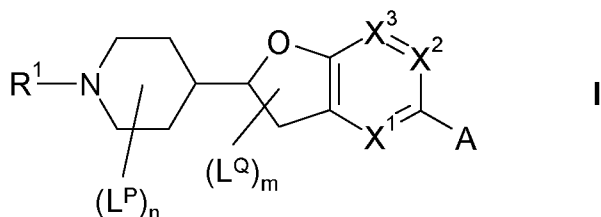


# FUSED DIHYDROFURANS AS GPR119 MODULATORS FOR THE TREATMENT OF DIABETES, OBESITY AND RELATED DISORDERS

## Field of the invention

The present invention relates to new compounds, in particular compounds of the formula I



wherein the groups  $R^1$ ,  $L^P$ ,  $L^Q$ ,  $X^1$ ,  $X^2$ ,  $X^3$ ,  $A$ ,  $n$  and  $m$  are defined as hereinafter, to processes for preparing such compounds, to pharmaceutical compositions, to their use as modulators of the G-protein-coupled receptor GPR119, to methods for their therapeutic use, in particular in diseases and conditions mediated by the modulation of the G-protein-coupled receptor GPR119, and to pharmaceutical compositions comprising them.

## Background of the invention

Diabetes mellitus is a serious metabolic disease which affects more than 100 million people worldwide. In the USA there are more than 12 million diabetics with 600,000 new cases diagnosed every year. The prevalence of diabetes mellitus is increasing, which means in particular a high frequency of complications as well, leading to a substantial impairment of quality of life and life expectancy. Because of diabetes-associated microvascular complications, in the industrialised countries type 2 diabetes is currently the most common cause of adult-onset loss of vision, renal insufficiency and amputations. In addition, type 2 diabetes is associated with a two- to five-fold increase in the risk of cardiovascular disease.

The UKPDS study (United Kingdom Prospective Diabetes Study) showed that intensive treatment with common therapeutic agents, e.g. metformin, sulphonylureas or insulin, results in only a limited improvement in glycaemic control (difference in the HbA1c value  $\sim 0.9\%$ ). Moreover, glycaemic control deteriorated considerably over

time even in patients in the intensive treatment group, and this was put down to a deterioration in beta cell function. Diabetes is also a major cause of damage to the retina at the back of the eye and increases the risk of cataract and glaucoma.

Finally, diabetes is associated with nerve damage, particularly in the legs and feet,

5 which affects the patient's ability to feel pain and contributes to serious infections. All in all, complications of diabetes are one of the major causes of death worldwide.

Adiposity (obesity) is the result of an imbalance between calorie intake and energy consumption. It correlates to a high degree with insulin resistance and diabetes.

10 However, the molecular mechanisms that are involved in obesity/diabetes syndromes are not yet clear. At an early stage of the development of obesity, an increased insulin secretion balances out the insulin resistance and protects the patient from hyperglycaemia. However, after a time, the beta cell function worsens and non-insulin-dependent diabetes develops in about 20% of the obese population. Obesity  
15 has thus become a critical risk factor for diabetes, but the factors that predispose one group of patients to a pathological change in insulin secretion as a response to the accumulation of fat are currently unknown. Obesity also significantly increases the risk of the development of cardiovascular disease. Diabetes is also implicated in the formation of kidney complaints, eye complaints and problems of the nervous system.  
20 Kidney disease, also known as nephropathy, sets in when the filtering mechanism of the kidneys is disrupted and proteins escape into the urine in excessive amounts and finally the kidney fails. Therefore there is a medical need for medicaments for preventing and/or treating metabolic disorders (particularly diabetes, predominantly type 2 diabetes) and the complications thereof. In particular there is a need for  
25 medicaments with good activity in terms of glycaemic control, disease-modifying properties and reducing cardiovascular morbidity and mortality, and which also have a better safety profile.

Dyslipidemia is a disorder of lipoprotein metabolism, including lipoprotein

30 overproduction or deficiency. Dyslipidemias may be manifested by elevation of the total cholesterol, LDL cholesterol and triglyceride and free fatty acid concentrations, and a decrease in high-density lipoprotein (HDL) cholesterol concentration in the blood. Dyslipidemia occurs often in situations including diabetes, a common cause of

lipidemia. For adults with diabetes, it has been recommended that the levels of LDL, HDL, and total cholesterol, and triglyceride be measured every year. Optimal LDL cholesterol levels for adults with diabetes are less than 100 mg/dL (2.60 mmol/L), optimal HDL cholesterol levels are equal to or greater than 40 mg/dL (1.02 mmol/L), and desirable triglyceride levels are less than 150 mg/dL (1.7 mmol/L).

