.53 (d, 1H).<br>LC-MS (Method 1):<br>$R_t$ = 0.65 min; m/z = 399 $(M+H)^+$.<br>Purification method: prep. HPLC:<br>Instrument: Waters Prep LC/MS system, column: XBridge C18 5 µm 100 x 30 mm. Eluent A: water, eluent B: acetonitrile, eluent C: 2% ammonia in water, eluent D: acetonitrile/water (80% by vol. / 20% by vol.), total flow rate: 80 ml/min, room temperature, wavelength: 200-400 nm, at-column injection (complete injection); gradient profile: eluent A 0 to 2 min 55 ml, eluent B 0 to 2 min 15 ml, eluent A 2 to 10 min from 55 ml to 31 ml and eluent B from 15 ml to 39 ml, 10 to 12 min 0 ml eluent A and 70 ml eluent B. Constant flow rate of eluent C and eluent D of 5 ml/min each over the entire run time. |

| | | |
|---|---|---|
| **147** | [(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]{2-[methyl(pyridin-2-ylmethyl)amino]-1,3-oxazol-4-yl}methanone<br>  <br>from 2-[methyl(pyridin-2-ylmethyl)amino]-1,3-oxazole-4-carboxylic acid and (3*R*)-3-methyl[1,4'-bipiperidine] hydrochloride (1:1) | $^1$H-NMR (400 MHz, DMSO-$d_6$, δ/ppm): 0.73-0.87 (m, 4H, therein at 0.81 (d, 3H)), 1.23-1.79 (m, 9H), 2.04 (br. t, 1H), 2.41-2.53 (m, 1H, partly hidden by DMSO), 2.58-2.77 (m, 3H), 2.82-3.00 (m, 1H), 3.08 (s, 3H), 4.32-4.53 (m, 1H), 4.53-4.72 (m, 3H, therein at 4.66 (s, 2H)), 7.24-7.33 (m, 2H), 7.77 (td, 1H), 7.89 (s, 1H), 8.48-8.55 (m, 1H).<br>LC-MS (Method 1):<br>$R_t$ = 0.65 min; m/z = 398 $(M+H)^+$.<br>Purification method: prep. HPLC: Instrument: Waters Prep LC/MS system, column: XBridge C18 5 µm 100 x 30 mm. Eluent A: water, eluent B: acetonitrile, eluent C: 2% ammonia in water, eluent D: acetonitrile/water (80% by vol. / 20% by vol.), total flow rate: 80 ml/min, room temperature, wavelength: 200-400 nm, at-column injection (complete injection); gradient profile: eluent A 0 to 2 min 55 ml, eluent B 0 to 2 min 15 ml, eluent A 2 to 10 min from 55 ml to 31 ml and eluent B from 15 ml to 39 ml, 10 to 12 min 0 ml eluent A and 70 ml eluent B. Constant flow rate of eluent C and eluent D of 5 ml/min each over the entire run time.<br>$[\alpha]_D^{20}$ = -9.47° (c = 0.250, methanol). |

| Example | Name / Structure / Starting material | Analytical data |
|---|---|---|
| 148 | [4-(6-azaspiro[3.5]nonan-6-yl)-3-methylpiperidin-1-yl]{2-[methyl(pyridin-2-ylmethyl)amino]-1,3-thiazol-5-yl}methanone (diastereomer mixture)<br>  <br>from 2-[methyl(pyridin-2-ylmethyl)amino]-1,3-thiazole-5-carboxylic acid and 6-[3-methylpiperidin-4-yl]-6-azaspiro[3.5]nonane dihydrochloride (diastereomer mixture) | LC-MS (Method 1):<br>$R_t$ = 0.85 min (75.7%)/0.92 min (24.3%); m/z = 454 $(M+H)^+$.<br>Purification method: prep. HPLC:<br>Instrument: Waters Prep LC/MS system, column: XBridge C18 5 µm 100 x 30 mm. Eluent A: water, eluent B: acetonitrile, eluent C: 2% ammonia in water, eluent D: acetonitrile/water (80% by vol./20% by vol.), total flow rate: 80 ml/min, room temperature, wavelength: 200-400 nm, at-column injection (complete injection); gradient profile: eluent A 0 to 2 min 70 ml, eluent B 0 to 2 min 0 ml, eluent A 2 to 10 min from 70 ml to 0 ml and eluent B from 0 ml to 70 ml, 10 to 12 min 0 ml eluent A and 70 ml eluent B. Constant flow rate of eluent C and eluent D of 5 ml/min each over the entire run time. |

**Example 149**

(2-{[(1*S*)-1-(3-Fluoropyridin-2-yl)ethyl](methyl)amino}-1,3-thiazol-5-yl)[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone formate (1:1)



Under argon, 100 mg (0.23 mmol) of (2-{[(1*S*)-1-(3-fluoropyridin-2-yl)ethyl]amino}-1,3-thiazol-5-yl)[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone was dissolved in 10 ml of $THF_{abs}$, and 14 mg Sodium Hydride (0.35 mmol, 60%) was added. The reaction solution was subsequently stirred at room temperature for 30 min. Then 0.02 ml (0.26 mmol) of iodomethane was added to the solution, which was stirred at room temperature overnight. Thereafter, saturated ammonium chloride solution and water were added to the reaction solution, which was extracted with ethyl acetate and, after the organic phase had been removed, was filtered through a hydrophobic filter (pleated filter, MN 616 WA 1/4, D = 12.5 cm), dried and concentrated to dryness under reduced pressure. After cooling to room temperature, the reaction mixture was purified by prep. HPLC.

Method:

Instrument: Waters Prep LC/MS system, column: Phenomenex Kinetex C18 5µm 100 x 30 mm. Eluent A: water, eluent B: acetonitrile, eluent C: 2% formic acid in water, eluent D: acetonitrile/water (80% by vol./20% by vol.), total flow rate: 80 ml/min, room temperature, wavelength: 200-400 nm, at-column injection (complete injection); gradient profile: eluent A 0 to 2 min 63 ml, eluent B 0 to 2 min 7 ml, eluent A 2 to 10 min from 63 ml to 39 ml and eluent B from 7 ml to 31 ml, 10 to 12 min 0 ml eluent A and 70 ml eluent B. Constant flow rate of eluent C and eluent D of 5 ml/min each over the entire run time.

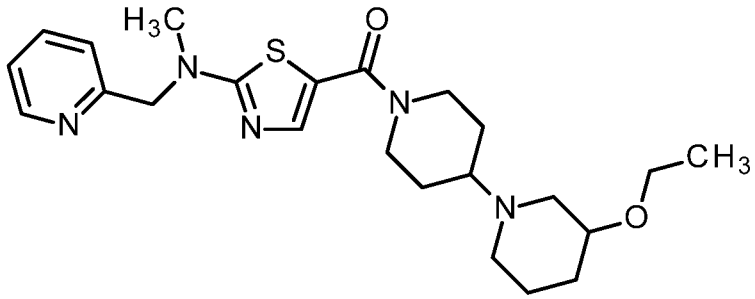
46 mg (0.10 mmol, 45% of theory) of the title compound was obtained.

LC-MS (Method 1): $R_t$ = 1.00 min; m/z = 446 $(M+H-HCO_2H)^+$.

$^1$H-NMR (400 MHz, DMSO-$d_6$, δ/ppm): 0.76-0.91 (m, 4H, therein at 0.82 (d, 3H)), 1.33-1.50 (m, 3H), 1.50-1.68 (m, 6H, therein at 1.58 (d, 3H)), 1.72-1.87 (m, 3H), 2.12 (br. t, 1H), 2.52-2.64 (m, 1H, partly hidden by DMSO), 2.75-2.85 (m, 2H), 2.86-2.98 (m, 5H, therein at 2.95 (s, 3H)), 4.29 (br. d, 2H), 5.79-5.88 (m, 1H), 7.46 (dt, 1H), 7.53 (s, 1H), 7.72 (ddd, 1H), 8.19 (s, 1H), 8.44 (dt, 1H).

**Example 150 and Example 151**

[3-Ethoxy[1,4'-bipiperidine]-1'-yl]{2-[methyl(pyridin-2-ylmethyl)amino]-1,3-thiazol-5-yl}methanone (*enantiomers 1 and 2*)



120 mg of the racemic mixture of [3-ethoxy[1,4'-bipiperidine]-1'-yl]{2-[methyl(pyridin-2-ylmethyl)amino]-1,3-thiazol-5-yl}methanone (Example 128) was separated into the enantiomers by preparative HPLC on a chiral phase [column: Daicel Chiralpak ID 5 µm, 250 x 20 mm; eluent: 20% n-heptane & 80% ethanol + 0.2% diethylamine; flow rate: 15 ml/min; temperature: 60°C, detection: 220 nm]: The two diastereomers were separately collected and lyophilized.

Example 150 (*enantiomer 1*):

[3-Ethoxy[1,4'-bipiperidine]-1'-yl]{2-[methyl(pyridin-2-ylmethyl)amino]-1,3-thiazol-5-yl}methanone

Yield: 48 mg

$R_t$ = 8.64 min; chemical purity > 94%; > 99% de

[Column: DAICEL Chiralpak ID, 5 µm 4.6 mm x 250 mm, flow rate: 1 ml/min, UV: 280 nm, temp.: 70°C, eluent: 100% ethanol + 0.2% DEA].

LC-MS (Method 1): $R_t$ = 0.74 min; MS (ESIpos): m/z = 444 $[M+H]^+$.

$^1$H-NMR (400 MHz, DMSO-$d_6$, δ/ppm): 0.98-1.12 (m, 4H, therein at 1.07 (t, 3H)), 1.28-1.44 (m, 3H), 1.58-1.67 (m, 1H), 1.74 (br. d, 2H), 1.85-1.99 (m, 2H), 2.08 (br. t, 1H), 2.48-2.60 (m, 1H, partly hidden by DMSO), 2.66 (br. d, 1H), 2.84-3.00 (m, 3H), 3.17 (s, 3H), 3.19-3.29 (m, 1H), 3.32-3.52 (m, 2H, partly hidden by $H_2O$), 4.28 (br. d, 2H), 4.80 (s, 2H), 7.24-7.33 (m, 2H), 7.50 (s, 1H), 7.77 (td, 1H), 8.53 (d, 1H).

$[\alpha]_{436\ nm}^{20}$ = -13.66° (c = 0.310, methanol).

Example 151 (*enantiomer 2*):

[3-Ethoxy[1,4'-bipiperidine]-1'-yl]{2-[methyl(pyridin-2-ylmethyl)amino]-1,3-thiazol-5-yl}methanone

Yield: 52 mg

$R_t$ = 9.72 min; chemical purity > 94%; > 98% de

[Column: DAICEL Chiralpak ID, 5 µm 4.6 mm x 250 mm, flow rate: 1 ml/min, UV: 280 nm, temp.: 70°C, eluent: 100% ethanol + 0.2% DEA].

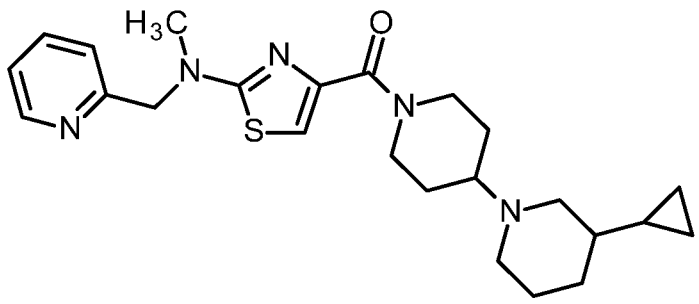
LC-MS (Method 1): $R_t$ = 0.73 min; MS (ESIpos): m/z = 444 $[M+H]^+$.

$^1$H-NMR (400 MHz, DMSO-$d_6$, δ/ppm): 0.99-1.12 (m, 4H, therein at 1.07 (t, 3H)), 1.28-1.45 (m, 3H), 1.57-1.67 (m, 1H), 1.74 (br. d, 2H), 1.85-2.00 (m, 2H), 2.08 (br. t, 1H), 2.48-2.60 (m, 1H, partly hidden by DMSO), 2.66 (br. d, 1H), 2.84-3.01 (m, 3H), 3.17 (s, 3H), 3.19-3.29 (m, 1H), 3.32-3.52 (m, 2H, partly hidden by $H_2O$), 4.28 (br. d, 2H), 4.80 (s, 2H), 7.24-7.33 (m, 2H), 7.50 (s, 1H), 7.77 (td, 1H), 8.53 (d, 1H).

$[\alpha]_{436\,nm}^{20}$ = +12.37° (c = 0.380, methanol).

**Example 152 and Example 153**

[3-Cyclopropyl[1,4'-bipiperidine]-1'-yl]{2-[methyl(pyridin-2-ylmethyl)amino]-1,3-thiazol-4-yl}methanone (*enantiomers 1 and 2*)




54 mg of the racemic mixture of [3-cyclopropyl[1,4'-bipiperidine]-1'-yl]{2-[methyl(pyridin-2-ylmethyl)amino]-1,3-thiazol-4-yl}methanone (Example 131) was separated into the enantiomers by preparative HPLC on a chiral phase [column: Daicel Chiralpak ID 5 µm, 250 x 20 mm; eluent: 80%

n-heptane & 20% ethanol + 0.2% diethylamine; flow rate: 20 ml/min; temperature: 50°C, detection: 220 nm]: The two diastereomers were separately collected and lyophilized.

Example 152 (*enantiomer 1*):

[3-Cyclopropyl[1,4'-bipiperidine]-1'-yl]{2-[methyl(pyridin-2-ylmethyl)amino]-1,3-thiazol-4-yl}methanone

Yield: 13 mg

$R_t$ = 5.27 min; chemical purity > 99%; > 99% ee.

[Column: Chiralpak ID-3, 3 µm, 100 mm x 4.6 mm; eluent: n-heptane/ethanol + 0.2% diethylamine 70:30; flow rate: 1 ml/min; temperature: 30°C; UV detection: 220 nm].

LC-MS (Method 1): $R_t$ = 0.91 min; MS (ESIpos): m/z = 440 $[M+H]^+$.

$^1$H-NMR (400 MHz, DMSO-$d_6$, δ/ppm): 0.02-0.09 (m, 2H), 0.29-0.39 (m, 2H), 0.44-0.56 (m, 1H), 0.59-0.72 (m, 1H), 0.91-1.06 (m, 1H), 1.19-1.40 (m, 3H), 1.43-1.55 (m, 1H), 1.60 (br. d, 1H), 1.70 (br. d, 2H), 1.96 (br. t, 1H), 2.06 (br. t, 1H), 2.40-2.56 (m, 1H, partly hidden by DMSO), 2.59-2.72 (m, 2H), 2.73-2.90 (m, 2H), 3.17 (s, 3H), 4.05-4.22 (m, 1H), 4.29-4.47 (m, 1H), 4.77 (br. d, 2H), 7.09 (s, 1H), 7.26 (d, 1H), 7.26-7.30 (m, 1H), 7.76 (td, 1H), 8.52 (d, 1H).

$[\alpha]_D^{20}$ = +14.09° (c = 0.395, methanol).

Example 153 (*enantiomer 2*):

[3-Cyclopropyl[1,4'-bipiperidine]-1'-yl]{2-[methyl(pyridin-2-ylmethyl)amino]-1,3-thiazol-4-yl}methanone

Yield: 13 mg

$R_t$ = 5.89 min; chemical purity > 99%; > 94.6% ee.

[Column: Chiralpak ID-3, 3 µm, 100 mm x 4.6 mm; eluent: n-heptane/ethanol + 0.2% diethylamine 70:30; flow rate: 1 ml/min; temperature: 30°C; UV detection: 220 nm].

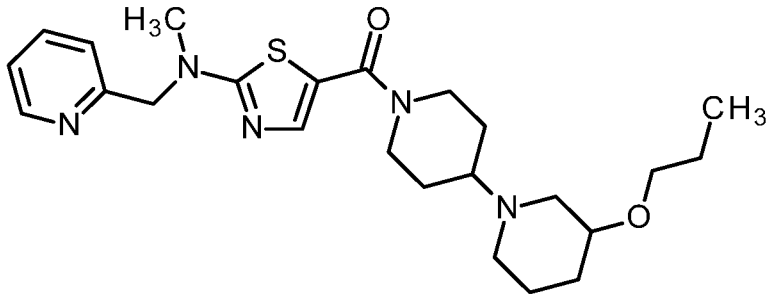
LC-MS (Method 1): $R_t$ = 0.90 min; MS (ESIpos): m/z = 440 $[M+H]^+$.

$^1$H-NMR (400 MHz, DMSO-$d_6$, δ/ppm): 0.02-0.09 (m, 2H), 0.29-0.39 (m, 2H), 0.44-0.56 (m, 1H), 0.59-0.72 (m, 1H), 0.91-1.06 (m, 1H), 1.19-1.40 (m, 3H), 1.43-1.55 (m, 1H), 1.60 (br. d, 1H), 1.70 (br. d, 2H), 1.96 (br. t, 1H), 2.06 (br. t, 1H), 2.40-2.56 (m, 1H, partly hidden by DMSO), 2.59-2.72 (m, 2H), 2.73-2.90 (m, 2H), 3.17 (s, 3H), 4.05-4.22 (m, 1H), 4.29-4.47 (m, 1H), 4.77 (br. d, 2H), 7.09 (s, 1H), 7.26 (d, 1H), 7.26-7.30 (m, 1H), 7.76 (td, 1H), 8.52 (d, 1H).

$[\alpha]_D^{20}$ = -13.02° (c = 0.320, methanol).

**Example 154 and Example 155**

{2-[Methyl(pyridin-2-ylmethyl)amino]-1,3-thiazol-5-yl}[3-propoxy[1,4'-bipiperidine]-1'-yl]methanone (*enantiomers 1 and 2*)




131 mg of the racemic mixture of {2-[methyl(pyridin-2-ylmethyl)amino]-1,3-thiazol-5-yl}[3-propoxy[1,4'-bipiperidine]-1'-yl]methanone (Example 126) was separated into the enantiomers by preparative HPLC on a chiral phase [column: YMC Chiralart Cellulose 5 µm, 250 x 20 mm; eluent: 50% n-heptane & 50% ethanol + 0.2% diethylamine; flow rate: 20 ml/min; temperature: 50°C, detection: 220 nm]: The two diastereomers were separately collected and lyophilized.

Example 154 (*enantiomer 1*):

{2-[Methyl(pyridin-2-ylmethyl)amino]-1,3-thiazol-5-yl}[3-propoxy[1,4'-bipiperidine]-1'-yl]methanone

Yield: 47 mg

$R_t$ = 1.67 min; chemical purity > 99%; > 99% ee.

[Column: YMC Chiralart Cellulose-SB, 3 µm, 50 mm x 4.6 mm; eluent: n-heptane/ethanol + 0.2% diethylamine 50:50; flow rate: 1 ml/min; temperature: 30°C; UV detection: 220 nm].

LC-MS (Method 1): $R_t$ = 0.82 min; MS (ESIpos): m/z = 458 $[M+H]^+$.

$^1$H-NMR (500 MHz, DMSO-$d_6$, δ/ppm): 0.84 (t, 3H), 0.99-1.09 (m, 1H), 1.29-1.41 (m, 3H), 1.41-1.50 (m, 2H), 1.62 (br. dt, 1H), 1.74 (br. d, 2H), 1.86-1.97 (m, 2H), 2.08 (td, 1H), 2.48-2.59 (m, 1H, partly hidden by DMSO), 2.66 (br. d, 1H), 2.86-2.99 (m, 3H), 3.17 (s, 3H), 3.18-3.26 (m, 1H), 3.30-3.40 (m, 2H, partly hidden by $H_2O$), 4.28 (br. d, 2H), 4.80 (s, 2H), 7.24-7.33 (m, 2H), 7.50 (s, 1H), 7.77 (td, 1H), 8.53 (d, 1H).

$[\alpha]_D^{20}$ = +14.34° (c = 0.265, methanol).

Example 155 (*enantiomer 2*):

{2-[Methyl(pyridin-2-ylmethyl)amino]-1,3-thiazol-5-yl}[3-propoxy[1,4'-bipiperidine]-1'-yl]methanone

Yield: 47 mg

$R_t$ = 2.43 min; chemical purity > 99%; > 99% ee.

[Column: YMC Chiralart Cellulose-SB, 3 µm, 50 mm x 4.6 mm; eluent: n-heptane/ethanol + 0.2% diethylamine 50:50; flow rate: 1 ml/min; temperature: 30°C; UV detection: 220 nm].