GPR119 is a G-protein coupled receptor (also known as GPCR2, RUP3, SNORF25 or GDIR) which is expressed predominantly in the beta cells of the pancreas and in the K- and L-cells of the intestine. The GPR119 receptor and isoforms have been identified in mammalian species including human, rat, mouse, hamster, chimpanzee, rhesus monkey, cattle and dog. The expression of GPR119 in the pancreas and particularly in the pancreatic  $\beta$ -cells led to the hypothesis that the GPR119 receptor could have effects upon insulin secretion. Activation of the receptor stimulates the cAMP signal pathway, increasing the intracellular levels of cAMP in these cells. This will lead to an improved diabetic situation by a dual action of such a compound: stimulation of cAMP in the beta cell occurs directly via activation of GPR119 in these cells and furthermore indirectly via stimulation of the release of neuroendocrine peptides like GIP and GLP-1 and PYY from the gut. The release of these peptides may have also additional beneficial effects, e.g. on food intake, gastric emptying and other yet unknown functions. Also, a GPR119 agonist can be expected to bring about an improvement in the beta cell function and the beta cell mass. In fact, activation of GPR119 stimulates insulin secretion in-vitro and in-vivo (in rodents) in a glucose-dependent manner. The discovery of two endogenous ligands, lysophosphatidylcholine (LPC) and oleoylethanolamide (OEA) as well as more potent GPR119 agonists have led to the characterization of GPR119 as both an insulin and incretin (GLP-1 and GIP) secretagogue receptor capable of lowering plasma glucose and thereby facilitating glycemic control without the risk of hypoglycemia (Biochem. Biophys. Res. Comm. 2005, 744-751; Cell Metabolism 2006, 167-175; Endocrinology 2007, 2601-9). It has recently been shown that GPR119 agonists effectively lower the blood glucose levels in diabetic rodents without the risk of hypoglycaemia. GPR119 knockout animals have shown that both insulin and incretin secretion induced by GPR119 agonists are dependent upon GPR119 receptor. In addition, it has been shown that GPR119 agonists decrease food intake resulting in weight loss

in Sprague Dawley rats. Therefore the GPR119 agonists may be expected to have a therapeutic benefit in metabolic diseases. Examples of such diseases include type 1 diabetes, type 2 diabetes, insufficient glucose tolerance, insulin resistance, hyperglycaemia, hyperlipidaemia, hypercholesterolaemia, dyslipidaemia, syndrome X, metabolic syndrome, obesity, high blood pressure, chronic systemic inflammation, retinopathy, neuropathy, nephropathy, atherosclerosis, endothelial dysfunction and bone-related diseases (such as osteoporosis, rheumatoid arthritis or osteoarthritis). For comparison and additional information also see

1. Dhayal, S., Morgan, N. G. The significance of GPR119 agonists as a future treatment for type 2 diabetes. *Drug News Perspect.* 2010, 23(7), 418-24.
2. Yoshida, S., Tanaka, H., Oshima, H., Yamazaki, T., Yonetoku, Y., Ohishi, T., Matsui, T., Shibasaki, M. AS1907417, a novel GPR119 agonist, as an insulinotropic and  $\beta$ -cell preservative agent for the treatment of type 2 diabetes. *Biochem Biophys Res Commun.* 2010, 400(4), 745-51.
3. Jones, R. M., Leonard, J. N., Buzard, D. J., Lehman, J. GPR119 agonists for the treatment of type 2 diabetes. *Expert Opinion on Therapeutic Patents* 2009, Vol. 19, No. 10: 1339-1359.

### **Aim of the present invention**

The aim of the present invention is to provide new compounds, in particular new 2,3-dihydro-benzofuran-2-yl-piperidine derivatives, which are active with regard to the G-protein-coupled receptor GPR119.

Another aim of the present invention is to provide new compounds, in particular new 2,3-dihydro-benzofuran-2-yl-piperidine derivatives, which are agonists of the G-protein-coupled receptor GPR119.