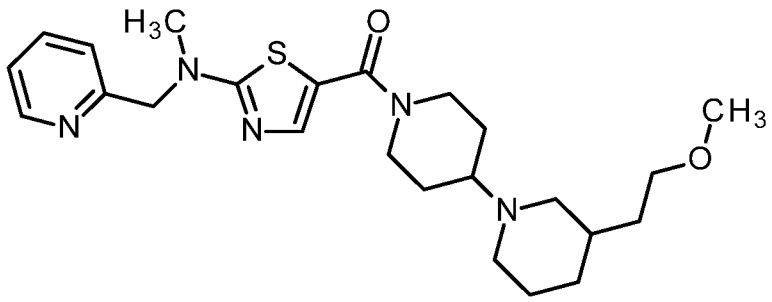
LC-MS (Method 1): $R_t$ = 0.83 min; MS (ESIpos): m/z = 458 $[M+H]^+$.

$^1$H-NMR (500 MHz, DMSO-$d_6$, δ/ppm): 0.84 (t, 3H), 0.99-1.09 (m, 1H), 1.29-1.41 (m, 3H), 1.41-1.50 (m, 2H), 1.62 (br. dt, 1H), 1.73 (br. d, 2H), 1.86-1.97 (m, 2H), 2.08 (td, 1H), 2.48-2.59 (m, 1H, partly hidden by DMSO), 2.66 (br. d, 1H), 2.84-2.99 (m, 3H), 3.17 (s, 3H), 3.18-3.26 (m, 1H), 3.30-3.41 (m, 2H, partly hidden by $H_2O$), 4.28 (br. d, 2H), 4.80 (s, 2H), 7.09 (s, 1H), 7.25-7.32 (m, 2H), 7.50 (s, 1H), 7.77 (td, 1H), 8.53 (d, 1H).

$[\alpha]_D^{20}$ = -15.87° (c = 0.250, methanol).

**Example 156 and Example 157**

[3-(2-Methoxyethyl)[1,4'-bipiperidine]-1'-yl]{2-[methyl(pyridin-2-ylmethyl)amino]-1,3-thiazol-5-yl}methanone (*enantiomers 1 and 2*)



190 mg of the racemic mixture of [3-(2-methoxyethyl)[1,4'-bipiperidine]-1'-yl]{2-[methyl(pyridin-2-ylmethyl)amino]-1,3-thiazol-5-yl}methanone (Example 127) was separated into the enantiomers by preparative HPLC on a chiral phase [column: Daicel Chiralpak IH 5 µm, 250 x 20 mm; eluent: 60% n-heptane & 40% ethanol + 0.2% diethylamine; flow rate: 20 ml/min; temperature: 30°C, detection: 220 nm]: The two diastereomers were separately collected and lyophilized.

Example 156 (*enantiomer 1*):

[3-(2-Methoxyethyl)[1,4'-bipiperidine]-1'-yl]{2-[methyl(pyridin-2-ylmethyl)amino]-1,3-thiazol-5-yl}methanone

Yield: 75 mg

$R_t$ = 7.77 min; chemical purity > 99%; > 99% ee.

[Column: Daicel Chiralpak IH, 5 µm, 250 mm x 4.6 mm; eluent: n-heptane/ethanol + 0.2% diethylamine 60:40; flow rate: 1 ml/min; temperature: 30°C; UV detection: 220 nm].

LC-MS (Method 1): $R_t$ = 0.74 min; MS (ESIpos): m/z = 458 $[M+H]^+$.

$^1$H-NMR (400 MHz, DMSO-$d_6$, δ/ppm): 0.78-0.92 (m, 1H), 1.28-1.45 (m, 5H), 1.46-1.61 (m, 2H), 1.61-1.69 (m, 1H), 1.73 (br. d, 2H), 1.83 (t, 1H), 2.09 (br. t, 1H), 2.45-2.57 (m, 1H, partly hidden by DMSO), 2.73 (br. t, 2H), 2.91 (br. t, 2H), 3.17 (s, 3H), 3.20 (s, 3H), 3.27-3.41 (m, 2H, partly hidden by $H_2O$), 4.28 (br. d, 2H), 4.80 (s, 2H), 7.24-7.33 (m, 2H), 7.50 (s, 1H), 7.77 (td, 1H), 8.53 (d, 1H).

$[\alpha]_{546nm}^{20}$ = +6.78° (c = 0.300, methanol).

Example 157 (*enantiomer 2*):

[3-(2-Methoxyethyl)[1,4'-bipiperidine]-1'-yl]{2-[methyl(pyridin-2-ylmethyl)amino]-1,3-thiazol-5-yl}methanone

Yield: 76 mg

$R_t$ = 10.29 min; chemical purity > 99%; > 99% ee.

[Column: Daicel Chiralpak IH, 5 µm, 250 mm x 4.6 mm; eluent: n-heptane/ethanol + 0.2% diethylamine 60:40; flow rate: 1 ml/min; temperature: 30°C; UV detection: 220 nm].

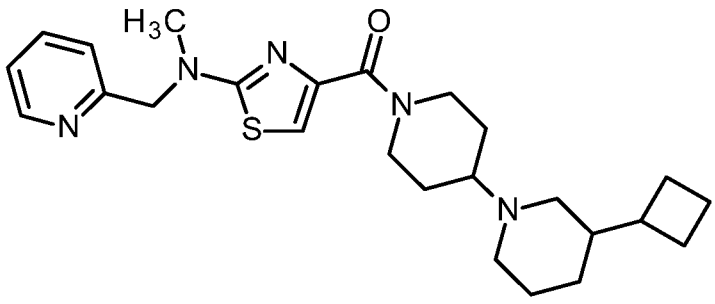
LC-MS (Method 1): $R_t$ = 0.75 min; MS (ESIpos): m/z = 458 $[M+H]^+$.

$^1$H-NMR (400 MHz, DMSO-$d_6$, δ/ppm): 0.78-0.92 (m, 1H), 1.28-1.45 (m, 5H), 1.46-1.61 (m, 2H), 1.61-1.69 (m, 1H), 1.73 (br. d, 2H), 1.83 (t, 1H), 2.09 (br. t, 1H), 2.45-2.57 (m, 1H, partly hidden by DMSO), 2.73 (br. t, 2H), 2.91 (br. t, 2H), 3.17 (s, 3H), 3.20 (s, 3H), 3.27-3.41 (m, 2H, partly hidden by $H_2O$), 4.28 (br. d, 2H), 4.80 (s, 2H), 7.24-7.33 (m, 2H), 7.50 (s, 1H), 7.77 (td, 1H), 8.53 (d, 1H).

$[\alpha]_{546nm}^{20}$ = -9.43° (c = 0.350, methanol).

**Example 158 and Example 159**

[3-Cyclobutyl[1,4'-bipiperidine]-1'-yl]{2-[methyl(pyridin-2-ylmethyl)amino]-1,3-thiazol-4-yl}methanone (*enantiomers 1 and 2*)



62 mg of the racemic mixture of [3-cyclobutyl[1,4'-bipiperidine]-1'-yl]{2-[methyl(pyridin-2-ylmethyl)amino]-1,3-thiazol-4-yl}methanone (Example 134) was separated into the enantiomers by preparative HPLC on a chiral phase [column: YMC Chiralart Cellulose-SC 5 µm, 250 x 20 mm; eluent: 80% n-heptane & 20% ethanol + 0.2% diethylamine; flow rate: 20 ml/min; temperature: 30°C, detection: 220 nm]: The two diastereomers were separately collected and lyophilized.

Example 158 (*enantiomer 1*):

[3-Cyclobutyl[1,4'-bipiperidine]-1'-yl]{2-[methyl(pyridin-2-ylmethyl)amino]-1,3-thiazol-4-yl}methanone

Yield: 13 mg

$R_t$ = 7.04 min; chemical purity > 99%; > 99% ee.

[Column: YMC Chiralart Cellulose-SC, 3 µm, 50 mm x 4.6 mm; eluent: n-heptane/ethanol + 0.2% diethylamine 80:20; flow rate: 1 ml/min; temperature: 30°C; UV detection: 220 nm].

LC-MS (Method 1): $R_t$ = 0.96 min; MS (ESIpos): m/z = 454 $[M+H]^+$.

$^1$H-NMR (400 MHz, DMSO-$d_6$, δ/ppm): 0.64-0.77 (m, 1H), 1.16-1.41 (m, 4H), 1.43-1.54 (m, 1H), 1.54-1.85 (m, 8H), 1.86-2.11 (m, 4H), 2.39-2.57 (m, 1H, partly hidden by DMSO), 2.56-2.73 (m, 3H), 2.74-2.88 (m, 1H), 3.17 (s, 3H), 4.06-4.22 (m, 1H), 4.29-4.47 (m, 1H), 4.77 (br. d, 2H), 7.08 (s, 1H), 7.20-7.30 (m, 2H), 7.75 (td, 1H), 8.52 (dd, 1H).

$[\alpha]_D^{20}$ = +9.82° (c = 0.285, methanol).

Example 159 (*enantiomer 2*):

[3-Cyclobutyl[1,4'-bipiperidine]-1'-yl]{2-[methyl(pyridin-2-ylmethyl)amino]-1,3-thiazol-4-yl}methanone

Yield: 12 mg

$R_t$ = 7.81 min; chemical purity > 99%; > 99% ee.

[Column: YMC Chiralart Cellulose-SC, 3 µm, 50 mm x 4.6 mm; eluent: n-heptane/ethanol + 0.2% diethylamine 80:20; flow rate: 1 ml/min; temperature: 30°C; UV detection: 220 nm].

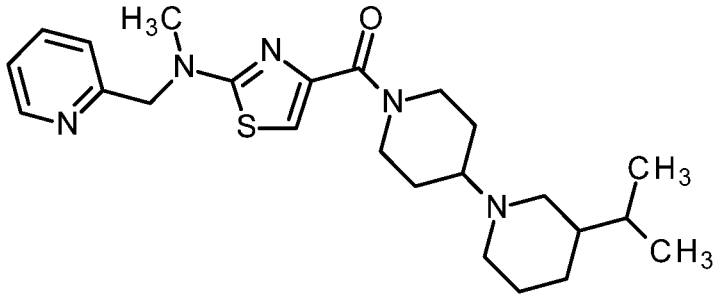
LC-MS (Method 1): $R_t$ = 0.96 min; MS (ESIpos): m/z = 454 $[M+H]^+$.

$^1$H-NMR (400 MHz, DMSO-$d_6$, δ/ppm): 0.64-0.77 (m, 1H), 1.16-1.41 (m, 4H), 1.43-1.54 (m, 1H), 1.54-1.85 (m, 8H), 1.86-2.11 (m, 4H), 2.39-2.57 (m, 1H, partly hidden by DMSO), 2.56-2.73 (m, 3H), 2.74-2.88 (m, 1H), 3.17 (s, 3H), 4.06-4.22 (m, 1H), 4.29-4.47 (m, 1H), 4.77 (br. d, 2H), 7.08 (s, 1H), 7.20-7.32 (m, 2H), 7.75 (br. t, 1H), 8.52 (br. d, 1H).

$[\alpha]_D^{20}$ = -10.94° (c = 0.32, methanol).

**Example 160 and Example 161**

[3-Isopropyl[1,4'-bipiperidine]-1'-yl]{2-[methyl(pyridin-2-ylmethyl)amino]-1,3-thiazol-4-yl}methanone (*enantiomers 1 and 2*)



83 mg of the racemic mixture of [3-isopropyl[1,4'-bipiperidine]-1'-yl]{2-[methyl(pyridin-2-ylmethyl)amino]-1,3-thiazol-4-yl}methanone (Example 133) was separated into the enantiomers by preparative HPLC on a chiral phase [column: Daicel Chiralpak ID 5 µm, 250 x 20 mm; eluent: 80% n-heptane & 20% ethanol + 0.2% diethylamine; flow rate: 15 ml/min; temperature: 38°C, detection: 220 nm]: The two diastereomers were separately collected and lyophilized.

Example 160 (*enantiomer 1*):

[3-Isopropyl[1,4'-bipiperidine]-1'-yl]{2-[methyl(pyridin-2-ylmethyl)amino]-1,3-thiazol-4-yl}methanone

Yield: 14 mg

$R_t$ = 3.69 min; chemical purity > 99%; > 99% ee.

[Column: Daicel Chiralpak ID-3, 3 µm, 50 mm x 4.6 mm; eluent: n-heptane/ethanol + 0.2% diethylamine 80:20; flow rate: 1 ml/min; temperature: 30°C; UV detection: 220 nm].

LC-MS (Method 1): $R_t$ = 0.92 min; MS (ESIpos): m/z = 442 $[M+H]^+$.

$^1$H-NMR (400 MHz, DMSO-$d_6$, δ/ppm): 0.84 (d, 6H), 1.10-1.45 (m, 7H), 1.45-1.80 (m, 4H), 1.80-1.95 (m, 1H), 2.04 (br. t, 1H), 2.58-2.89 (m, 4H), 3.17 (s, 3H), 4.06-4.24 (m, 1H), 4.32-4.50 (m, 1H), 4.77 (br. d, 2H), 7.09 (s, 1H), 7.19-7.31 (m, 2H), 7.70-7.79 (m, 1H), 8.52 (d, 1H).

$[\alpha]_D^{20}$ = +3.40° (c = 0.245, methanol).

Example 161 (*enantiomer 2*):

[3-Isopropyl[1,4'-bipiperidine]-1'-yl]{2-[methyl(pyridin-2-ylmethyl)amino]-1,3-thiazol-4-yl}methanone

Yield: 16 mg

$R_t$ = 3.99 min; chemical purity > 99%; > 89% ee.

[Column: Daicel Chiralpak ID-3, 3 µm, 50 mm x 4.6 mm; eluent: n-heptane/ethanol + 0.2% diethylamine 80:20; flow rate: 1 ml/min; temperature: 30°C; UV detection: 220 nm].

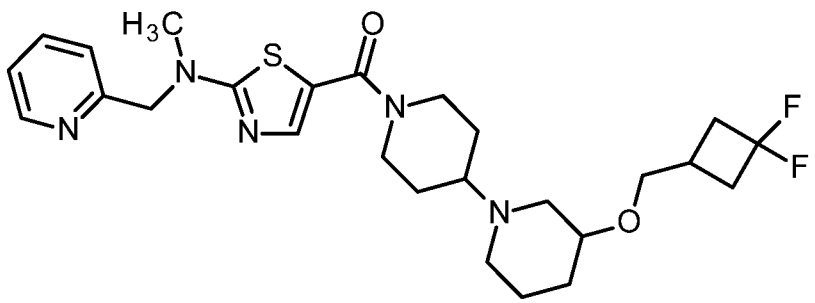
LC-MS (Method 1): $R_t$ = 0.96 min; MS (ESIpos): m/z = 442 $[M+H]^+$.

$^1$H-NMR (400 MHz, DMSO-$d_6$, δ/ppm): 0.84 (d, 6H), 1.10-1.45 (m, 7H), 1.45-1.80 (m, 4H), 1.80-1.95 (m, 1H), 2.04 (br. t, 1H), 2.58-2.89 (m, 4H), 3.17 (s, 3H), 4.06-4.24 (m, 1H), 4.32-4.50 (m, 1H), 4.77 (br. d, 2H), 7.09 (s, 1H), 7.19-7.31 (m, 2H), 7.70-7.79 (m, 1H), 8.52 (d, 1H).

$[\alpha]_D^{20}$ = -2.16° (c = 0.185, methanol).

**Example 162 and Example 163**

{3-[(3,3-Difluorocyclobutyl)methoxy][1,4'-bipiperidine]-1'-yl]{2-[methyl(pyridin-2-ylmethyl)amino]-1,3-thiazol-5-yl}methanone (*enantiomers 1 and 2*)




23 mg of the racemic mixture of {3-[(3,3-difluorocyclobutyl)methoxy][1,4'-bipiperidine]-1'-yl}{2-[methyl(pyridin-2-ylmethyl)amino]-1,3-thiazol-5-yl}methanone (Example 137) was separated into the enantiomers by preparative HPLC on a chiral phase [column: Daicel Chiralpak IB 5 µm, 250 x

20 mm; eluent: 70% n-heptane & 30% ethanol + 0.2% diethylamine; flow rate: 20 ml/min; temperature: 50°C, detection: 220 nm]: The two diastereomers were separately collected and lyophilized.

Example 162 (*enantiomer 1*):

{3-[(3,3-Difluorocyclobutyl)methoxy][1,4'-bipiperidine]-1'-yl}{2-[methyl(pyridin-2-ylmethyl)amino]-1,3-thiazol-5-yl}methanone

Yield: 7 mg

$R_t$ = 2.34 min; chemical purity > 99%; > 99% ee.

[Column: Daicel Chiralpak IB-3, 3 µm, 50 mm x 4.6 mm; eluent: n-heptane/ethanol + 0.2% diethylamine 70:30; flow rate: 1 ml/min; temperature: 30°C; UV detection: 220 nm].

LC-MS (Method 1): $R_t$ = 0.96 min; MS (ESIpos): m/z = 520 $[M+H]^+$.

$^1$H-NMR (500 MHz, DMSO-$d_6$, δ/ppm): 1.01-1.13 (m, 1H), 1.30-1.44 (m, 3H), 1.59-1.67 (m, 1H), 1,73 (br. d, 2H), 1.87-1.93 (m, 1H), 1.97 (br. t, 1H), 2.10 (br. t, 1H), 2.23-2.35 (m, 3H), 2.52-2.63 (m, 3H), 2.62-2.69 (m, 1H), 2.85-2.98 (m, 3H), 3.17 (s, 3H), 3.23-3.30 (m, 1H), 3.41-3.51 (m, 2H), 4.28 (br. d, 2H), 4.80 (s, 2H), 7.25-7.32 (m, 2H), 7.50 (s, 1H), 7.77 (td, 1H), 8.53 (d, 1H).

$[\alpha]_{436nm}^{20}$ = +7.33° (c = 0.350, methanol).

Example 163 (*enantiomer 2*):

{3-[(3,3-Difluorocyclobutyl)methoxy][1,4'-bipiperidine]-1'-yl}{2-[methyl(pyridin-2-ylmethyl)amino]-1,3-thiazol-5-yl}methanone

Yield: 7 mg

$R_t$ = 5.13 min; chemical purity > 99%; > 99% ee.

[Column: Daicel Chiralpak IB-3, 3 µm, 50 mm x 4.6 mm; eluent: n-heptane/ethanol + 0.2% diethylamine 70:30; flow rate: 1 ml/min; temperature: 30°C; UV detection: 220 nm].

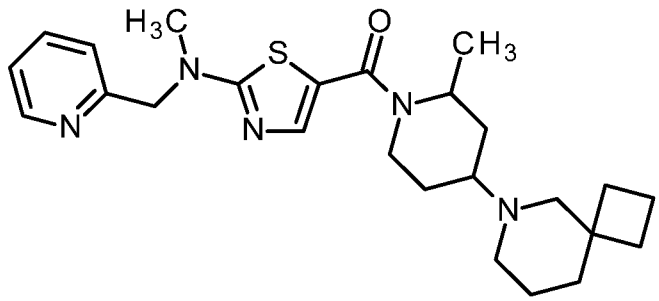
LC-MS (Method 1): $R_t$ = 0.96 min; MS (ESIpos): m/z = 520 $[M+H]^+$.

$^1$H-NMR (500 MHz, DMSO-$d_6$, δ/ppm): 1.01-1.13 (m, 1H), 1.30-1.44 (m, 3H), 1.59-1.67 (m, 1H), 1,73 (br. d, 2H), 1.87-1.93 (m, 1H), 1.97 (br. t, 1H), 2.10 (br. t, 1H), 2.23-2.35 (m, 3H), 2.52-2.63 (m, 3H), 2.62-2.69 (m, 1H), 2.85-2.98 (m, 3H), 3.17 (s, 3H), 3.23-3.30 (m, 1H), 3.41-3.51 (m, 2H), 4.28 (br. d, 2H), 4.80 (s, 2H), 7.25-7.32 (m, 2H), 7.50 (s, 1H), 7.77 (td, 1H), 8.53 (d, 1H).

$[\alpha]_{436nm}^{20}$ = -9.37° (c = 0.345, methanol).

**Example 164 to Example 167**

[4-(6-Azaspiro[3.5]nonan-6-yl)-2-methylpiperidin-1-yl]{2-[methyl(pyridin-2-ylmethyl)amino]-1,3-thiazol-5-yl}methanone (*isomers 1 to 4*)



19 mg of the diastereomer mixture of [4-(6-azaspiro[3.5]nonan-6-yl)-2-methylpiperidin-1-yl]{2-[methyl(pyridin-2-ylmethyl)amino]-1,3-thiazol-5-yl}methanone (Example 142) was separated into the diastereomers by preparative HPLC on a chiral phase [column: Daicel Chiralcel OX-H 5 µm, 250 x 20 mm; eluent: 60% n-heptane & 40% isopropanol + 0.2% diethylamine; flow rate: 20 ml/min; temperature: 40°C, detection: 220 nm]: The two diastereomers were separately collected and lyophilized.