A further aim of the present invention is to provide new compounds, in particular new 2,3-dihydro-benzofuran-2-yl-piperidine derivatives, which have an activating effect on the G-protein-coupled receptor GPR119 *in vitro* and/or *in vivo* and possess suitable pharmacological and pharmacokinetic properties to use them as medicaments.

A further aim of the present invention is to provide effective GPR119 agonists, in particular for the treatment of metabolic disorders, for example diabetes, dyslipidemia and/or obesity.

- 5 A further aim of the present invention is to provide methods for treating a disease or condition mediated by the activation the G-protein-coupled receptor GPR119 in a patient.

- 10 A further aim of the present invention is to provide a pharmaceutical composition comprising at least one compound according to the invention.

A further aim of the present invention is to provide a combination of at least one compound according to the invention with one or more additional therapeutic agents.

- 15 A further aim of the present invention is to provide methods for the synthesis of the new compounds, in particular 2,3-dihydro-benzofuran-2-yl-piperidine derivatives.

A further aim of the present invention is to provide starting and/or intermediate compounds suitable in methods for the synthesis of the new compounds.

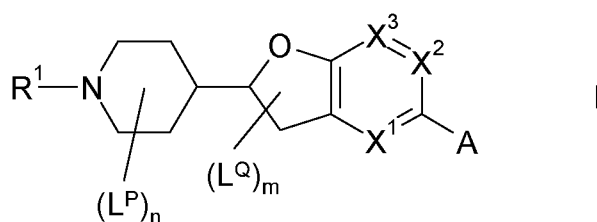
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Further aims of the present invention become apparent to the one skilled in the art by the description hereinbefore and in the following and by the examples.

## 25 **Object of the Invention**

It has now been found that the compounds according to the invention described in more detail hereinafter have surprising and particularly advantageous properties, and in particular as GPR119 agonists.

- 30 In a first aspect the invention thus relates to a compound of formula I



wherein

$R^1$  is selected from the group  $R^1$ -G1 consisting of a 5- or 6-membered  
 5 heteroaromatic ring which contains 1, 2 or 3 heteroatoms independently of  
 each other selected from N, O and S; and wherein optionally a second ring  
 may be condensed to said heteroaromatic ring, wherein said second ring is  
 unsaturated or aromatic and 5- or 6-membered and may contain 1, 2 or 3  
 heteroatoms independently of each other selected from N, O and S, and  
 10 wherein in said second ring 1 or 2  $-CH_2$ -groups may be optionally replaced  
 by  $-N(R^N)-$ ,  $-C(=O)-$ ,  $-S(=O)-$  or  $-S(=O)_2-$ , and

wherein in said heteroaromatic ring and/or said second ring the H-atom in  
 one or more NH groups may be optionally replaced by  $R^N$ , and

15 wherein each of said heteroaromatic ring and/or second ring independently of  
 each other may be optionally substituted with one or more substituents  
 selected from  $L^A$ ; and

20 wherein said heteroaromatic ring or said second ring may be optionally  
 substituted with a group  $R^C$ ; and

$R^N$  independently of each other is selected from the group  $R^N$ -G1 consisting of  
 H,  $C_{1-4}$ -alkyl,  $C_{1-4}$ -alkyl- $C(=O)-$ , and  $C_{1-4}$ -alkyl- $S(=O)_2-$ ; and

A is selected from the group A-G1 consisting of a 1,2,3,6-tetrahydropyridin-4-yl  
 ring substituted at the N with  $C_{1-4}$ -alkyl- $S(=O)_2-$ , a phenyl ring, and a 5- or 6-  
 membered heteroaromatic ring which contains 1, 2 or 3 heteroatoms  
 independently of each other selected from N, O and S; and wherein  
 30 optionally a second ring may be condensed to said phenyl ring or

heteroaromatic ring, wherein said second ring is unsaturated or aromatic and 5- or 6-membered and may contain 1, 2 or 3 heteroatoms independently of each other selected from N, O and S, and wherein in said second ring 1 or 2 -CH<sub>2</sub>-groups may be optionally replaced by -N(R<sup>N</sup>)-, -C(=O)-, -S(=O)- or -S(=O)<sub>2</sub>-, and

wherein in said heteroaromatic ring and/or said second ring the H-atom in one or more NH groups may be optionally replaced by R<sup>N</sup>, and

wherein each of said phenyl ring, heteroaromatic ring and/or second ring independently of each other may be optionally substituted with one or more substituents selected from L<sup>A</sup>; and

wherein said phenyl ring, heteroaromatic ring or second ring may be optionally substituted with a group T; and