Example 164 (*isomer 1*):

[4-(6-Azaspiro[3.5]nonan-6-yl)-2-methylpiperidin-1-yl]{2-[methyl(pyridin-2-ylmethyl)amino]-1,3-thiazol-5-yl}methanone

Yield: 2 mg

$R_t$ = 3.82 min; chemical purity > 99%; > 99% ee.

[Column: Daicel Chiralpak OX-3, 3 µm, 50 mm x 4.6 mm; eluent: n-heptane/isopropanol + 0.2% diethylamine 50:50; flow rate: 1 ml/min; temperature: 30°C; UV detection: 220 nm].

LC-MS (Method 1): $R_t$ = 0.89 min; MS (ESIpos): m/z = 454 $[M+H]^+$.

Example 165 (*isomer 2*):

[4-(6-Azaspiro[3.5]nonan-6-yl)-2-methylpiperidin-1-yl]{2-[methyl(pyridin-2-ylmethyl)amino]-1,3-thiazol-5-yl}methanone

Yield: 5.5 mg

$R_t$ = 4.12 min; chemical purity > 99%; > 99% ee.

[Column: Daicel Chiralpak OX-3, 3 µm, 50 mm x 4.6 mm; eluent: n-heptane/isopropanol + 0.2% diethylamine 50:50; flow rate: 1 ml/min; temperature: 30°C; UV detection: 220 nm].

LC-MS (Method 1): $R_t$ = 0.89 min; MS (ESIpos): m/z = 454 $[M+H]^+$.

$^1$H-NMR (400 MHz, DMSO-$d_6$, δ/ppm): 1.21 (d, 3H), 1.32-1.46 (m, 4H), 1.57-1.88 (m, 9H), 2.07 (s, 2H), 2.19-2.46 (m, 4H), 3.17 (s, 3H), 3.22-3.37 (m, 1H, partly hidden by $H_2O$), 3.87-3.96 (m, 1H), 4.13-4.24 (m, 1H), 4.80 (s, 2H), 7.23-7.33 (m, 2H), 7.49 (s, 1H), 7.77 (td, 1H), 8.53 (d, 1H).

Example 166 (*isomer 3*):

[4-(6-Azaspiro[3.5]nonan-6-yl)-2-methylpiperidin-1-yl]{2-[methyl(pyridin-2-ylmethyl)amino]-1,3-thiazol-5-yl}methanone

Yield: 2 mg

$R_t$ = 4.71 min; chemical purity > 99%; > 99% ee.

[Column: Daicel Chiralpak OX-3, 3 µm, 50 mm x 4.6 mm; eluent: n-heptane/isopropanol + 0.2% diethylamine 50:50; flow rate: 1 ml/min; temperature: 30°C; UV detection: 220 nm].

LC-MS (Method 1): $R_t$ = 0.89 min; MS (ESIpos): m/z = 454 $[M+H]^+$.

Example 167 (*isomer 4*):

[4-(6-Azaspiro[3.5]nonan-6-yl)-2-methylpiperidin-1-yl]{2-[methyl(pyridin-2-ylmethyl)amino]-1,3-thiazol-5-yl}methanone

Yield: 4.8 mg

$R_t$ = 5.24 min; chemical purity > 99%; > 99% ee.

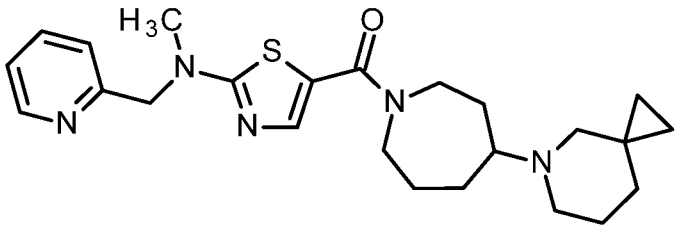
[Column: Daicel Chiralpak OX-3, 3 µm, 50 mm x 4.6 mm; eluent: n-heptane/isopropanol + 0.2% diethylamine 50:50; flow rate: 1 ml/min; temperature: 30°C; UV detection: 220 nm].

LC-MS (Method 1): $R_t$ = 0.89 min; MS (ESIpos): m/z = 454 $[M+H]^+$.

$^1$H-NMR (400 MHz, DMSO-$d_6$, δ/ppm): 1.27 (d, 3H), 1.32-1.47 (m, 4H), 1.56-1.89 (m, 9H), 2.07 (s, 2H), 2.17-2.47 (m, 4H), 3.17 (s, 3H), 3.22-3.37 (m, 1H, partly hidden by $H_2O$), 3.87-3.96 (m, 1H), 4.13-4.24 (m, 1H), 4.80 (s, 2H), 7.24-7.33 (m, 2H), 7.49 (s, 1H), 7.77 (td, 1H), 8.53 (d, 1H).

**Example 168 and Example 169**

[4-(5-Azaspiro[2.5]octan-5-yl)azepan-1-yl]{2-[methyl(pyridin-2-ylmethyl)amino]-1,3-thiazol-5-yl}methanone (*enantiomers 1 and 2*)



38 mg of the racemic mixture of [4-(5-azaspiro[2.5]octan-5-yl)azepan-1-yl]{2-[methyl(pyridin-2-ylmethyl)amino]-1,3-thiazol-5-yl}methanone (Example 138) was separated into the enantiomers by preparative HPLC on a chiral phase [column: Daicel Chiralcel OJ-H 5 µm, 250 x 20 mm; eluent: 75% n-heptane & 25% ethanol + 0.2% diethylamine; flow rate: 17 ml/min; temperature: 35°C, detection: 220 nm]: The two diastereomers were separately collected and lyophilized.

Example 168 (*enantiomer 1*):

[4-(5-Azaspiro[2.5]octan-5-yl)azepan-1-yl]{2-[methyl(pyridin-2-ylmethyl)amino]-1,3-thiazol-5-yl}methanone

Yield: 13 mg

$R_t$ = 1.48 min; chemical purity > 99%; > 99% ee.

[Column: Daicel Chiralcel OJ-3, 3 µm, 50 mm x 4.6 mm; eluent: n-heptane/ethanol + 0.2% diethylamine 70:30; flow rate: 1 ml/min; temperature: 30°C; UV detection: 220 nm].

LC-MS (Method 1): $R_t$ = 0.77 min; MS (ESIpos): m/z = 440 $[M+H]^+$.

$^1$H-NMR (500 MHz, DMSO-$d_6$, δ/ppm): 0.16-0.29 (m, 4H), 1.16-1.28 (m, 1H), 1.32-1.45 (m, 1H), 1.47-1.58 (m, 3H), 1,59-1.70 (m, 1H), 1.70-1.79 (m, 1H), 1.79-1.93 (m, 2H), 2.15 (s, 2H), 2.34-2.47 (m, 3H), 3.17 (s, 3H), 3.26-3.50 (m, 1H, partly hidden by $H_2O$), 3.58-3.79 (m, 2H), 4.80 (s, 2H), 7.23-7.32 (m, 2H), 7.50 (s, 1H), 7.77 (td, 1H), 8.53 (d, 1H).

$[\alpha]_D^{20}$ = +38.58° (c = 0.495, methanol).

Example 169 (*enantiomer 2*):

[4-(5-Azaspiro[2.5]octan-5-yl)azepan-1-yl]{2-[methyl(pyridin-2-ylmethyl)amino]-1,3-thiazol-5-yl}methanone

Yield: 14 mg

$R_t$ = 1.85 min; chemical purity > 99%; > 90% ee.

[Column: Daicel Chiralcel OJ-3, 3 µm, 50 mm x 4.6 mm; eluent: n-heptane/ethanol + 0.2% diethylamine 70:30; flow rate: 1 ml/min; temperature: 30°C; UV detection: 220 nm].

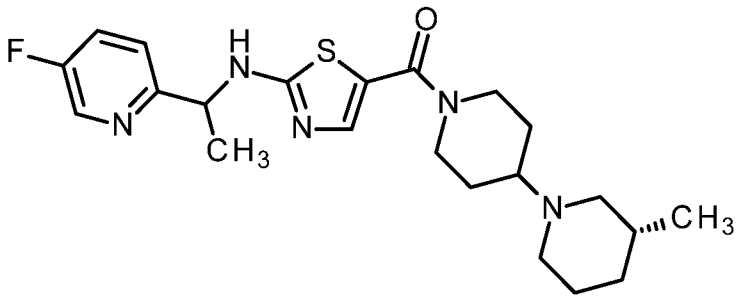
LC-MS (Method 1): $R_t$ = 0.77 min; MS (ESIpos): m/z = 440 $[M+H]^+$.

$^1$H-NMR (500 MHz, DMSO-$d_6$, δ/ppm): 0.16-0.29 (m, 4H), 1.16-1.28 (m, 1H), 1.32-1.45 (m, 1H), 1.47-1.58 (m, 3H), 1,59-1.70 (m, 1H), 1.70-1.79 (m, 1H), 1.79-1.93 (m, 2H), 2.15 (s, 2H), 2.34-2.47 (m, 3H), 3.17 (s, 3H), 3.26-3.50 (m, 1H, partly hidden by $H_2O$), 3.58-3.79 (m, 2H), 4.80 (s, 2H), 7.23-7.32 (m, 2H), 7.50 (s, 1H), 7.77 (td, 1H), 8.53 (d, 1H).

$[\alpha]_D^{20}$ = -36.40° (c = 0.500, methanol).

**Example 170 and Example 171**

(2-{[1-(5-Fluoropyridin-2-yl)ethyl]amino}-1,3-thiazol-5-yl)[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone (*diastereomers 1 and 2*)



38 mg of the diastereomer mixture of (2-{[1-(5-fluoropyridin-2-yl)ethyl]amino}-1,3-thiazol-5-yl)[(3R)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone (Example 39) was separated into the diastereomers by preparative HPLC on a chiral phase [column: Daicel Chiralpak IE 5 µm, 250 x 20 mm; eluent: 50% n-heptane & 50% ethanol + 0.2% diethylamine; flow rate: 20 ml/min, temperature: 40°C, detection: 220 nm]: The two diastereomers were separately collected and lyophilized.

Example 170 (*diastereomer 1*):

(2-{[1-(5-Fluoropyridin-2-yl)ethyl]amino}-1,3-thiazol-5-yl)[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone

Yield: 15 mg

$R_t$ = 3.06 min; chemical purity > 99%; > 99% ee.

[Column: Daicel Chiralpak IE-3, 3 µm, 50 mm x 4.6 mm; eluent: n-heptane/ethanol + 0.2% diethylamine 50:50; flow rate: 1 ml/min; temperature: 30°C; UV detection: 220 nm].

LC-MS (Method 1): $R_t$ = 0.89 min; MS (ESIpos): m/z = 432 $[M+H]^+$.

$^1$H-NMR (400 MHz, DMSO-$d_6$, δ/ppm): 0.74-0.89 (m, 4H, therein at 0.81 (d. 3H)), 1.28-1.48 (m, 6H, therein at 1.46 (d, 3H)), 1.48-1.68 (m, 3H), 1.69-1.81 (m, 3H), 2.06 (br. t, 1H), 2.45-2.57 (m, 1H, partly hidden by DMSO), 2.70-2.80 (m, 2H), 2.88 (br. t, 2H), 4.24 (br. d, 2H), 4.86-4.96 (m, 1H), 7.35 (s, 1H), 7.45 (dd,1H), 7.69 (td, 1H), 8.51 (d, 1H), 8.62 (d, 1H).

$[\alpha]_D^{20}$ = +11.38° (c = 0.1875, methanol).

Example 171 (*diastereomer 2*):

(2-{[1-(5-Fluoropyridin-2-yl)ethyl]amino}-1,3-thiazol-5-yl)[(3*R*)-3-methyl[1,4'-bipiperidine]-1'-yl]methanone

Yield: 14 mg

$R_t$ = 3.96 min; chemical purity > 99%; > 89% ee.

[Column: Daicel Chiralpak IE-3, 3 µm, 50 mm x 4.6 mm; eluent: n-heptane/ethanol + 0.2% diethylamine 50:50; flow rate: 1 ml/min; temperature: 30°C; UV detection: 220 nm].

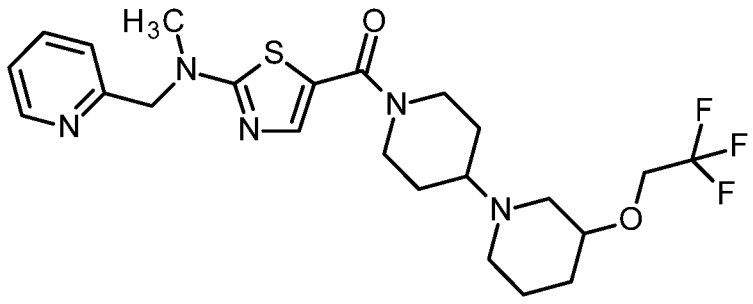
LC-MS (Method 1): $R_t$ = 0.86 min; MS (ESIpos): m/z = 432 $[M+H]^+$.

$^1$H-NMR (400 MHz, DMSO-$d_6$, δ/ppm): 0.74-0.89 (m, 4H, therein at 0.81 (d. 3H)), 1.28-1.48 (m, 6H, therein at 1.46 (d, 3H)), 1.48-1.67 (m, 3H), 1.68-1.79 (m, 3H), 2.04 (br. t, 1H), 2.43-2.53 (m, 1H, partly hidden by DMSO), 2.69-2.78 (m, 2H), 2.88 (br. t, 2H), 4.24 (br. d, 2H), 4.86-4.96 (m, 1H), 7.35 (s, 1H), 7.45 (dd,1H), 7.69 (td, 1H), 8.51 (d, 1H), 8.62 (d, 1H).

$[\alpha]_D^{20}$ = -15.58° (c = 0.1925, methanol).

**Example 172 and Example 173**

{2-[Methyl(pyridin-2-ylmethyl)amino]-1,3-thiazol-5-yl}[3-(2,2,2-trifluoroethoxy)[1,4'-bipiperidine]-1'-yl]methanone (*enantiomers 1 and 2*)




120 mg of the racemic mixture of {2-[methyl(pyridin-2-ylmethyl)amino]-1,3-thiazol-5-yl}[3-(2,2,2-trifluoroethoxy)[1,4'-bipiperidine]-1'-yl]methanone (Example 141) was separated into the enantiomers by preparative HPLC on a chiral phase [column: Daicel Chiralpak IG 5 µm, 250 x 20 mm; eluent: 10% n-heptane & 90% ethanol + 0.2% diethylamine; flow rate: 15 ml/min; temperature: 40°C, detection: 220 nm]: The two diastereomers were separately collected and lyophilized.

Example 172 (*enantiomer 1*):

{2-[Methyl(pyridin-2-ylmethyl)amino]-1,3-thiazol-5-yl}[3-(2,2,2-trifluoroethoxy)[1,4'-bipiperidine]-1'-yl]methanone

Yield: 36 mg

$R_t$ = 3.39 min; chemical purity > 99%; > 99% ee.

[Column: Daicel Chiralpak IG-3, 3 µm, 50 mm x 4.6 mm; eluent: n-heptane/ethanol + 0.2% diethylamine 20:80; flow rate: 1 ml/min; temperature: 30°C; UV detection: 220 nm].

LC-MS (Method 3): $R_t$ = 1.41 min; MS (ESIpos): m/z = 498 $[M+H]^+$.

$^1$H-NMR (400 MHz, DMSO-$d_6$, δ/ppm): 1.07-1.20 (m, 1H), 1.29-1.48 (m, 3H), 1.60-1.69 (m, 1H), 1.74 (br. d, 2H), 1.88-1.97 (m, 1H), 2.03 (br. t, 1H), 2.13 (br. t, 1H), 2.48-2.62 (m, 1H, partly hidden by DMSO), 2.62-2.69 (m, 1H), 2.85-3.02 (m, 3H), 3.29 (s, 3H), 3.43-3.51 (m, 1H), 4.01-4.12 (m, 2H), 4.29 (br. d, 2H), 4.80 (s, 2H), 7.24-7.33 (m, 2H), 7.50 (s,1H), 7.78 (td, 1H), 8.53 (d, 1H).

$[\alpha]_{436nm}^{20}$ = +18.25° (c = 0.270, methanol).

Example 173 (*enantiomer 2*):

{2-[Methyl(pyridin-2-ylmethyl)amino]-1,3-thiazol-5-yl}[3-(2,2,2-trifluoroethoxy)[1,4'-bipiperidine]-1'-yl]methanone

Yield: 37 mg

$R_t$ = 4.66 min; chemical purity > 99%; > 98% ee.

[Column: Daicel Chiralpak IG-3, 3 µm, 50 mm x 4.6 mm; eluent: n-heptane/ethanol + 0.2% diethylamine 20:80; flow rate: 1 ml/min; temperature: 30°C; UV detection: 220 nm].

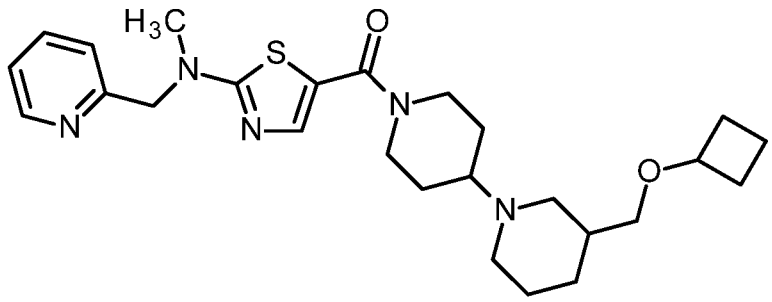
LC-MS (Method 3): $R_t$ = 1.41 min; MS (ESIpos): m/z = 498 $[M+H]^+$.

$^1$H-NMR (400 MHz, DMSO-$d_6$, δ/ppm): 1.07-1.20 (m, 1H), 1.29-1.48 (m, 3H), 1.60-1.69 (m, 1H), 1.74 (br. d, 2H), 1.88-1.97 (m, 1H), 2.03 (br. t, 1H), 2.13 (br. t, 1H), 2.48-2.62 (m, 1H, partly hidden by DMSO), 2.62-2.69 (m, 1H), 2.85-3.02 (m, 3H), 3.29 (s, 3H), 3.43-3.51 (m, 1H), 4.01-4.12 (m, 2H), 4.29 (br. d, 2H), 4.80 (s, 2H), 7.24-7.33 (m, 2H), 7.50 (s,1H), 7.78 (td, 1H), 8.53 (d, 1H).

$[\alpha]_{436nm}^{20}$ = -13.23° (c = 0.325, methanol).

**Example 174 and Example 175**

{3-[(Cyclobutyloxy)methyl][1,4'-bipiperidine]-1'-yl}{2-[methyl(pyridin-2-ylmethyl)amino]-1,3-thiazol-5-yl}methanone (*enantiomers 1 and 2*)



23 mg of the racemic mixture of {3-[(cyclobutyloxy)methyl][1,4'-bipiperidine]-1'-yl}{2-[methyl(pyridin-2-ylmethyl)amino]-1,3-thiazol-5-yl}methanone (Example 139) was separated into the enantiomers by preparative HPLC on a chiral phase [column: Daicel Chiralpak IG 5 µm, 250 x 20 mm; eluent: 0% n-heptane & 100% ethanol + 0.2% diethylamine; flow rate: 15 ml/min; temperature: 40°C, detection: 280 nm]: The two diastereomers were separately collected and lyophilized.

Example 174 (*enantiomer 1*):

{3-[(Cyclobutyloxy)methyl][1,4'-bipiperidine]-1'-yl}{2-[methyl(pyridin-2-ylmethyl)amino]-1,3-thiazol-5-yl}methanone

Yield: 9.5 mg

$R_t$ = 35.34 min; chemical purity > 99%; > 99% ee.

[Column: Daicel Chiralpak IG, 5 µm, 250 mm x 4.6 mm; eluent: n-heptane/ethanol + 0.2% diethylamine 0:100; flow rate: 1 ml/min; temperature: 40°C; UV detection: 300 nm].

LC-MS (Method 3): $R_t$ = 1.55 min; MS (ESIpos): m/z = 484 $[M+H]^+$.

$^1$H-NMR (400 MHz, DMSO-$d_6$, δ/ppm): 0.82-0.98 (m, 1H), 1.29-1.50 (m, 4H), 1.53-1.70 (m, 4H), 1.70-1.83 (m, 4H), 1.90 (br. t, 1H), 2.06-2.18 (m, 3H), 2.13 (br. t, 1H), 2.47-2.57 (m, 1H, hidden by

DMSO), 2.72 (br. d, 1H), 2.82 (br. d, 1H), 2.91 (br. t, 2H), 3.04-3.14 (m, 2H), 3.17 (s, 3H), 3.77-3.87 (m, 1H), 4.28 (br. d, 2H), 4.80 (s, 2H), 7.24-7.33 (m, 2H), 7.50 (s,1H), 7.77 (td, 1H), 8.53 (d, 1H).

$[\alpha]_{436nm}^{20}$ = +8.06° (c = 0.430, methanol).

Example 175 (*enantiomer 2*):

{3-[(Cyclobutyloxy)methyl][1,4'-bipiperidine]-1'-yl}{2-[methyl(pyridin-2-ylmethyl)amino]-1,3-thiazol-5-yl}methanone

Yield: 8.5 mg

$R_t$ = 38.53 min; chemical purity > 99%; > 98% ee.

[Column: Daicel Chiralpak IG, 5 µm, 250 mm x 4.6 mm; eluent: n-heptane/ethanol + 0.2% diethylamine 0:100; flow rate: 1 ml/min; temperature: 40°C; UV detection: 300 nm].

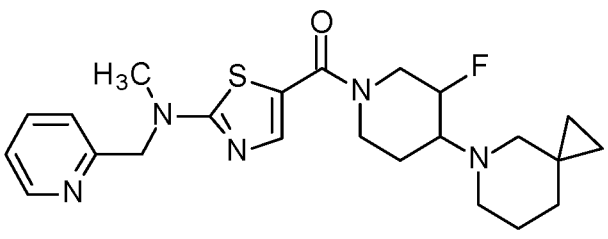
LC-MS (Method 3): $R_t$ = 1.55 min; MS (ESIpos): m/z = 484 $[M+H]^+$.

$^1$H-NMR (400 MHz, DMSO-$d_6$, δ/ppm): 0.82-0.96 (m, 1H), 1.29-1.49 (m, 4H), 1.54-1.71 (m, 4H), 1.71-1.83 (m, 4H), 1.91 (br. t, 1H), 2.06-2.17 (m, 3H), 2.13 (br. t, 1H), 2.47-2.57 (m, 1H, hidden by DMSO), 2.73 (br. d, 1H), 2.82 (br. d, 1H), 2.91 (br. t, 2H), 3.05-3.14 (m, 2H), 3.17 (s, 3H), 3.78-3.86 (m, 1H), 4.28 (br. d, 2H), 4.80 (s, 2H), 7.24-7.33 (m, 2H), 7.50 (s,1H), 7.77 (td, 1H), 8.53 (d, 1H).

$[\alpha]_{436nm}^{20}$ = -7.45° (c = 0.340, methanol).

**Example 176**

4-(5-Azaspiro[2.5]octan-5-yl)-3-fluoropiperidin-1-yl]{2-[methyl(pyridin-2-ylmethyl)amino]-1,3-thiazol-5-yl}methanone (*isomer mixture*)

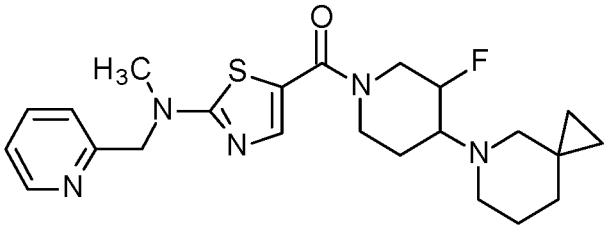


To a solution of 2-[methyl(pyridin-2-ylmethyl)amino]-1,3-thiazole-5-carboxylic acid (200 mg, 802 µmol) and 5-(3-fluoropiperidin-4-yl)-5-azaspiro[2.5]octane hydrochloride (*racemic*) (200 mg, 802 µmol) in 8 ml of acetonitrile were successively added *N*,*N*-diisopropylethylamine (560 µl, 3.2 mmol) and propylphosphonic anhydride in ethyl acetate (620 µl, 50% purity, 1.0 mmol), and the mixture was stirred at room temperature for 2.5 h. The reaction mixture was diluted with acetonitrile, acidified with formic acid and purified by preparative HPLC (column: Chromatorex C18 10 µm, 250 x 30 mm, eluent A: water, B: acetonitrile; gradient: 0.0 min 15% B; 4.5 min 30% B; 11.5 min 50% B; 12 min 100% B; 18 min 100% B; flow rate: 50 ml/min; 0.1% formic acid). The product-containing fractions were combined and lyophilized. The residue was applied to Isolute® and purified using a Biotage® cartridge (28 g Sfähr NH; DCM/MeOH gradient: 2-20% MeOH; flow rate: 25 ml/min). The product-containing fractions were combined and concentrated, and dried under high vacuum. This gave 97.0 mg (82% purity, 22% of theory) of the target compound.

LC-MS (Method 1): $R_t$ = 0.80 min; MS (ESIpos): m/z = 444 $[M+H]^+$.

**Example 177 and Example 178**

4-(5-Azaspiro[2.5]octan-5-yl)-3-fluoropiperidin-1-yl]{2-[methyl(pyridin-2-ylmethyl)amino]-1,3-thiazol-5-yl}methanone (*isomers 1 and 2*)



97 mg of the isomer mixture of 4-(5-azaspiro[2.5]octan-5-yl)-3-fluoropiperidin-1-yl]{2-[methyl(pyridin-2-ylmethyl)amino]-1,3-thiazol-5-yl}methanone (Example 176) was separated into the isomers by preparative HPLC on a chiral phase [column: Chiralpak AY-H, 5 µm, 20 x 250 mm; eluent: 100% ethanol + 0.2% diethylamine; flow rate: 15 ml/min; temperature: 70°C, detection: 220 nm]: The two diastereomers were separately collected and lyophilized.

Example 177 (*isomer 1*):

4-(5-Azaspiro[2.5]octan-5-yl)-3-fluoropiperidin-1-yl]{2-[methyl(pyridin-2-ylmethyl)amino]-1,3-thiazol-5-yl}methanone

Yield: 32 mg

$R_t$ = 13.92 min; chemical purity > 99%; > 99% de

[Column: Daicel Chiralpak AY-H 5 µm, 4.6 mm x 250 mm; eluent: n-heptane/ethanol + 0.2% diethylamine 0:100; flow rate: 1 ml/min; temperature: 70°C; UV detection: 220 nm].

LC-MS (Method 1): $R_t$ = 0.75 min; MS (ESIpos): m/z = 444 $[M+H]^+$.

$^1$H-NMR (400 MHz, DMSO-d6) δ [ppm]: 0.230 (3.61), 0.254 (3.04), 0.273 (0.55), 1.222 (0.65), 1.235 (1.48), 1.250 (1.43), 1.263 (0.71), 1.553 (1.10), 1.564 (1.38), 1.577 (1.02), 1.629 (0.41), 1.653 (0.74), 1.704 (0.49), 1.714 (0.53), 1.735 (0.43), 1.745 (0.42), 2.259 (0.50), 2.287 (2.04), 2.302 (1.72), 2.330 (0.49), 2.495 (5.55), 2.499 (11.59), 2.504 (16.00), 2.508 (11.84), 2.512 (5.92), 2.564 (1.33), 2.590 (1.26), 3.169 (15.80), 4.336 (0.57), 4.370 (0.55), 4.462 (0.52), 4.805 (6.26), 4.940 (0.69), 5.062 (0.69), 7.264 (1.69), 7.283 (2.33), 7.291 (1.07), 7.298 (1.13), 7.310 (1.02), 7.483 (5.50), 7.752 (0.93), 7.757 (0.95), 7.771 (1.66), 7.776 (1.65), 7.791 (0.82), 7.795 (0.81), 8.525 (1.29), 8.527 (1.30), 8.537 (1.32).

$[\alpha]_D^{20}$ = -23.14° (c = 0.255, methanol).

Example 178 (*isomer 2*):

4-(5-Azaspiro[2.5]octan-5-yl)-3-fluoropiperidin-1-yl]{2-[methyl(pyridin-2-ylmethyl)amino]-1,3-thiazol-5-yl}methanone

Yield: 32 mg

$R_t$ = 23.76 min; chemical purity > 99%; > 99% de

[Column: Daicel Chiralpak AY-H 5 µm, 4.6 mm x 250 mm; eluent: n-heptane/ethanol + 0.2% diethylamine 0:100; flow rate: 1 ml/min; temperature: 70°C; UV detection: 220 nm].

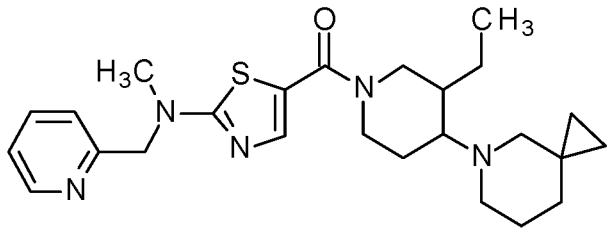
LC-MS (Method 1): $R_t$ = 0.76 min; MS (ESIpos): m/z = 444 $[M+H]^+$

$^1$H-NMR (400 MHz, DMSO-d6) δ [ppm]: -0.016 (0.59), -0.008 (16.00), 0.223 (1.41), 0.246 (1.19), 1.228 (0.58), 1.243 (0.55), 1.546 (0.41), 1.556 (0.53), 2.280 (0.79), 2.293 (0.65), 2.570 (0.74), 2.583 (0.48), 3.161 (6.69), 3.377 (0.46), 4.796 (2.47), 7.256 (0.67), 7.275 (0.96), 7.283 (0.41), 7.290 (0.46), 7.303 (0.42), 7.474 (2.33), 7.764 (0.69), 7.768 (0.70), 8.519 (0.51), 8.529 (0.51).

$[\alpha]_D^{20}$ = +22.67° (c = 0.350, methanol).

**Example 179**

4-(5-Azaspiro[2.5]octan-5-yl)-3-ethylpiperidin-1-yl]{2-[methyl(pyridin-2-ylmethyl)amino]-1,3-thiazol-5-yl}methanone (*isomer mixture*)

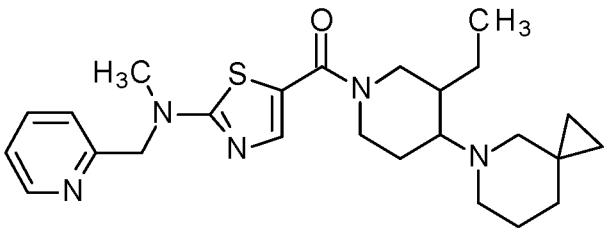


To a solution of 2-[methyl(pyridin-2-ylmethyl)amino]-1,3-thiazole-5-carboxylic acid (200 mg, 802 µmol) and 5-(3-ethylpiperidin-4-yl)-5-azaspiro[2.5]octane hydrochloride (*racemic*) (202 mg, 780 µmol) in 8 ml of acetonitrile were successively added *N*,*N*-diisopropylethylamine (560 µl, 3.2 mmol) and propylphosphonic anhydride in ethyl acetate (620 µl, 50% purity, 1.0 mmol), and the mixture was stirred at room temperature for 2.5 h. The reaction mixture was diluted with acetonitrile, acidified with formic acid and purified by preparative HPLC (column: Chromatorex C18 10 µm, 250 x 30 mm, eluent A: water, B: acetonitrile; gradient: 0.0 min 15% B; 4.5 min 30% B; 11.5 min 50% B; 12 min 100% B; 18 min 100% B; flow rate: 50 ml/min; 0.1% formic acid). The product-containing fractions were combined and lyophilized. The residue was applied to Isolute® and purified using a Biotage® cartridge (28 g Sfähr NH; DCM/MeOH gradient: 2-20% MeOH; flow rate: 25 ml/min). The product-containing fractions were combined and concentrated, and dried under high vacuum. This gave 108 mg (75% purity, 23% of theory) of the target compound.

LC-MS (Method 1): $R_t$ = 0.88 min; MS (ESIpos): m/z = 454 $[M+H]^+$.

**Example 180 and Example 181**

4-(5-Azaspiro[2.5]octan-5-yl)-3-ethylpiperidin-1-yl]{2-[methyl(pyridin-2-ylmethyl)amino]-1,3-thiazol-5-yl}methanone (*isomers 1 and 2*)



108 mg of the isomer mixture of 4-(5-azaspiro[2.5]octan-5-yl)-3-ethylpiperidin-1-yl]{2-[methyl(pyridin-2-ylmethyl)amino]-1,3-thiazol-5-yl}methanone (Example 179) was separated into the isomers by preparative HPLC on a chiral phase [column: Daicel Chiralpak AY-H, 5 µm, 20 x 250 mm; eluent: 100% ethanol + 0.2% diethylamine; flow rate: 15 ml/min; temperature: 70°C, detection: 220 nm]: The two diastereomers were separately collected and lyophilized.

Example 180 (*isomer 1*):

4-(5-Azaspiro[2.5]octan-5-yl)-3-ethylpiperidin-1-yl]{2-[methyl(pyridin-2-ylmethyl)amino]-1,3-thiazol-5-yl}methanone

Yield: 27 mg

$R_t$ = 8.43 min; chemical purity > 99%; > 99% de

[Column: Daicel Chiralpak AY-H 5 µm, 4.6 mm x 250 mm; eluent: n-heptane/ethanol + 0.2% diethylamine 0:100; flow rate: 1 ml/min; temperature: 70°C; UV detection: 220 nm].

LC-MS (Method 4): $R_t$ = 0.90 min; MS (ESIpos): m/z = 454 $[M+H]^+$

$^1$H-NMR (500 MHz, DMSO-d6) δ [ppm]: -0.013 (0.42), -0.006 (11.87), 0.212 (0.56), 0.216 (0.54), 0.228 (1.88), 0.237 (3.55), 0.246 (1.06), 0.267 (0.96), 0.281 (0.54), 0.746 (1.19), 0.760 (2.50), 0.775 (1.42), 1.184 (0.42), 1.196 (0.55), 1.267 (0.44), 1.277 (0.61), 1.291 (0.65), 1.302 (0.59), 1.461 (0.43), 1.474 (0.41), 1.559 (1.12), 1.570 (1.52), 1.581 (1.01), 1.694 (0.48), 1.714 (0.47), 1.733 (0.52), 1.738 (0.52), 1.759 (0.46), 2.073 (2.02), 2.081 (2.22), 2.104 (0.44), 2.120 (0.66), 2.127 (0.41), 2.136 (0.41), 2.143 (0.62), 2.518 (0.44), 3.163 (16.00), 4.251 (0.46), 4.279 (0.44), 4.341 (0.47), 4.368 (0.46), 4.757 (0.42), 4.789 (2.84), 4.799 (2.84), 4.832 (0.42), 7.247 (1.49), 7.262 (1.61), 7.275 (0.79), 7.277 (0.75), 7.285 (0.83), 7.286 (0.84), 7.290 (0.95), 7.300 (0.89), 7.301 (0.80), 7.475 (6.36), 7.746 (0.91), 7.750 (0.94), 7.761 (1.60), 7.765 (1.64), 7.777 (0.83), 7.780 (0.84), 8.514 (0.91), 8.516 (1.07), 8.517 (1.12), 8.519 (0.99), 8.523 (0.97), 8.525 (1.12), 8.527 (1.10), 8.529 (0.96).

$[\alpha]_D^{20}$ = +44.27° (c = 0.250, methanol).

Example 181 (*isomer 2*):

4-(5-Azaspiro[2.5]octan-5-yl)-3-ethylpiperidin-1-yl]{2-[methyl(pyridin-2-ylmethyl)amino]-1,3-thiazol-5-yl}methanone

Yield: 33 mg

$R_t$ = 11.81 min; chemical purity > 99%; > 99% de

[Column: Daicel Chiralpak AY-H 5 µm, 4.6 mm x 250 mm; eluent: n-heptane/ethanol + 0.2% diethylamine 0:100; flow rate: 1 ml/min; temperature: 70°C; UV detection: 220 nm].

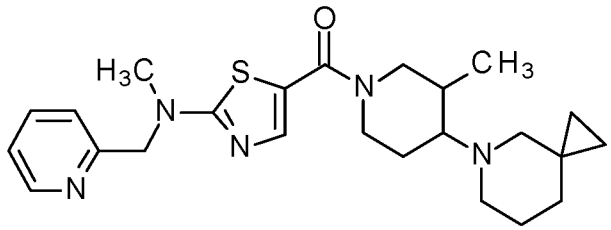
LC-MS (Method 4): $R_t$ = 0.90 min; MS (ESIpos): m/z = 454 $[M+H]^+$

$^1$H-NMR (400 MHz, DMSO-d6) δ [ppm]: -0.014 (0.49), 0.210 (0.64), 0.229 (2.89), 0.237 (4.06), 0.249 (1.27), 0.265 (1.23), 0.283 (0.52), 0.742 (1.48), 0.761 (3.36), 0.779 (1.91), 0.921 (0.43), 1.168 (0.46), 1.185 (0.52), 1.200 (0.77), 1.213 (0.51), 1.239 (0.48), 1.249 (0.48), 1.272 (0.75), 1.287 (0.85), 1.304 (0.75), 1.320 (0.46), 1.443 (0.42), 1.461 (0.50), 1.477 (0.47), 1.543 (0.43), 1.557 (1.24), 1.571 (1.68), 1.584 (1.13), 1.691 (0.56), 1.727 (0.86), 1.768 (0.52), 2.076 (2.72), 2.081 (2.89), 2.109 (0.75), 2.118 (0.78), 2.138 (0.48), 2.148 (0.77), 2.278 (0.48), 2.292 (0.46), 2.856 (0.47), 2.898 (0.46), 3.163 (16.00), 3.319 (0.41), 3.328 (0.46), 3.346 (0.84), 3.406 (1.75), 3.421 (0.86), 3.430 (0.45), 3.452 (0.55), 4.248 (0.56), 4.283 (0.55), 4.338 (0.64), 4.372 (0.61), 4.790 (3.36), 4.797 (3.36), 7.245 (1.70), 7.265 (1.86), 7.272 (1.05), 7.284 (0.97), 7.290 (1.10), 7.303 (1.04), 7.475 (6.09), 7.742 (0.94), 7.746 (0.97), 7.761 (1.66), 7.765 (1.67), 7.780 (0.82), 7.785 (0.82), 8.516 (1.30), 8.527 (1.31).

$[\alpha]_D^{20}$ = -44.96° (c = 0.430, methanol).

**Example 182**

4-(5-Azaspiro[2.5]octan-5-yl)-3-methylpiperidin-1-yl]{2-[methyl(pyridin-2-ylmethyl)amino]-1,3-thiazol-5-yl}methanone (*isomer mixture*)

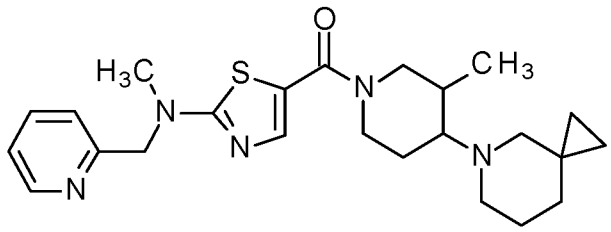


To a solution of 2-[methyl(pyridin-2-ylmethyl)amino]-1,3-thiazole-5-carboxylic acid (127 mg, 511 µmol) and 5-(3-methylpiperidin-4-yl)-5-azaspiro[2.5]octane hydrochloride (*racemic*) (125 mg, 511 µmol) in 6 ml of acetonitrile were successively added *N*,*N*-diisopropylethylamine (560 µl, 3.2 mmol) and propylphosphonic anhydride in ethyl acetate (400 µl, 50% purity, 660 µmol), and the mixture was stirred at room temperature for 2.5 h. The reaction mixture was diluted with acetonitrile, acidified with formic acid and purified by preparative HPLC (column: Chromatorex C18 10 µm, 250 x 30 mm, eluent A: water, B: acetonitrile; gradient: 0.0 min 15% B; 4.5 min 30% B; 11.5 min 50% B; 12 min 100% B; 18 min 100% B; flow rate: 50 ml/min; 0.1% formic acid). The product-containing fractions were combined and lyophilized. The residue was applied to Isolute® and purified using a Biotage® cartridge (28 g Sfähr NH; DCM/MeOH gradient: 2-20% MeOH; flow rate: 25 ml/min). The product-containing fractions were combined and concentrated, and dried under high vacuum. This gave 68 mg (100% purity, 30% of theory) of the target compound.