T is selected from the group T-G1 consisting of F, Cl, Br, I, CN, OH, NO<sub>2</sub>, C<sub>1-6</sub>-alkyl-, C<sub>1-6</sub>-alkenyl-, C<sub>1-6</sub>-alkynyl-, C<sub>3-6</sub>-cycloalkyl, C<sub>1-6</sub>-alkyl-O-, C<sub>3-6</sub>-cycloalkyl-O-, C<sub>1-6</sub>-alkyl-S-, HO-C(=O)-, C<sub>1-6</sub>-alkyl-O-C(=O)-, C<sub>1-4</sub>-alkyl-C(=O)-, C<sub>3-6</sub>-cycloalkyl-C(=O)-, C<sub>1-4</sub>-alkyl-S(=O)-, C<sub>1-4</sub>-alkyl-S(=O)<sub>2</sub>-, R<sup>NT1</sup>R<sup>NT2</sup>N-, R<sup>NT1</sup>R<sup>NT2</sup>N-C(=O)-, R<sup>NT1</sup>R<sup>NT2</sup>N-S(=O)<sub>2</sub>-, R<sup>NT1</sup>R<sup>NT2</sup>N-C(=O)-(R<sup>N</sup>)N-, heterocyclyl, heterocyclyl-O-, aryl, aryl-O-, heteroaryl and heteroaryl-O-, wherein each alkyl, alkenyl, alkynyl, and cycloalkyl group may be optionally substituted with one or more substituents independently of each other selected from F, Cl, CN, OH, C<sub>1-3</sub>-alkyl, C<sub>3-6</sub>-cycloalkyl, C<sub>1-3</sub>-alkyl-O-, R<sup>NT1</sup>R<sup>NT2</sup>N-, R<sup>NT1</sup>R<sup>NT2</sup>N-C(=O)-, C<sub>1-4</sub>-alkyl-S(=O)-, C<sub>1-4</sub>-alkyl-S(=O)<sub>2</sub>-, R<sup>NT1</sup>R<sup>NT2</sup>N-S(=O)<sub>2</sub>-, aryl, heteroaryl, and heterocyclyl, and

wherein aryl denotes phenyl or naphthyl, and

wherein heteroaryl is a 5- or 6-membered aromatic ring which contains 1, 2, 3 or 4 heteroatoms independently of each other selected from N, O and S, wherein the H-atom in one or more NH groups may be optionally replaced by

$R^N$ ; and

wherein heterocyclyl is a 4- to 7-membered unsaturated or saturated carbocyclic ring in which 1 or 2  $-CH_2$ -groups independently of each other are replaced by  $NR^N$ , O,  $-C(=O)-$ , S,  $-S(=O)-$  or  $-S(=O)_2-$ , and/or in which a  $-CH-$  group is replaced by N; and

wherein each aryl, heteroaryl or heterocyclyl group may be optionally substituted with one or more substituents independently of each other selected from  $L^A$ ; and

$R^{NT1}$  is selected from the group  $R^{NT1}$ -G1 consisting of H,  $C_{1-6}$ -alkyl,  $C_{3-6}$ -cycloalkyl,  $C_{1-6}$ -alkyl- $C(=O)-$ ,  $C_{1-6}$ -alkyl- $S(=O)_2$ , heterocyclyl, aryl and heteroaryl,

wherein each alkyl and cycloalkyl group may be optionally substituted with one or more substituents independently of each other selected from the group consisting of F, OH, CN,  $C_{1-4}$ -alkyl,  $C_{1-4}$ -alkyl-O-,  $R^N_2N$ ,  $C_{1-4}$ -alkyl- $S(=O)_2$ ,  $C_{3-6}$ -cycloalkyl, heterocyclyl, phenyl and heteroaryl; and

wherein heterocyclyl may be optionally substituted with one or more substituents independently of each other selected from F,  $C_{1-4}$ -alkyl,  $R^N_2N$ , OH and  $C_{1-4}$ -alkyl-O-; and

wherein heterocyclyl is a  $C_{4-7}$ -cycloalkyl ring in which 1 or 2  $-CH_2$ -groups independently of each other are replaced by  $NR^N$ , O,  $C(=O)$ , S,  $S(=O)$  or  $S(=O)_2$ ; and

wherein aryl is phenyl or naphthyl; and

wherein heteroaryl is a 5- or 6-membered aromatic ring which contains 1, 2 or 3 heteroatoms independently of each other selected from N, O and S, wherein the H-atom in one or more NH groups may be optionally replaced by  $R^N$ ; and

wherein aryl and heteroaryl may be optionally substituted with one or more substituents  $L^A$ ; and