LC-MS (Method 1): $R_t$ = 0.81 min; MS (ESIpos): m/z = 440 $[M+H]^+$.

**Example 183 and Example 184**

4-(5-Azaspiro[2.5]octan-5-yl)-3-methylpiperidin-1-yl]{2-[methyl(pyridin-2-ylmethyl)amino]-1,3-thiazol-5-yl}methanone (*isomers 1 and 2*)



68 mg of the isomer mixture of 4-(5-azaspiro[2.5]octan-5-yl)-3-ethylpiperidin-1-yl]{2-[methyl(pyridin-2-ylmethyl)amino]-1,3-thiazol-5-yl}methanone (Example 182) was separated into the isomers by preparative HPLC on a chiral phase [column: Daicel Chiralpak AY-H, 5 µm, 20 x 250 mm; eluent: 100% ethanol + 0.2% diethylamine; flow rate: 15 ml/min; temperature: 60°C, detection: 220 nm]: The two diastereomers were separately collected and lyophilized.

Example 183 (*isomer 1*):

4-(5-Azaspiro[2.5]octan-5-yl)-3-methylpiperidin-1-yl]{2-[methyl(pyridin-2-ylmethyl)amino]-1,3-thiazol-5-yl}methanone

Yield: 28 mg

$R_t$ = 10.96 min; chemical purity > 99%; > 99% de

[Column: Daicel Chiralpak AY-H 5 µm, 4.6 mm x 250 mm; eluent: n-heptane/ethanol + 0.2% diethylamine 0:100; flow rate: 1 ml/min; temperature: 70°C; UV detection: 220 nm].

LC-MS (Method 4): $R_t$ = 0.83 min; MS (ESIpos): m/z = 440 $[M+H]^+$

$^1$H-NMR (400 MHz, DMSO-d6) δ [ppm]: -0.014 (0.63), 0.237 (4.03), 0.246 (1.81), 0.257 (2.12), 0.267 (1.56), 0.280 (0.61), 0.738 (4.43), 0.755 (4.63), 1.154 (0.46), 1.172 (0.48), 1.186 (0.65), 1.300 (0.94), 1.316 (0.75), 1.330 (0.74), 1.558 (1.16), 1.572 (1.61), 1.585 (1.06), 1.731 (0.56), 1.760 (0.50), 2.058 (0.54), 2.085 (2.49), 2.099 (2.87), 2.126 (0.90), 2.272 (0.44), 2.830 (0.41), 2.993 (0.40), 3.161 (16.00), 3.317 (0.73), 3.325 (1.04), 3.346 (0.59), 3.351 (1.18), 3.410 (2.80), 3.420 (2.54), 3.440 (1.15), 3.449 (0.62), 3.454 (0.62), 4.134 (0.70), 4.165 (0.67), 4.265 (0.52), 4.298 (0.53), 4.793 (3.83), 4.796 (3.85), 7.257 (1.64), 7.276 (2.53), 7.287 (0.96), 7.293 (1.05), 7.306 (0.99), 7.478 (6.07), 7.748 (0.92), 7.752 (0.95), 7.767 (1.63), 7.771 (1.63), 7.786 (0.81), 7.790 (0.79), 8.520 (1.25), 8.530 (1.24).

$[\alpha]_D^{20}$ = +30.44° (c = 0.265, methanol).

Example 184 (*isomer 2*):

4-(5-Azaspiro[2.5]octan-5-yl)-3-methylpiperidin-1-yl]{2-[methyl(pyridin-2-ylmethyl)amino]-1,3-thiazol-5-yl}methanone

Yield: 26 mg

$R_t$ = 12.94 min; chemical purity > 99%; > 99% de

[Column: Daicel Chiralpak AY-H 5 µm, 4.6 mm x 250 mm; eluent: n-heptane/ethanol + 0.2% diethylamine 0:100; flow rate: 1 ml/min; temperature: 70°C; UV detection: 220 nm].

LC-MS (Method 4): $R_t$ = 0.82 min; MS (ESIpos): m/z = 440 $[M+H]^+$

$^1$H-NMR (400 MHz, DMSO-d6) δ [ppm]: 0.237 (4.52), 0.246 (2.15), 0.256 (2.47), 0.267 (1.80), 0.738 (4.82), 0.755 (4.98), 1.154 (0.52), 1.172 (0.54), 1.186 (0.75), 1.299 (1.08), 1.315 (0.85), 1.331 (0.87), 1.558 (1.33), 1.572 (1.82), 1.585 (1.24), 1.732 (0.66), 1.761 (0.57), 2.057 (0.71), 2.084 (3.04), 2.098 (3.47), 2.126 (1.08), 2.270 (0.52), 2.829 (0.49), 2.963 (0.44), 2.996 (0.45), 3.160 (16.00), 3.319 (0.76), 3.330 (1.02), 3.336 (1.01), 3.433 (1.20), 3.449 (0.63), 4.132 (0.78), 4.166 (0.77), 4.264 (0.61), 4.297 (0.58), 4.796 (4.30), 7.257 (1.76), 7.276 (2.76), 7.287 (1.05), 7.293 (1.17), 7.305 (1.05), 7.478 (6.01), 7.748 (0.94), 7.752 (0.95), 7.767 (1.66), 7.771 (1.66), 7.786 (0.82), 7.790 (0.81), 8.520 (1.36), 8.530 (1.37).

$[\alpha]_D^{20}$ = -23.53° (c = 0.255, methanol).

**B. Assessment of pharmacological efficacy**

The pharmacological activity of the compounds of the invention can be demonstrated by *in vitro* and *in vivo* studies as known to the person skilled in the art. The application examples which follow describe the biological action of the compounds of the invention, without restricting the invention to these examples. Binding studies (B-1.) and activity studies (B-2.) were carried out for in vitro characterization of receptor/substance interaction and determination of biological activity, respectively.

B-1. *In vitro radioligand binding studies for determination of the dissociation constants $K_i$ at the human adrenoreceptor ADRA2C (Eurofins Panlabs Discovery Services, Taiwan, Ltd)*

A competition assay based on [$^3$H] rauwolscine as radioliganden was used to determine the binding affinity of the test substances at the human ADRA2C receptor.

To configure the competition assay, the equilibrium dissociation constant $K_d$ of the radioligand [$^3$H] rauwolscine was determined in a saturation experiment. To this end, homogenates of CHO-K1 cells recombinantly expressing the human ADRA2C receptor were incubated with increasing concentrations of the radiotracers for 1 h at 4°C in binding buffer (50 mM Tris-hydrochloric acid, 1 mM EDTA, pH 7.4). Unspecific binding was determined by addition of an excess of the not radioactively labelled ligand prazosin (10 µM). The radioactivity was determined in a scintiation counter.

The competition experiments were carried out in the presence of 0.5 nM [$^3$H] rauwolscine and increasing concentrations of the test substances to be characterized under the conditions described above. The substance concentration which displaces 50% of the radiolabelled ligand is referred to as $IC_{50}$ value.

The $IC_{50}$ value measured in the competition experiment and the $K_d$ value from the saturation experiment, using the Cheng Prusoff equation [Cheng Y, Prusoff WH. Relationship between the inhibition constant (Ki) and the concentration of inhibitor which causes 50 per cent inhibition (I50) of an enzymatic reaction. Biochem Pharmacol. 22 (23): 3099–108. doi:10.1016/0006-2952(73)90196-2. PMID 4202581 PMID: 4202581], was used to calculate the equilibrium constant Ki of the inhibitor, which describes the affinity of the test substances for the receptor.

Formula 1

$$Ki = \frac{IC50}{\left(1+\frac{L}{Kd}\right)}$$

Cheng Prusoff equation. $K_i$ = equilibrium constant of the inhibitor, $IC_{50}$ = concentration which displaces 50% of the ligand, $K_d$ = equilibrium constant of the ligand, L = concentration of the ligand

Table 1 below shows the binding affinity to the human ADRA2C receptor (Ki [nM]) and the half-maximal inhibition of the human ADRA2C receptor (IC50 [nM]) of representative embodiments of the invention:

Table 1

| Example No. | hAR$\alpha_{2C}$ $IC_{50}$ [nM] | hAR$\alpha_{2C}$ $K_i$ [nM] |
|---|---|---|
| 26 | 0.96 | 0.43 |

The data in Table 1 show that the test substances listed both bind to the human ADRA2C receptor and block the biological activity of the human ADRA2C receptor. Accordingly, the results in Table 1 confirm the mechanism of action of the compounds of the invention as ADRA2C inhibitors.

B-2. *In vitro* activity assay to determine the inhibition of recombinant ADRA2C

The human ADRA2C receptor belongs to the G protein(guanine-dependent protein)-coupled receptors, the main function of which is the transduction of signals into the interior of the cell.
The investigations of the inhibition of the recombinant human ADRA2C receptors were carried out with stabily transfected CHO-K1 cells coexpressing the $G_{\alpha q}$ protein and the calcium-sensitive photoprotein aequorin. In this recombinant system, binding of the agonists noradrenaline to the ADRA2C receptor leads, after activation of a signal cascade, to calcium release from intracellular stores, which is detected by the intracellular calcium sensor aequorin as a bioluminescent signal. The method is described in detail in the reference below. [Wunder F., Kalthof B., Muller T., Hueser J. Functional Cell-Based Assays in Microliter Volumes for Ultra-High Throughput Screening. Combinatorial Chemistry & High Throughput Screening, Volume 11, Number 7, 2008, pp. 495-504(10). doi.org/10.2174/138620708785204054]
The activity of the test substances was determined via their ability to inhibit the agonist-induced increase of the bioluminescence signal. The concentration which can block half of this signal increase is referred to as $IC_{50}$. The $IC_{50}$ value is calculated using the 4 parameter logistic function (Hill function):

Formula 2: Hill function

$$Y(x) = Bottom + \frac{Top - Bottom}{1 + 10^{(logIC50 + x) - HillSlope}}$$

Top= upper threshold, Bottom = lower threshold, Slope = slope, $IC_{50}$ = turning point

Table 2 below lists the $IC_{50}$ values from this assay determined for individual working examples of the invention (some as mean values from multiple independent individual determinations):

Table 2

| Example No. | $AR\alpha_{2C}$ $IC_{50}$ [nM] |
|---|---|
| 2 | 52 |
| 3 | 360 |
| 4 | 1.3 |
| 5 | 56 |
| 6 | 120 |
| 7 | 160 |
| 8 | 340 |
| 9 | 17 |
| 10 | 29 |
| 11 | 0.9 |
| 12 | 2.3 |
| 13 | 5.1 |
| 14 | 7.4 |
| 15 | 270 |
| 16 | 14.7 |
| 17 | 577 |
| 18 | 140 |
| 19 | 9.3 |
| 20 | 25.5 |
| 21 | 12 |
| 22 | 82.5 |
| 23 | 56 |

| Example No. | $AR\alpha_{2C}$ $IC_{50}$ [nM] |
|---|---|
| 24 | 3.85 |
| 25 | 37 |
| 26 | 0.87 |
| 27 | 2.2 |
| 28 | 1.65 |
| 29 | 1.7 |
| 30 | 0.9 |
| 31 | 0.42 |
| 32 | 0.49 |
| 33 | 0.18 |
| 34 | 2.7 |
| 35 | 2.1 |
| 36 | 1 |
| 37 | 0.25 |
| 38 | 1.1 |
| 39 | 1.2 |
| 40 | 0.35 |
| 41 | 5.4 |
| 42 | 1.8 |
| 43 | 15 |
| 47 | 2.1 |
| 48 | 3.6 |

| Example No. | ARα2C IC50 [nM] |
|---|---|
| 49 | 119 |
| 50 | 1.75 |
| 51 | 89 |
| 52 | 1.99 |
| 53 | 3.25 |
| 54 | 1.77 |
| 57 | 195 |
| 58 | 89 |
| 59 | 4 |
| 60 | 0.8 |
| 61 | 3.98 |
| 62 | 3.27 |
| 63 | 44 |
| 64 | 0.7 |
| 65 | 4.95 |
| 66 | 0.82 |
| 67 | 157 |
| 68 | 88 |
| 69 | 81 |
| 70 | 17 |
| 71 | 19 |
| 72 | 8 |
| 73 | 86 |
| 74 | 36 |
| 75 | 15 |
| 76 | 0.6 |
| 77 | 59 |
| 78 | 8 |

| Example No. | ARα2C IC50 [nM] |
|---|---|
| 79 | 3.55 |
| 80 | 0.4 |
| 81 | 40 |
| 82 | 3.2 |
| 83 | 20 |
| 84 | 14 |
| 85 | 1.83 |
| 86 | 7.4 |
| 87 | 1.35 |
| 88 | 6080 |
| 89 | 77 |
| 90 | 1.68 |
| 91 | 2.2 |
| 92 | 92 |
| 93 | 15 |
| 94 | 10 |
| 95 | 285 |
| 97 | 0.84 |
| 98 | 71 |
| 99 | 1.32 |
| 100 | 2.1 |
| 101 | 620 |
| 103 | 2.1 |
| 104 | 80 |
| 105 | 1.93 |
| 106 | 1.7 |
| 107 | 50 |
| 109 | 1.8 |

| Example No. | ARα2C IC50 [nM] |
|---|---|
| 110 | 1350 |
| 112 | 0.87 |
| 113 | 3.7 |
| 115 | 280 |
| 116 | 8.4 |
| 118 | 3.4 |
| 119 | 185 |
| 120 | 7 |
| 121 | 2.15 |
| 122 | 3.7 |
| 123 | 1.9 |
| 124 | 4.3 |
| 125 | 2.1 |
| 126 | 5.5 |
| 128 | 21 |
| 129 | 4 |
| 130 | 250 |
| 131 | 76 |
| 132 | 27 |
| 133 | 22 |
| 134 | 9.6 |
| 135 | 6500 |
| 136 | 635 |
| 137 | 370 |
| 138 | 39 |
| 139 | 3.2 |
| 140 | 12 |
| 141 | 215 |

| Example No. | ARα2C IC50 [nM] |
|---|---|
| 142 | 8.2 |
| 143 | 1850 |
| 144 | 398 |
| 145 | 475 |
| 146 | 3550 |
| 147 | 250 |
| 148 | 62 |
| 149 | 42 |
| 150 | 13 |
| 151 | 2100 |
| 152 | 28 |
| 153 | 550 |
| 154 | 13 |
| 155 | 1150 |
| 156 | 41 |
| 157 | 4930 |
| 160 | 23 |
| 161 | 105 |
| 162 | 8050 |
| 163 | 37 |
| 164 | 14 |
| 165 | 115 |
| 166 | 24 |
| 167 | 125 |
| 168 | 160 |
| 169 | 80 |
| 170 | 28 |
| 171 | 4.3 |

| Example No. | ARα2C IC50 [nM] |
|---|---|
| 172 | 43 |
| 173 | 2800 |
| 174 | 3.1 |
| 175 | 115 |
| 177 | 2.1 |

| Example No. | ARα2C IC50 [nM] |
|---|---|
| 178 | 9.4 |
| 180 | 1550 |
| 181 | 365 |
| 183 | 160 |
| 184 | 9 |

The data in Table 2 show that the test substances listed block the biological activity of the human ADRA2C receptor. Accordingly, the results in Table 1 confirm the mechanism of action of the compounds of the invention as ADRA2C inhibitors.

B-3. Animal model of obstructive sleep apnoea in the pig

Using negative pressure, it is possible to induce collapse and thus obstruction of the upper respiratory tract in anesthetized, spontaneously breathing pigs [Wirth *et al.*, *Sleep* 36, 699-708 (2013)].

German Landrace pigs are used for the model. The pigs are anesthetized and tracheotomized. One cannula each is inserted into the rostral and the caudal part of the trachea. Using a T connector, the rostral cannula is connected on the one hand to a device generating negative pressures and on the other hand to the caudal cannula. Using a T connector, the caudal cannula is connected to the rostral cannula and to a tube which allows spontaneous breathing circumventing the upper respiratory tract. By appropriate closing and opening of the tubes it is thus possible for the pig to change from normal nasal breathing to breathing via the caudal cannula during the time when the upper respiratory tract is isolated and connected to the device for generating negative pressures.

At certain points in time, the collapsibility of the upper respiratory tract is tested by having the pig breathe via the caudal cannula and applying negative pressures of -50, -100 and -150 cm water head ($cmH_2O$) to the upper respiratory tract. This causes the upper respiratory tract to collapse, which manifests itself in an interruption of the airflow and a pressure drop in the tube system. This test is conducted prior to the administration of the test substance and at certain intervals after the administration of the test substance. An appropriately effective test substance can prevent this collapse of the respiratory tract in the inspiratory phase.

Administration of the test substance can be intranasal, intravenous, subcutaneous, intraperitoneal, intraduodenal or intragastral.

## C. Working examples of pharmaceutical compositions

The compounds of the invention can be converted to pharmaceutical preparations as follows:

**Tablet:**

Composition:

100 mg of the compound of the invention, 50 mg of lactose (monohydrate), 50 mg of corn starch (native), 10 mg of polyvinylpyrrolidone (PVP 25) (BASF, Ludwigshafen, Germany) and 2 mg of magnesium stearate.

Tablet weight 212 mg, diameter 8 mm, radius of curvature 12 mm.

Production:

The mixture of compound of the invention, lactose and starch is granulated with a 5% solution (w/w) of the PVP in water. The granules are dried and then mixed with the magnesium stearate for 5 minutes. This mixture is compressed using a conventional tableting press (see above for format of the tablet). The guide value used for the pressing is a pressing force of 15 kN.

**Suspension for oral administration:**

Composition:

1000 mg of the compound of the invention, 1000 mg of ethanol (96%), 400 mg of Rhodigel® (xanthan gum from FMC, Pennsylvania, USA) and 99 g of water.

10 ml of oral suspension correspond to a single dose of 100 mg of the compound of the invention.

Production:

The Rhodigel is suspended in ethanol; the compound of the invention is added to the suspension. The water is added while stirring. The mixture is stirred for about 6 h until the swelling of the Rhodigel is complete.

**Solution for oral administration:**

Composition:

500 mg of the compound of the invention, 2.5 g of polysorbate and 97 g of polyethylene glycol 400. 20 g of oral solution correspond to a single dose of 100 mg of the compound of the invention.

Production:

The compound of the invention is suspended in the mixture of polyethylene glycol and polysorbate with stirring. The stirring operation is continued until dissolution of the compound of the invention is complete.

**i.v. solution:**

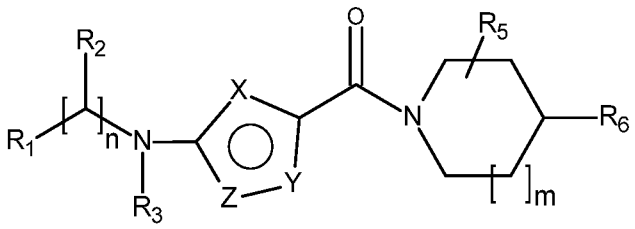
The compound of the invention is dissolved in a concentration below the saturation solubility in a physiologically acceptable solvent (e.g. isotonic saline solution, glucose solution 5% and/or PEG 400 solution 30%). The solution is subjected to sterile filtration and dispensed into sterile and pyrogen-free injection vessels.

**Solution for nasal administration:**

The compound of the invention is dissolved in a concentration below the saturation solubility in a physiologically acceptable solvent (e.g. purified water, phosphate buffer, citrate buffer). The solution may contain further additives for isotonization, for preservation, for adjusting the pH, for improvement in the solubility and/or for stabilization.

## Claims

1. A compound of the general formula (I)



(I)

in which

X is S, N or O;

Y is N, S or O,

where, when X is S, Z is N;

where, when X is O, Z is N;

Y is $CR_4$, O or $NR_4$,

where, when X is N and Z is N, Y is O;

where, when X is S, Y is $CR_4$ or $NR_4$;

$R_1$ is 5- to 10-membered heteroaryl, phenyl, ($C_4$-$C_{10}$)-heterocycloalkyl or ($C_3$-$C_{10}$)-cycloalkyl,

in which 5- to 10-membered heteroaryl may be substituted by 1 to 3 substituents selected independently from the group of ($C_1$-$C_4$)-alkyl, ($C_1$-$C_4$)-alkoxy, halogen;

where ($C_1$-$C_4$)-alkyl may be up to trisubstituted by halogen,

where ($C_1$-$C_4$)-alkoxy may be up to trisubstituted by halogen,

in which phenyl may be substituted by 1 to 2 substituents selected independently from the group of ($C_1$-$C_4$)-alkyl, ($C_3$-$C_5$)-cycloalkyl, ($C_1$-$C_4$)-alkoxy, cyano, hydroxy, halogen;

where ($C_1$-$C_4$)-alkyl may be up to trisubstituted by halogen,

in which ($C_3$-$C_{10}$)-cycloalkyl and ($C_4$-$C_{10}$)-heterocycloalkyl may be substituted by 1 to 2 substituents selected independently from the group of ($C_1$-$C_4$)-alkyl, ($C_3$-$C_5$)-cycloalkyl, ($C_1$-$C_4$)-alkoxy, cyano, hydroxy, halogen;

where ($C_1$-$C_4$)-alkyl may be up to trisubstituted by halogen,

in which ($C_3$-$C_{10}$)-cycloalkyl and ($C_4$-$C_{10}$)-heterocycloalkyl may be fused to 5- to 10-membered heteroaryl,

where 5- to 10-membered heteroaryl may be substituted by 1 to 2 substituents selected independently from the group of ($C_1$-$C_4$)-alkyl, ($C_1$-$C_4$)-alkoxy and halogen;

$R_2$ is hydrogen, ($C_1$-$C_4$)-alkyl or ($C_3$-$C_5$)-cycloalkyl;

in which ($C_1$-$C_4$)-alkyl may be up to trisubstituted by halogen,

in which ($C_1$-$C_4$)-alkyl may be substituted by cyano or ($C_1$-$C_4$)-alkoxy,

in which ($C_3$-$C_5$)-cycloalkyl may be up to trisubstituted by halogen,

or

together with the carbon atom to which $R_2$ is bonded forms a ($C_3$-$C_4$)-cycloalkyl ring,

or

$R_1$ and $R_2$ together form a ($C_5$-$C_8$)-cycloalkyl or ($C_5$-$C_{10}$)-heterocycloalkyl ring,

in which ($C_5$-$C_8$)-cycloalkyl may be fused to 5- to 10-membered heteroaryl,

where 5- to 10-membered heteroaryl may be substituted by 1 to 2 substituents selected independently from the group of ($C_1$-$C_4$)-alkyl, ($C_1$-$C_4$)-alkoxy and halogen;

in which ($C_3$-$C_{10}$)-heterocycloalkyl may be fused to 5- to 10-membered heteroaryl,

where 5- to 10-membered heteroaryl may be substituted by 1 to 2 substituents selected independently from the group of ($C_1$-$C_4$)-alkyl, ($C_1$-$C_4$)-alkoxy and halogen;

$R_3$ is hydrogen, ($C_1$-$C_4$)-alkyl,

in which ($C_1$-$C_4$)-alkyl may be up to trisubstituted by halogen,

$R_4$ in $CR_4$ is hydrogen, ($C_1$-$C_4$)-alkyl, ($C_3$-$C_4$)-cycloalkyl, phenyl, halogen;

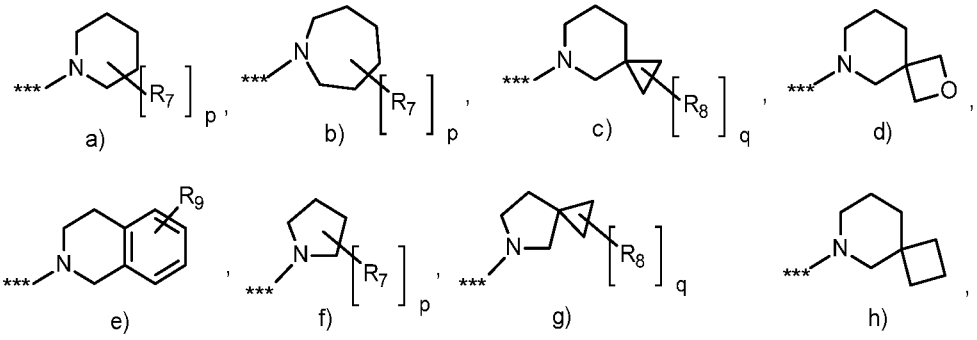
in which ($C_1$-$C_4$)-alkyl may be up to trisubstituted by halogen and phenyl may be substituted by halogen,

in $NR_4$ is absent or is hydrogen, ($C_1$-$C_4$)-alkyl, ($C_3$-$C_4$)-cycloalkyl, phenyl;

in which ($C_1$-$C_4$)-alkyl may be up to trisubstituted by halogen and phenyl may be substituted by halogen,

$R_5$ is hydrogen, ($C_1$-$C_4$)-alkyl, ($C_1$-$C_4$)-alkoxy, halogen,

$R_6$ is a group of formula a), b), c), d), e), f) or g)




,

in which *** marks the attachment to the adjacent piperidine ring,

in which $R_7$ is hydrogen, ($C_1$-$C_4$)-alkyl, ($C_3$-$C_4$)-cycloalkyl, ($C_1$-$C_4$)-alkoxy, ($C_3$-$C_4$)-cycloalkoxy, phenyl,

where ($C_1$-$C_4$)-alkyl may be substituted by ($C_3$-$C_4$)-cycloalkyl, ($C_1$-$C_4$)-alkoxy, ($C_3$-$C_4$)-cycloalkoxy and up to trisubstituted by halogen,

where ($C_1$-$C_4$)-alkoxy may be substituted by ($C_3$-$C_4$)-cycloalkyl and up to trisubstituted by halogen,

where ($C_3$-$C_4$)-cycloalkyl may be substituted by monofluoromethyl, difluoromethyl or trifluoromethyl and up to disubstituted by halogen,

where ($C_1$-$C_4$)-alkoxy may be substituted by ($C_3$-$C_4$)-cycloalkyl and up to trisubstituted by halogen,

where ($C_3$-$C_4$)-cycloalkyl may be mono- or disubstituted by halogen,

where ($C_3$-$C_4$)-cycloalkoxy may be up to disubstituted by halogen,

in which $R_8$ is hydrogen or fluorine,

in which $R_9$ is hydrogen, ($C_1$-$C_4$)-alkyl, ($C_1$-$C_4$)-alkoxy, halogen;

where ($C_1$-$C_4$)-alkyl may be substituted by ($C_1$-$C_4$)-alkoxy,

n represents 0 or 1,

m represents 0, 1 or 2,

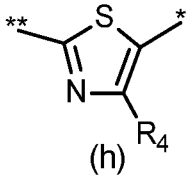
p represents 0, 1 or 2 and

q represents 0, 1 or 2,

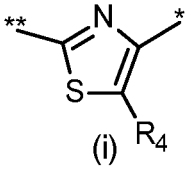
and the salts, solvates and solvates of the salts thereof.

2. Compounds of the formula (I) according to Claim 1, in which

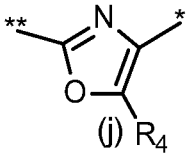
X, Y and Z are chosen such that the aromatic 5-membered ring has the structural formula h), i), j), k), r) or p),



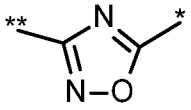
(h),



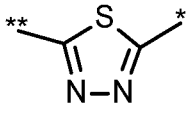
(i),



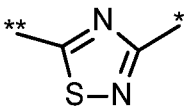
(j),



(k),



(r),



(p),

in which * marks the attachment to the carbonyl group and ** the attachment to the nitrogen atom of the adjacent amino group and

$R_1$ is pyridinyl, pyrazolyl, thiazolyl, thienyl, phenyl, tetrahydropyranyl or cyclohexyl,

in which pyridinyl may be substituted by 1 to 2 substituents selected independently from the group of ($C_1$-$C_2$)-alkyl, fluorine, chlorine, trifluoromethyl, trifluoromethoxy,

in which pyrazolyl may be substituted by 1 to 2 substituents selected independently from the group of ($C_1$-$C_2$)-alkyl, fluorine, chlorine, trifluoromethyl,

in which thiazolyl may be substituted by chlorine,

in which thienyl may be substituted by fluorine,

in which phenyl may be substituted by 1 to 2 substituents selected independently from the group of ($C_1$-$C_2$)-alkyl, ($C_3$-$C_4$)-cycloalkyl, methoxy, cyano, hydroxy, fluorine, chlorine, trifluoromethyl,

in which cyclohexyl and tetrahydropyranyl may be fused to pyridyl,

$R_2$ is hydrogen, methyl,

in which methyl may be substituted by cyano or methoxy,

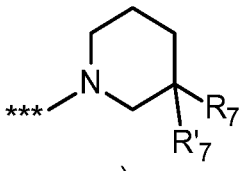
$R_3$ is hydrogen, ($C_1$-$C_2$)-alkyl;

$R_4$ is hydrogen, methyl, ethyl, cyclopropyl, trifluoromethyl, bromine, chlorine, phenyl;

where phenyl may be substituted by chlorine,

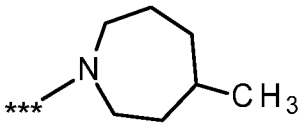
$R_5$ is hydrogen, fluorine;

$R_6$ is a group of the formula a), b''), c') or h),



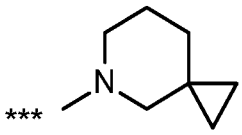
a)

,



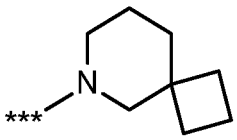
b'')

,



c')

,



h)

,

in which *** marks the attachment to the adjacent piperidine ring,

in which $R_7$ or $R'_7$ is independently hydrogen, ($C_1$-$C_4$)-alkyl, ($C_3$-$C_4$)-cycloalkyl, ($C_1$-$C_2$)-alkoxy, ($C_3$-$C_4$)-cycloalkoxy, monofluoromethyl, difluoromethyl, trifluoromethyl, difluoromethoxy, phenyl,

where ($C_1$-$C_4$)-alkyl may be substituted by methoxy, n-butoxy, cyclopropyl, cyclobutoxy and up to disubstituted by fluorine,

where methoxy may be substituted by cyclopropyl, cyclobutyl, trifluoromethyl,

where cyclopropyl may be substituted by monofluoromethyl, difluoromethyl, trifluoromethyl,

where cyclopropyl may be up to disubstituted by fluorine,

where n-butoxy may be up to disubstituted by fluorine,

where ($C_1$-$C_2$)-alkoxy may be substituted by cyclopropyl, cyclobutyl, cyclobutoxy, trifluoromethyl and

where cyclopropyl and cyclobutyl may be up to disubstituted by fluorine,

where ($C_3$-$C_4$)-cycloalkoxy may be up to disubstituted by fluorine,

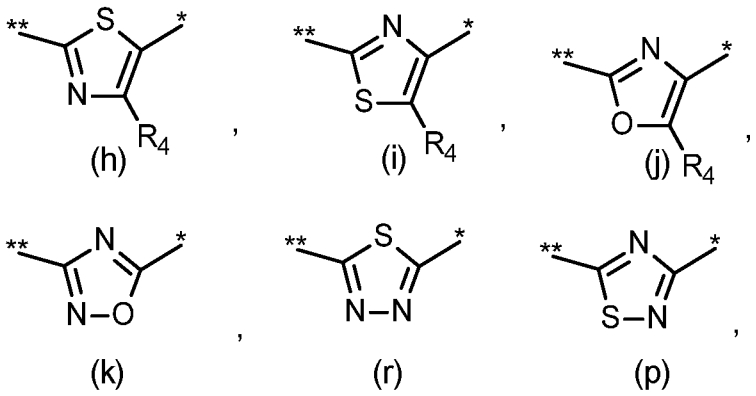
n represents 0 or 1 and

m represents 1 or 2,

and the salts, solvates and solvates of the salts thereof.

3. Compounds of the formula (I) according to Claim 1, in which

X, Y and Z are chosen such that the aromatic 5-membered ring has the structural formula h), i), j), k), r) or p),




in which * marks the attachment to the carbonyl group and ** the attachment to the nitrogen atom of the adjacent amino group and

$R_1$ is pyridinyl, 2-ethylpyridinyl, 4,6-dimethylpyridinyl, 3,5-difluoropyridinyl, 3-fluoropyridinyl, 4-trifluoromethylpyridinyl, 6-trifluoromethylpyridinyl, 5-chloro-3-fluoropyridinyl, 3-chloro-5-fluoropyridinyl, 3-methylpyridinyl, 4-methylpyridinyl, 6-methylpyridinyl, 3-chloropyridinyl, 5-chloropyridinyl, 6-trifluoromethoxypyridinyl, phenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 3-methoxyphenyl, 4-trifluoromethylphenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 3-hydroxyphenyl, 2,5-difluorophenyl, 5-chloro-2-hydroxyphenyl, 5-fluoro-2-methoxyphenyl, 5-chloro-2-fluorophenyl, 2-chloro-5-fluorophenyl, 2-chloro-4-fluorophenyl, 3-cyano-4-fluorophenyl, 2-cyclopropylphenyl, 4-chloro-1-methyl-1H-pyrazolyl, 5-chloro-1,3-thiazolyl, 5-fluoro-2-thienyl;

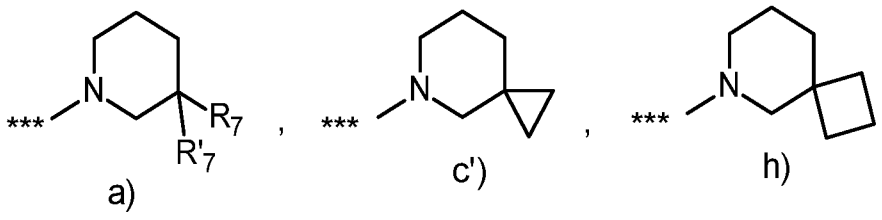
$R_2$ is hydrogen or methyl;

$R_3$ is hydrogen, methyl;

$R_4$ is hydrogen, ethyl or trifluoromethyl;

$R_5$ is hydrogen, methyl or fluorine;

$R_6$ is a group of the formula a), c') or h)



in which *** marks the attachment to the adjacent piperidine ring,

in which $R_7$ and $R'_7$ are independently hydrogen, methyl, ethyl, n-propyl, isopropyl, tert-butyl, 2-fluoroethyl, cyclopropyl, cyclobutyl, cyclopropylmethyl, methoxy, ethoxy, methoxymethyl, monofluoromethyl, difluoromethyl, trifluoromethyl, difluoromethoxy, 3,3-difluorocyclobutylmethoxy, cyclobutylmethoxy, cyclopropylmethoxy, cyclopropylmethoxymethyl, cyclobutyloxymethyl, 3-fluorobutyloxymethyl, 3,3-difluorocyclobutylmethoxymethyl, 2,2,2-trifluoroethoxy, 2,2,2-trifluoroethoxymethyl, 2,2-difluorocyclopropylmethoxy, cyclobutyloxy, 3,3-difluorocyclobutyloxy, fluoromethylcyclopropylmethoxy, difluoromethylcyclopropylmethoxy, trifluoromethylcyclopropylmethoxy, fluorine;

n represents 1 and

m represents 1,

and the salts, solvates and solvates of the salts thereof.

4. Compounds of the formula (I) according to Claim 1, in which

X, Y and Z are 1,3-thiazolyl, 1,3-oxazolyl, 1,2,4-oxadiazolyl;

$R_1$ is pyridinyl, 2-ethylpyridinyl, 4,6-dimethylpyridinyl, 3,5-difluoropyridinyl, 3-fluoropyridinyl, 4-trifluoromethylpyridinyl, 6-trifluoromethylpyridinyl, 5-chloro-3-fluoropyridinyl, 3-chloro-5-fluoropyridinyl, 3-methylpyridinyl, 4-methylpyridinyl, 6-methylpyridinyl, 3-chloropyridinyl, 5-chloropyridinyl, 6-trifluoromethoxypyridinyl, phenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 3-methoxyphenyl, 4-trifluoromethylphenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 3-hydroxyphenyl, 2,5-difluorophenyl, 5-chloro-2-hydroxyphenyl, 5-fluoro-2-methoxyphenyl, 5-chloro-2-fluorophenyl, 2-chloro-5-fluorophenyl, 2-chloro-4-fluorophenyl, 3-cyano-4-fluorophenyl, 2-cyclopropylphenyl, 4-chloro-1-methyl-1H-pyrazolyl, 5-chloro-1,3-thiazolyl, 5-fluoro-2-thienyl;

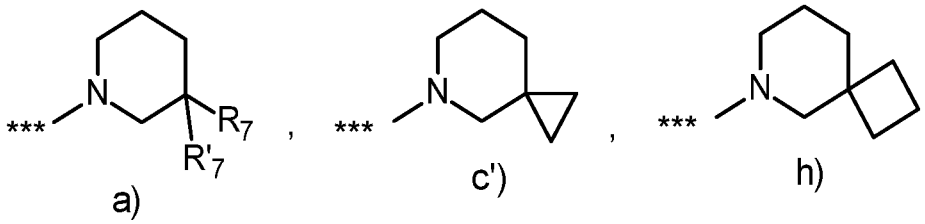
$R_2$ is hydrogen or methyl;

$R_3$ is hydrogen, methyl;

$R_4$ is hydrogen or methyl, ethyl, trifluoromethyl;

$R_5$ is hydrogen, methyl or fluorine;

$R_6$ is a group of the formula a), or c') or h)




in which *** marks the attachment to the adjacent piperidine ring,

in which $R_7$ and $R'_7$ are independently hydrogen, methyl, ethyl, n-propyl, isopropyl, tert-butyl, 2-fluoroethyl, cyclopropyl, cyclobutyl, cyclopropylmethyl, methoxy, ethoxy, methoxymethyl, monofluoromethyl, difluoromethyl, trifluoromethyl, difluoromethoxy, 3,3-difluorocyclobutylmethoxy, cyclobutylmethoxy, cyclopropylmethoxy, cyclopropylmethoxymethyl, cyclobutyloxymethyl, 3-fluorobutyloxymethyl, 3,3-difluorocyclobutylmethoxymethyl, 2,2,2-trifluoroethoxy, 2,2,2-trifluoroethoxymethyl, 2,2-difluorocyclopropylmethoxy, cyclobutyloxy, 3,3-difluorocyclobutyloxy, fluoromethylcyclopropylmethoxy, difluoromethylcyclopropylmethoxy, trifluoromethylcyclopropylmethoxy, fluorine;

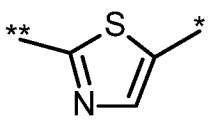
n represents 1 and

m represents 1,

and the salts, solvates and solvates of the salts thereof.

5. Compounds of the formula (I) according to Claim 1, in which

X, Y and Z are chosen such that the aromatic 5-membered ring has the structural formula h'),




(h')

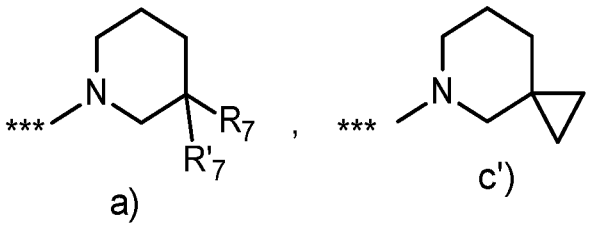
$R_1$ is pyridinyl, 2-ethylpyridinyl, 4,6-dimethylpyridinyl, 3,5-difluoropyridinyl, 3-fluoropyridinyl, 4-trifluoromethylpyridinyl, 6-trifluoromethylpyridinyl, 5-chloro-3-fluoropyridinyl, 3-chloro-5-fluoropyridinyl, 3-methylpyridinyl, 4-methylpyridinyl, 6-methylpyridinyl, 3-chloropyridinyl, 5-chloropyridinyl, 6-trifluoromethoxypyridinyl, phenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 3-methoxyphenyl, 4-trifluoromethylphenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 3-hydroxyphenyl, 2,5-difluorophenyl, 5-chloro-2-hydroxyphenyl, 5-fluoro-2-methoxyphenyl, 5-chloro-2-fluorophenyl, 2-chloro-5-fluorophenyl, 2-chloro-4-fluorophenyl, 3-cyano-4-fluorophenyl, 2-cyclopropylphenyl, 4-chloro-1-methyl-1H-pyrazolyl, 5-chloro-1,3-thiazolyl, 5-fluoro-2-thienyl;

$R_2$ is hydrogen or methyl;

$R_3$ is hydrogen or methyl;

$R_5$ is hydrogen, fluorine;

$R_6$ is a group of the formula a) or c')




in which *** marks the attachment to the adjacent piperidine ring,

in which $R_7$ and $R'_7$ are independently hydrogen, methyl, ethyl, n-propyl, isopropyl, tert-butyl, 2-fluoroethyl, cyclopropyl, cyclobutyl, cyclopropylmethyl, methoxy, ethoxy, methoxymethyl, monofluoromethyl, difluoromethyl, trifluoromethyl, difluoromethoxy, 3,3-difluorocyclobutylmethoxy, cyclobutylmethoxy, cyclopropylmethoxy, cyclopropylmethoxymethyl, cyclobutyloxymethyl, 3-fluorobutyloxymethyl, 3,3-difluorocyclobutylmethoxymethyl, 2,2,2-trifluoroethoxy, 2,2,2-trifluoroethoxymethyl, 2,2-difluorocyclopropylmethoxy, cyclobutyloxy, 3,3-difluorocyclobutyloxy, fluoromethylcyclopropylmethoxy, difluoromethylcyclopropylmethoxy, trifluoromethylcyclopropylmethoxy, fluorine;

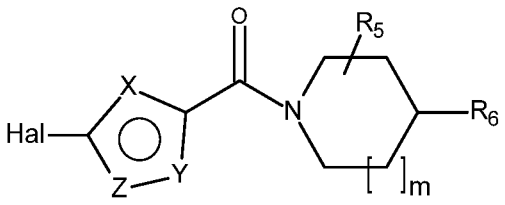
n represents 1 and

m represents 1,

and the salts, solvates and solvates of the salts thereof.

6. Process for preparing the compounds of the formula (I) or salts thereof, solvates thereof or solvates of the salts thereof, where

[A] compounds of the formula (II)



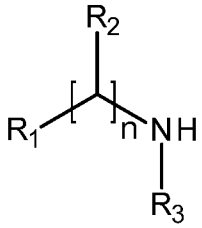
(II)

in which

X, Y, Z, $R_5$, $R_6$, and m have definitions given above,

Hal is a leaving group, preferably chlorine, bromine, iodine, or methylsulfonyl,

are reacted in the presence of a base with compounds of the formula (III)

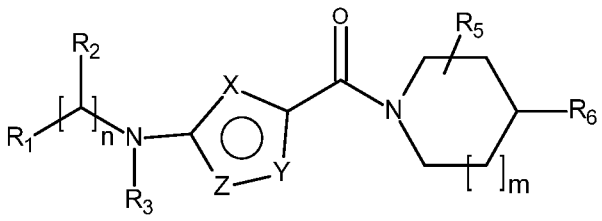


(III)

in which

$R_1$, $R_2$ and $R_3$ and n have the definitions given above,

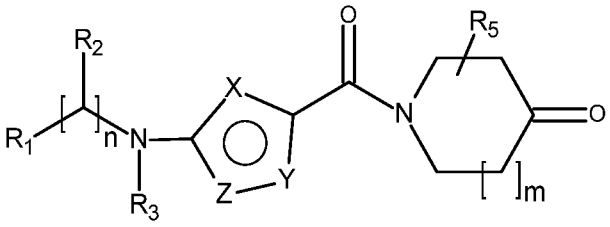
to give compounds of the formula (I-A)



(I-A)

or

[B] compounds of the formula (IV)

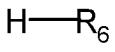


(IV)

in which

X, Y, Z, $R_1$, $R_2$, $R_3$, $R_4$ and $R_5$ and n and m have the definitions given above,

are reacted with compounds of the formula (V)

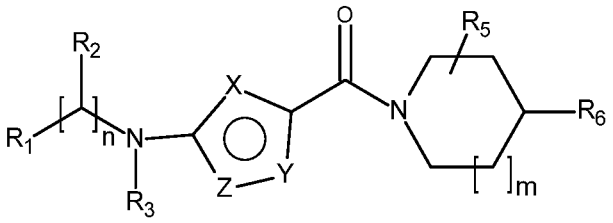


(V)

in which

$R_6$ has the definition given above,

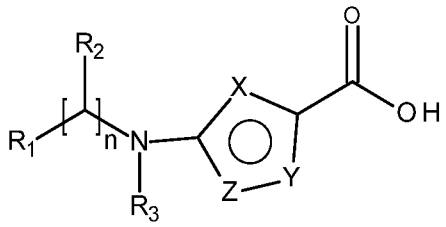
in the presence of a reducing agent and optionally an acid, preferably alkali metal borohydrides and acetic acid, to give compounds of the formula (I-B)



(I-B)

or

[C] compounds of the formula (VI)

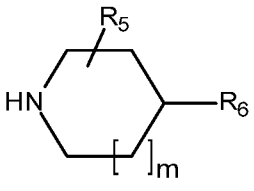


(VI)

in which

X, Y, Z, $R_1$, $R_2$ and $R_3$ and n have the definitions given above,

are reacted with compounds of the formula (VII)

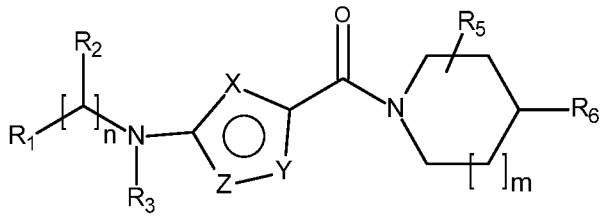


(VII)

in which

$R_5$ and $R_6$ and m have the definitions given above,

in the presence of a condensing or activating agent, preferably a phosphorus compound, to give compounds of the formula (I-C)



(I-C),

and the compounds of the formulae (I-A), (I-B), (I-C) thus obtained are optionally separated into their enantiomers and/or diastereomers and/or optionally converted with the appropriate (*i*) solvents and/or (*ii*) acids to the solvates, salts and/or solvates of the salts thereof.

7. Compound as defined in any of claims 1 to 5 for treatment and/or prevention of diseases.

8. Compound as defined in any of Claims 1 to 5 for use in a method for treatment and/or prevention of breathing difficulties, dysphagia, peripheral and cardiac vascular disorders and disorders of the peripheral and central nervous system.

9. Compound as defined in any of Claims 1 to 5 for use in a method for treatment and/or prevention of breathing difficulties including sleep-induced breathing difficulties such as central and obstructive sleep apnoea, snoring (primary and obstructive snoring), dysphagia, peripheral and cardiac vascular disorders including diabetic microangiopathies and disorders of the peripheral and central nervous system including neurodegenerative and neuroinflammatory disorders.

10. Compound as defined in any of Claims 1 to 5 for use in a method for treatment and/or prevention of breathing difficulties including sleep-induced breathing difficulties such as, *inter alia*, obstructive sleep apnoea (in adults and children), primary snoring, obstructive snoring (upper airway resistance syndrome, heavy snoring, hypopnoea syndrome), central sleep apnoea, Cheyne-Stokes respiration, primary sleep apnoea of infancy, apparent life-threatening event, central sleep apnoea as a result of the use of medicaments or the use of other substances, obesity hypoventilation syndrome, disrupted central respiratory drive, sudden infant death, primary alveolar hypoventilation syndrome, postoperative hypoxia and apnoea, muscular respiratory disorders, respiratory disorders following long-term ventilation, respiratory disorders during adaptation in high mountains, acute and chronic pulmonary diseases with hypoxia and hypercapnia, sleep-related non-obstructive alveolar hypoventilation and the congenital central alveolar hypoventilation syndrome and dysphagia.

11. Compound as defined in any of Claims 1 to 5 for use in a method for treatment and/or prevention of peripheral and cardiac vascular disorders including diabetic microangiopathies, diabetic ulcers at the extremities, in particular for promoting wound healing of diabetic foot ulcers, diabetic heart failure, diabetic coronary microvascular cardiac disorders, peripheral and cardiac vascular disorders, thromboembolic disorders and ischaemias, peripheral circulatory disorders, Raynaud's phenomenon, systemic scleroderma, CREST syndrome, microcirculation disorders and intermittent claudication.

12. Compound as defined in any of Claims 1 to 5 for use in a method for treatment and/or prevention of disorders of the peripheral and central nervous system, including dementia, depression, schizophrenia, attention deficit disorder with or without hyperactivity (ADHS), Tourette's syndrome, post-traumatic stress disorder, obsessive-compulsive disorder, blepharospasm or other focal dystonias, drug-induced psychosis, temporal lobe epilepsy with psychosis, panic disorder, disorders caused by changes in sexual hormones, multiple sclerosis, Alzheimer's disease, Parkinson's disease, Huntington's disease.

13. Medicament comprising a compound as defined in any of Claims 1 to 5 in combination with one or more inert, nontoxic, pharmaceutically suitable excipients.

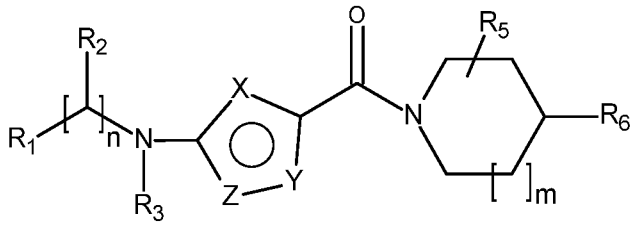
14. Medicament, comprising a compound as defined in any of Claims 1 to 5 in combination with one or more further active compounds selected from the group consisting of respiratory stimulants, psychostimulating compounds, serotonin reuptake inhibitors, noradrenergic, serotonergic and tricyclic antidepressants, P2X3 antagonists, sGC stimulators, mineralocorticoid receptor antagonists, antiinflammatory drugs, immunomodulators, immunosuppressives and cytotoxic drugs.

15. Medicament according to Claim 13 or 14 for treatment and/or prevention of breathing difficulties, including sleep-induced breathing difficulties such as central and obstructive sleep apnoea, snoring (primary and obstructive snoring), dysphagia, peripheral and cardiac vascular disorders, including diabetic microangiopathies and disorders of the peripheral and central nervous system, including neurodegenerative and neuroinflammatory disorders.

16. Method for treatment and/or prevention of breathing difficulties including sleep-induced breathing difficulties such as central and obstructive sleep apnoea, snoring (primary and obstructive snoring), dysphagia, peripheral and cardiac vascular disorders including diabetic microangiopathies and disorders of the peripheral and central nervous system including neurodegenerative and neuroinflammatory disorders in humans and animals by administration of an effective amount of at least one compound as defined in any of Claims 1 to 5, or of a medicament as defined in any of Claims 13 to 15.

AMENDED CLAIMS
received by the International Bureau on 03 February 2025 (03.02.2025)

1. A compound of the general formula (I)



(I)

in which

X is S, N or O;

Z is N, S or O,

where, when X is S, Z is N;

where, when X is O, Z is N;

Y is $CR_4$, O or $NR_4$,

where, when X is N and Z is N, Y is O;

where, when X is S, Y is $CR_4$ or $NR_4$;

$R_1$ is 5- to 10-membered heteroaryl, phenyl, ($C_4$-$C_{10}$)-heterocycloalkyl or ($C_3$-$C_{10}$)-cycloalkyl,

in which 5- to 10-membered heteroaryl may be substituted by 1 to 3 substituents selected independently from the group of ($C_1$-$C_4$)-alkyl, ($C_1$-$C_4$)-alkoxy, halogen;

where ($C_1$-$C_4$)-alkyl may be up to trisubstituted by halogen,

where ($C_1$-$C_4$)-alkoxy may be up to trisubstituted by halogen,

in which phenyl may be substituted by 1 to 2 substituents selected independently from the group of ($C_1$-$C_4$)-alkyl, ($C_3$-$C_5$)-cycloalkyl, ($C_1$-$C_4$)-alkoxy, cyano, hydroxy, halogen;

where ($C_1$-$C_4$)-alkyl may be up to trisubstituted by halogen,

in which ($C_3$-$C_{10}$)-cycloalkyl and ($C_4$-$C_{10}$)-heterocycloalkyl may be substituted by 1 to 2 substituents selected independently from the group of ($C_1$-$C_4$)-alkyl, ($C_3$-$C_5$)-cycloalkyl, ($C_1$-$C_4$)-alkoxy, cyano, hydroxy, halogen;

where ($C_1$-$C_4$)-alkyl may be up to trisubstituted by halogen,

in which ($C_3$-$C_{10}$)-cycloalkyl and ($C_4$-$C_{10}$)-heterocycloalkyl may be fused to 5- to 10-membered heteroaryl,

where 5- to 10-membered heteroaryl may be substituted by 1 to 2 substituents selected independently from the group of ($C_1$-$C_4$)-alkyl, ($C_1$-$C_4$)-alkoxy and halogen;

$R_2$ is hydrogen, ($C_1$-$C_4$)-alkyl or ($C_3$-$C_5$)-cycloalkyl;

in which ($C_1$-$C_4$)-alkyl may be up to trisubstituted by halogen,

in which ($C_1$-$C_4$)-alkyl may be substituted by cyano or ($C_1$-$C_4$)-alkoxy,

in which ($C_3$-$C_5$)-cycloalkyl may be up to trisubstituted by halogen,

or

together with the carbon atom to which $R_2$ is bonded forms a ($C_3$-$C_4$)-cycloalkyl ring,

or

$R_1$ and $R_2$ together form a ($C_5$-$C_8$)-cycloalkyl or ($C_5$-$C_{10}$)-heterocycloalkyl ring,

in which ($C_5$-$C_8$)-cycloalkyl may be fused to 5- to 10-membered heteroaryl,

where 5- to 10-membered heteroaryl may be substituted by 1 to 2 substituents selected independently from the group of ($C_1$-$C_4$)-alkyl, ($C_1$-$C_4$)-alkoxy and halogen;

in which ($C_3$-$C_{10}$)-heterocycloalkyl may be fused to 5- to 10-membered heteroaryl,

where 5- to 10-membered heteroaryl may be substituted by 1 to 2 substituents selected independently from the group of ($C_1$-$C_4$)-alkyl, ($C_1$-$C_4$)-alkoxy and halogen;

$R_3$ is hydrogen, ($C_1$-$C_4$)-alkyl,

in which ($C_1$-$C_4$)-alkyl may be up to trisubstituted by halogen,

$R_4$ in $CR_4$ is hydrogen, ($C_1$-$C_4$)-alkyl, ($C_3$-$C_4$)-cycloalkyl, phenyl, halogen;

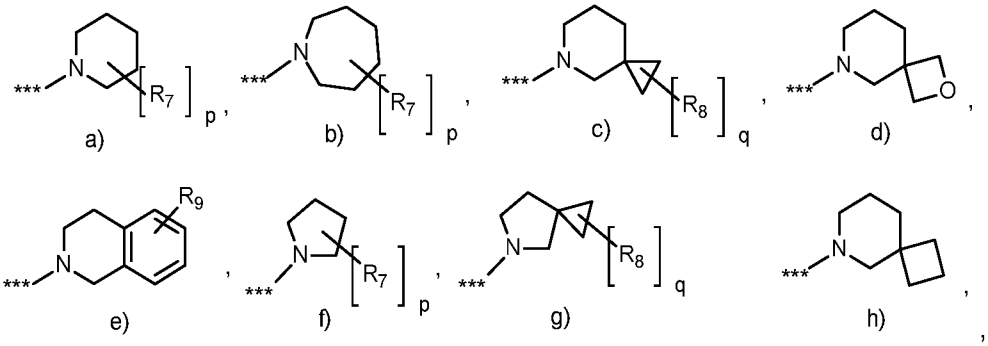
in which ($C_1$-$C_4$)-alkyl may be up to trisubstituted by halogen and phenyl may be substituted by halogen,

in $NR_4$ is absent or is hydrogen, ($C_1$-$C_4$)-alkyl, ($C_3$-$C_4$)-cycloalkyl, phenyl;

in which ($C_1$-$C_4$)-alkyl may be up to trisubstituted by halogen and phenyl may be substituted by halogen,

$R_5$ is hydrogen, ($C_1$-$C_4$)-alkyl, ($C_1$-$C_4$)-alkoxy, halogen,

$R_6$ is a group of formula a), b), c), d), e), f) or g)




in which *** marks the attachment to the adjacent piperidine ring,

in which $R_7$ is hydrogen, ($C_1$-$C_4$)-alkyl, ($C_3$-$C_4$)-cycloalkyl, ($C_1$-$C_4$)-alkoxy, ($C_3$-$C_4$)-cycloalkoxy, phenyl,

where ($C_1$-$C_4$)-alkyl may be substituted by ($C_3$-$C_4$)-cycloalkyl, ($C_1$-$C_4$)-alkoxy, ($C_3$-$C_4$)-cycloalkoxy and up to trisubstituted by halogen,

where ($C_1$-$C_4$)-alkoxy may be substituted by ($C_3$-$C_4$)-cycloalkyl and up to trisubstituted by halogen,

where ($C_3$-$C_4$)-cycloalkyl may be substituted by monofluoromethyl, difluoromethyl or trifluoromethyl and up to disubstituted by halogen,

where ($C_1$-$C_4$)-alkoxy may be substituted by ($C_3$-$C_4$)-cycloalkyl and up to trisubstituted by halogen,

where ($C_3$-$C_4$)-cycloalkyl may be mono- or disubstituted by halogen,

where ($C_3$-$C_4$)-cycloalkoxy may be up to disubstituted by halogen,

in which $R_8$ is hydrogen or fluorine,

in which $R_9$ is hydrogen, ($C_1$-$C_4$)-alkyl, ($C_1$-$C_4$)-alkoxy, halogen;

where ($C_1$-$C_4$)-alkyl may be substituted by ($C_1$-$C_4$)-alkoxy,

n represents 0 or 1,

m represents 0, 1 or 2,

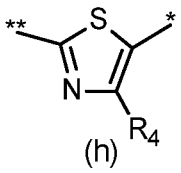
p represents 0, 1 or 2 and

q represents 0, 1 or 2,

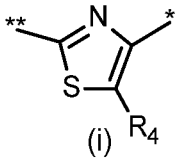
or the salts, solvates or solvates of the salts thereof.

2. Compounds of the formula (I) according to Claim 1, in which

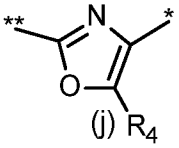
the aromatic 5-membered ring comprising X, Y and Z is chosen from the aromatic 5-membered rings having the structural formulae h), i), j), k), r) and p),



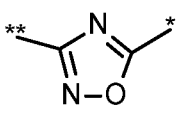
(h) ,



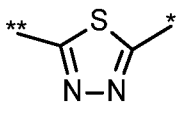
(i) ,



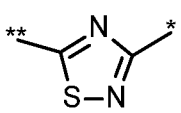
(j) ,



(k) ,



(r)



(p) ,



AMENDED SHEET (ARTICLE 19)

in which * marks the attachment to the carbonyl group and ** the attachment to the nitrogen atom of the adjacent amino group and

$R_1$ is pyridinyl, pyrazolyl, thiazolyl, thienyl, phenyl, tetrahydropyranyl or cyclohexyl,

in which pyridinyl may be substituted by 1 to 2 substituents selected independently from the group of $(C_1$-$C_2)$-alkyl, fluorine, chlorine, trifluoromethyl, trifluoromethoxy,

in which pyrazolyl may be substituted by 1 to 2 substituents selected independently from the group of $(C_1$-$C_2)$-alkyl, fluorine, chlorine, trifluoromethyl,

in which thiazolyl may be substituted by chlorine,

in which thienyl may be substituted by fluorine,

in which phenyl may be substituted by 1 to 2 substituents selected independently from the group of $(C_1$-$C_2)$-alkyl, $(C_3$-$C_4)$-cycloalkyl, methoxy, cyano, hydroxy, fluorine, chlorine, trifluoromethyl,

in which cyclohexyl and tetrahydropyranyl may be fused to pyridyl,

$R_2$ is hydrogen, methyl,

in which methyl may be substituted by cyano or methoxy,

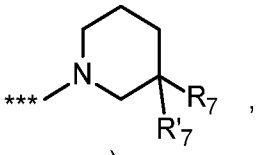
$R_3$ is hydrogen, $(C_1$-$C_2)$-alkyl;

$R_4$ is hydrogen, methyl, ethyl, cyclopropyl, trifluoromethyl, bromine, chlorine, phenyl;

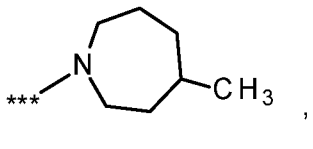
where phenyl may be substituted by chlorine,

$R_5$ is hydrogen, fluorine;

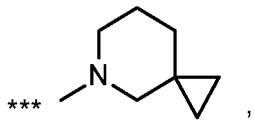
$R_6$ is a group of the formula a), b''), c') or h),



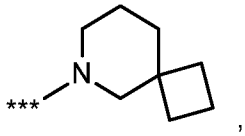

a)




b'')




c')




h)

in which *** marks the attachment to the adjacent piperidine ring,

in which $R_7$ or $R'_7$ is independently hydrogen, $(C_1\text{-}C_4)$-alkyl, $(C_3\text{-}C_4)$-cycloalkyl, $(C_1\text{-}C_2)$-alkoxy, $(C_3\text{-}C_4)$-cycloalkoxy, monofluoromethyl, difluoromethyl, trifluoromethyl, difluoromethoxy, phenyl,

where $(C_1\text{-}C_4)$-alkyl may be substituted by methoxy, n-butoxy, cyclopropyl, cyclobutoxy and up to disubstituted by fluorine,

where methoxy may be substituted by cyclopropyl, cyclobutyl, trifluoromethyl,

where cyclopropyl may be substituted by monofluoromethyl, difluoromethyl, trifluoromethyl,

where cyclopropyl may be up to disubstituted by fluorine,

where n-butoxy may be up to disubstituted by fluorine,

where $(C_1\text{-}C_2)$-alkoxy may be substituted by cyclopropyl, cyclobutyl, cyclobutoxy, trifluoromethyl and

where cyclopropyl and cyclobutyl may be up to disubstituted by fluorine,

where $(C_3\text{-}C_4)$-cycloalkoxy may be up to disubstituted by fluorine,

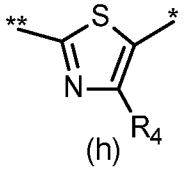
n represents 0 or 1 and

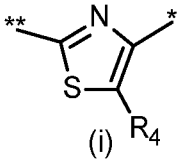
m represents 1 or 2,

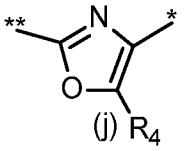
or the salts, solvates or solvates of the salts thereof.

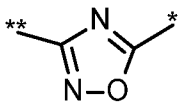
3. Compounds of the formula (I) according to Claim 1, in which

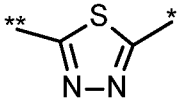
the aromatic 5-membered ring comprising X, Y and Z is chosen from the aromatic 5-membered rings having the structural formulae h), i), j), k), r) and p),

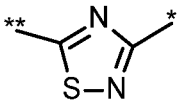

(h)


(i)


(j)


(k)


(r)


(p)

in which * marks the attachment to the carbonyl group and ** the attachment to the nitrogen atom of the adjacent amino group and

$R_1$ is pyridinyl, 2-ethylpyridinyl, 4,6-dimethylpyridinyl, 3,5-difluoropyridinyl, 3-fluoropyridinyl, 4-trifluoromethylpyridinyl, 6-trifluoromethylpyridinyl, 5-chloro-3-fluoropyridinyl, 3-chloro-5-fluoropyridinyl, 3-methylpyridinyl, 4-methylpyridinyl, 6-methylpyridinyl, 3-chloropyridinyl, 5-chloropyridinyl, 6-trifluoromethoxypyridinyl, phenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 3-methoxyphenyl, 4-trifluoromethylphenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 3-hydroxyphenyl, 2,5-difluorophenyl, 5-chloro-2-hydroxyphenyl, 5-fluoro-2-methoxyphenyl, 5-chloro-2-fluorophenyl, 2-chloro-5-fluorophenyl, 2-chloro-4-fluorophenyl, 3-cyano-4-fluorophenyl, 2-cyclopropylphenyl, 4-chloro-1-methyl-1H-pyrazolyl, 5-chloro-1,3-thiazolyl, 5-fluoro-2-thienyl;

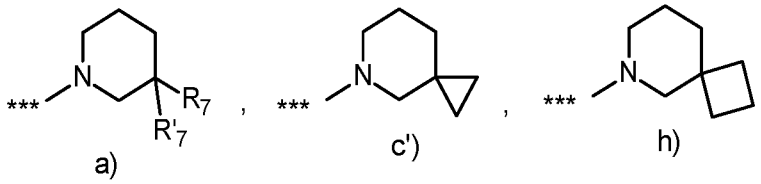
$R_2$ is hydrogen or methyl;

$R_3$ is hydrogen, methyl;

$R_4$ is hydrogen, ethyl or trifluoromethyl;

$R_5$ is hydrogen, methyl or fluorine;

$R_6$ is a group of the formula a), c') or h)




in which *** marks the attachment to the adjacent piperidine ring,

in which $R_7$ and $R'_7$ are independently hydrogen, methyl, ethyl, n-propyl, isopropyl, tert-butyl, 2-fluoroethyl, cyclopropyl, cyclobutyl, cyclopropylmethyl, methoxy, ethoxy, methoxymethyl, monofluoromethyl, difluoromethyl, trifluoromethyl, difluoromethoxy, 3,3-difluorocyclobutylmethoxy, cyclobutylmethoxy, cyclopropylmethoxy, cyclopropylmethoxymethyl, cyclobutyloxymethyl, 3-fluorobutyloxymethyl, 3,3-difluorocyclobutylmethoxymethyl, 2,2,2-trifluoroethoxy, 2,2,2-trifluoroethoxymethyl, 2,2-difluorocyclopropylmethoxy, cyclobutyloxy, 3,3-difluorocyclobutyloxy, fluoromethylcyclopropylmethoxy, difluoromethylcyclopropylmethoxy, trifluoromethylcyclopropylmethoxy, fluorine;

n represents 1 and

m represents 1,

or the salts, solvates or solvates of the salts thereof.

4. Compounds of the formula (I) according to Claim 1, in which

the aromatic 5-membered ring comprising X, Y and Z is chosen from 1,3-thiazolyl, 1,3-oxazolyl, and 1,2,4-oxadiazolyl;

$R_1$ is pyridinyl, 2-ethylpyridinyl, 4,6-dimethylpyridinyl, 3,5-difluoropyridinyl, 3-fluoropyridinyl, 4-trifluoromethylpyridinyl, 6-trifluoromethylpyridinyl, 5-chloro-3-fluoropyridinyl, 3-chloro-5-fluoropyridinyl, 3-methylpyridinyl, 4-methylpyridinyl, 6-methylpyridinyl, 3-chloropyridinyl, 5-chloropyridinyl, 6-trifluoromethoxypyridinyl, phenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 3-methoxyphenyl, 4-trifluoromethylphenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2-fluorophenyl, 3-fluorophenyl, 4-

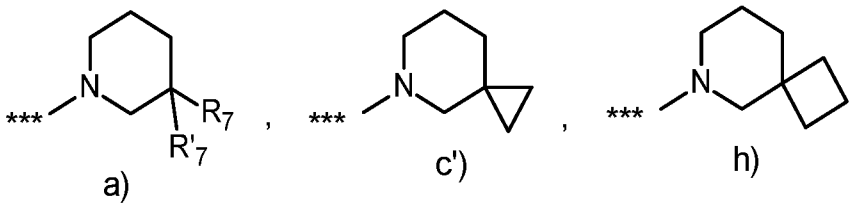
fluorophenyl, 3-hydroxyphenyl, 2,5-difluorophenyl, 5-chloro-2-hydroxyphenyl, 5-fluoro-2-methoxyphenyl, 5-chloro-2-fluorophenyl, 2-chloro-5-fluorophenyl, 2-chloro-4-fluorophenyl, 3-cyano-4-fluorophenyl, 2-cyclopropylphenyl, 4-chloro-1-methyl-1H-pyrazolyl, 5-chloro-1,3-thiazolyl, 5-fluoro-2-thienyl;

$R_2$ is hydrogen or methyl;

$R_3$ is hydrogen, methyl;

$R_5$ is hydrogen, methyl or fluorine;

$R_6$ is a group of the formula a), or c') or h)




in which *** marks the attachment to the adjacent piperidine ring,

in which $R_7$ and $R'_7$ are independently hydrogen, methyl, ethyl, n-propyl, isopropyl, tert-butyl, 2-fluoroethyl, cyclopropyl, cyclobutyl, cyclopropylmethyl, methoxy, ethoxy, methoxymethyl, monofluoromethyl, difluoromethyl, trifluoromethyl, difluoromethoxy, 3,3-difluorocyclobutylmethoxy, cyclobutylmethoxy, cyclopropylmethoxy, cyclopropylmethoxymethyl, cyclobutyloxymethyl, 3-fluorobutyloxymethyl, 3,3-difluorocyclobutylmethoxymethyl, 2,2,2-trifluoroethoxy, 2,2,2-trifluoroethoxymethyl, 2,2-difluorocyclopropylmethoxy, cyclobutyloxy, 3,3-difluorocyclobutyloxy, fluoromethylcyclopropylmethoxy, difluoromethylcyclopropylmethoxy, trifluoromethylcyclopropylmethoxy, fluorine;

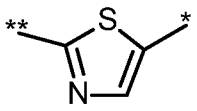
n represents 1 and

m represents 1,

or the salts, solvates or solvates of the salts thereof.

5. Compounds of the formula (I) according to Claim 1, in which

the aromatic 5-membered ring comprising X, Y and Z is the aromatic 5-membered ring having the structural formula h'),



(h')

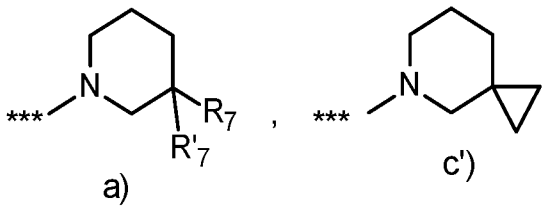
$R_1$ is pyridinyl, 2-ethylpyridinyl, 4,6-dimethylpyridinyl, 3,5-difluoropyridinyl, 3-fluoropyridinyl, 4-trifluoromethylpyridinyl, 6-trifluoromethylpyridinyl, 5-chloro-3-fluoropyridinyl, 3-chloro-5-fluoropyridinyl, 3-methylpyridinyl, 4-methylpyridinyl, 6-methylpyridinyl, 3-chloropyridinyl, 5-chloropyridinyl, 6-trifluoromethoxypyridinyl, phenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 3-methoxyphenyl, 4-trifluoromethylphenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 3-hydroxyphenyl, 2,5-difluorophenyl, 5-chloro-2-hydroxyphenyl, 5-fluoro-2-methoxyphenyl, 5-chloro-2-fluorophenyl, 2-chloro-5-fluorophenyl, 2-chloro-4-fluorophenyl, 3-cyano-4-fluorophenyl, 2-cyclopropylphenyl, 4-chloro-1-methyl-1H-pyrazolyl, 5-chloro-1,3-thiazolyl, 5-fluoro-2-thienyl;

$R_2$ is hydrogen or methyl;

$R_3$ is hydrogen or methyl;

$R_5$ is hydrogen, fluorine;

$R_6$ is a group of the formula a) or c')



a) c')

in which *** marks the attachment to the adjacent piperidine ring,

in which $R_7$ and $R'_7$ are independently hydrogen, methyl, ethyl, n-propyl, isopropyl, tert-butyl, 2-fluoroethyl, cyclopropyl, cyclobutyl, cyclopropylmethyl, methoxy, ethoxy, methoxymethyl, monofluoromethyl, difluoromethyl, trifluoromethyl, difluoromethoxy, 3,3-difluorocyclobutylmethoxy, cyclobutylmethoxy, cyclopropylmethoxy, cyclopropylmethoxymethyl, cyclobutyloxymethyl, 3-fluorobutyloxymethyl, 3,3-difluorocyclobutylmethoxymethyl, 2,2,2-trifluoroethoxy, 2,2,2-trifluoroethoxymethyl, 2,2-difluorocyclopropylmethoxy, cyclobutyloxy, 3,3-difluorocyclobutyloxy, fluoromethylcyclopropylmethoxy, difluoromethylcyclopropylmethoxy, trifluoromethylcyclopropylmethoxy, fluorine;

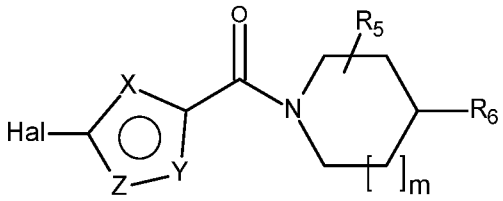
n represents 1 and

m represents 1,

or the salts, solvates or solvates of the salts thereof.

6. Process for preparing the compounds of the formula (I) or salts thereof, solvates thereof or solvates of the salts thereof, where

[A] compounds of the formula (II)



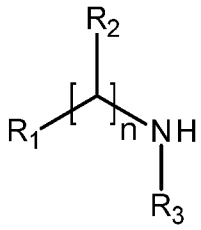

(II)

in which

X, Y, Z, $R_5$, $R_6$, and m have definitions given above,

Hal is a leaving group, preferably chlorine, bromine, iodine, or methylsulfonyl,

are reacted in the presence of a base with compounds of the formula (III)

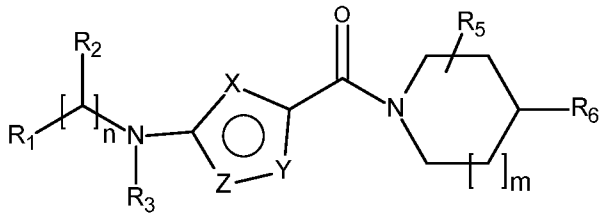


(III)

in which

$R_1$, $R_2$ and $R_3$ and n have the definitions given above,

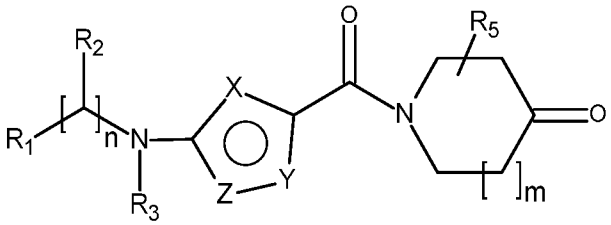
to give compounds of the formula (I-A)



(I-A)

or

[B] compounds of the formula (IV)

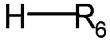


(IV)

in which

X, Y, Z, $R_1$, $R_2$, $R_3$, $R_4$ and $R_5$ and n and m have the definitions given above,

are reacted with compounds of the formula (V)

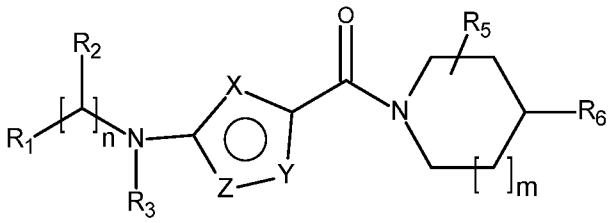


(V)

in which

$R_6$ has the definition given above,

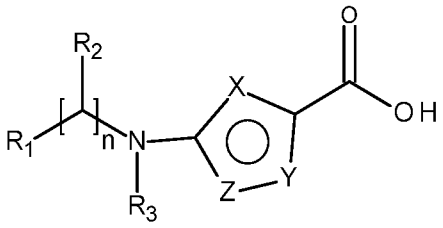
in the presence of a reducing agent and optionally an acid, preferably alkali metal borohydrides and acetic acid, to give compounds of the formula (I-B)



(I-B)

or

[C] compounds of the formula (VI)

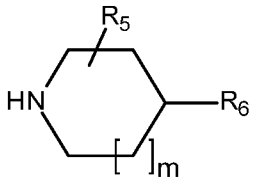


(VI)

in which

X, Y, Z, $R_1$, $R_2$ and $R_3$ and n have the definitions given above,

are reacted with compounds of the formula (VII)

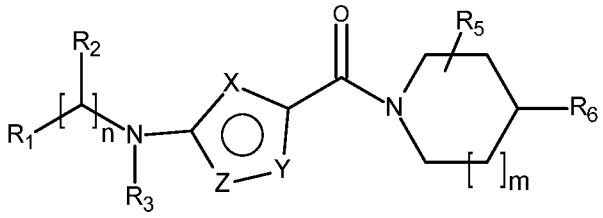


(VII)

in which

$R_5$ and $R_6$ and m have the definitions given above,

in the presence of a condensing or activating agent, preferably a phosphorus compound, to give compounds of the formula (I-C)



(I-C),

and the compounds of the formulae (I-A), (I-B), (I-C) thus obtained are optionally separated into their enantiomers and/or diastereomers and/or optionally converted with the appropriate (*i*) solvents and/or (*ii*) acids to the solvates, salts and/or solvates of the salts thereof.

7. Compound as defined in any of claims 1 to 5 for treatment and/or prevention of diseases.

8. Compound as defined in any of Claims 1 to 5 for use in a method for treatment and/or prevention of breathing difficulties, dysphagia, peripheral and cardiac vascular disorders and disorders of the peripheral and central nervous system.

9. Compound as defined in any of Claims 1 to 5 for use in a method for treatment and/or prevention of breathing difficulties including sleep-induced breathing difficulties such as central and obstructive sleep apnoea, snoring (primary and obstructive snoring), dysphagia, peripheral and cardiac vascular disorders including diabetic microangiopathies and disorders of the peripheral and central nervous system including neurodegenerative and neuroinflammatory disorders.

10. Compound as defined in any of Claims 1 to 5 for use in a method for treatment and/or prevention of breathing difficulties including sleep-induced breathing difficulties such as, *inter alia*, obstructive sleep apnoea (in adults and children), primary snoring, obstructive snoring (upper airway resistance syndrome, heavy snoring, hypopnoea syndrome), central sleep apnoea, Cheyne-Stokes respiration, primary sleep apnoea of infancy, apparent life-threatening event, central sleep apnoea as a result of the use of medicaments or the use of other substances, obesity hypoventilation syndrome, disrupted central respiratory drive, sudden infant death, primary alveolar hypoventilation syndrome, postoperative hypoxia

and apnoea, muscular respiratory disorders, respiratory disorders following long-term ventilation, respiratory disorders during adaptation in high mountains, acute and chronic pulmonary diseases with hypoxia and hypercapnia, sleep-related non-obstructive alveolar hypoventilation and the congenital central alveolar hypoventilation syndrome and dysphagia.

11. Compound as defined in any of Claims 1 to 5 for use in a method for treatment and/or prevention of peripheral and cardiac vascular disorders including diabetic microangiopathies, diabetic ulcers at the extremities, in particular for promoting wound healing of diabetic foot ulcers, diabetic heart failure, diabetic coronary microvascular cardiac disorders, peripheral and cardiac vascular disorders, thromboembolic disorders and ischaemias, peripheral circulatory disorders, Raynaud's phenomenon, systemic scleroderma, CREST syndrome, microcirculation disorders and intermittent claudication.

12. Compound as defined in any of Claims 1 to 5 for use in a method for treatment and/or prevention of disorders of the peripheral and central nervous system, including dementia, depression, schizophrenia, attention deficit disorder with or without hyperactivity (ADHS), Tourette's syndrome, post-traumatic stress disorder, obsessive-compulsive disorder, blepharospasm or other focal dystonias, drug-induced psychosis, temporal lobe epilepsy with psychosis, panic disorder, disorders caused by changes in sexual hormones, multiple sclerosis, Alzheimer's disease, Parkinson's disease, Huntington's disease.

13. Medicament comprising a compound as defined in any of Claims 1 to 5 in combination with one or more inert, nontoxic, pharmaceutically suitable excipients.

14. Medicament, comprising a compound as defined in any of Claims 1 to 5 in combination with one or more further active compounds selected from the group consisting of respiratory stimulants, psychostimulating compounds, serotonin reuptake inhibitors, noradrenergic, serotonergic and tricyclic antidepressants, P2X3 antagonists, sGC stimulators, mineralocorticoid receptor antagonists,

antiinflammatory drugs, immunomodulators, immunosuppressives and cytotoxic drugs.

15. Medicament according to Claim 13 or 14 for treatment and/or prevention of breathing difficulties, including sleep-induced breathing difficulties such as central and obstructive sleep apnoea, snoring (primary and obstructive snoring), dysphagia, peripheral and cardiac vascular disorders, including diabetic microangiopathies and disorders of the peripheral and central nervous system, including neurodegenerative and neuroinflammatory disorders.

16. Method for treatment and/or prevention of breathing difficulties including sleep-induced breathing difficulties such as central and obstructive sleep apnoea, snoring (primary and obstructive snoring), dysphagia, peripheral and cardiac vascular disorders including diabetic microangiopathies and disorders of the peripheral and central nervous system including neurodegenerative and neuroinflammatory disorders in humans and animals by administration of an effective amount of at least one compound as defined in any of Claims 1 to 5, or of a medicament as defined in any of Claims 13 to 15.

# INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2024/077295

**A. CLASSIFICATION OF SUBJECT MATTER**

INV. A61P9/00 A61P11/00 A61P25/28 A61P29/00 A61P43/00
C07D413/14 C07D417/14 C07D491/052
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)
C07D

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

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

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

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

[x] See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

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

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"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 20 November 2024 | 02/12/2024 |

| Name and mailing address of the ISA/ | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040,<br>Fax: (+31-70) 340-3016 | Bedel, Christian |

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# INTERNATIONAL SEARCH REPORT

International application No
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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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**Information on patent family members**

**International application No**
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