5  $R^{NT2}$  is selected from the group  $R^{NT2}$ -G1 consisting of H and  $C_{1-6}$ -alkyl; or

$R^{NT1}$  and  $R^{NT2}$  are linked to form one group selected from the group  $R^{NT1}R^{NT2}$ -G1 consisting of a  $C_{3-5}$ -alkylene group, wherein 1 or 2  $-CH_2$ -groups independently of each other are replaced by  $NR^N$ , O,  $C(=O)$ , S,  $S(=O)$  or  $S(=O)_2$ ; and which may be optionally substituted with one or more substituents independently of each other selected from F,  $C_{1-4}$ -alkyl,  $(R^N)_2N$ , OH and  $C_{1-4}$ -alkyl-O-;

15  $L^A$  is selected from the group  $L^A$ -G1 consisting of F, Cl, Br, CN, OH,  $NO_2$ ,  $C_{1-4}$ -alkyl-,  $C_{1-4}$ -alkyl-O-,  $(R^N)_2N-C(=O)$ ,  $(R^N)_2N$ -, and  $C_{1-4}$ -alkyl- $S(=O)_2$ -, wherein each alkyl group may be optionally substituted with one or more substituents independently of each other selected from F, Cl, CN, OH and  $C_{1-3}$ -alkyl-O-; and

20  $L^P$  is selected from the group  $L^P$ -G1 consisting of F and  $C_{1-3}$ -alkyl, wherein the alkyl group may be substituted with one or more F-atoms; and

$L^Q$  is selected from the group  $L^Q$ -G1 consisting of F and  $C_{1-3}$ -alkyl, wherein the alkyl group may be substituted with one or more F-atoms; and

25  $R^C$  is selected from the group  $R^C$ -G1 consisting of F, Cl, Br, I, CN, OH,  $NO_2$ ,  $C_{1-6}$ -alkyl-,  $C_{1-6}$ -alkenyl-,  $C_{1-6}$ -alkynyl-,  $C_{3-6}$ -cycloalkyl,  $C_{1-6}$ -alkyl-O-,  $C_{3-6}$ -cycloalkyl-O-,  $C_{1-6}$ -alkyl-S-,  $HO-C(=O)$ -,  $C_{1-6}$ -alkyl-O- $C(=O)$ -,  $C_{1-4}$ -alkyl- $C(=O)$ -,  $C_{3-6}$ -cycloalkyl- $C(=O)$ -,  $C_{1-4}$ -alkyl- $S(=O)$ -,  $C_{1-4}$ -alkyl- $S(=O)_2$ -,  $R^{NT1}R^{NT2}N$ -,  $R^{NT1}R^{NT2}N-C(=O)$ -,  $R^{NT1}R^{NT2}N-S(=O)_2$ -,  $R^{NT1}R^{NT2}N-C(=O)-(R^N)N$ -,  
 30 heterocyclyl, heterocyclyl-O-, aryl, aryl-O-, heteroaryl and heteroaryl-O-, wherein each alkyl, alkenyl, alkynyl, and cycloalkyl group may be optionally substituted with one or more substituents independently of each other

selected from F, Cl, CN, OH, C<sub>1-3</sub>-alkyl, C<sub>3-6</sub>-cycloalkyl, C<sub>1-3</sub>-alkyl-O-,  
 $R^{NT1}R^{NT2}N-$ ,  $R^{NT1}R^{NT2}N-C(=O)-$ , C<sub>1-4</sub>-alkyl-S(=O)-, C<sub>1-4</sub>-alkyl-S(=O)<sub>2</sub>-,  
 $R^{NT1}R^{NT2}N-S(=O)_2-$ , aryl, heteroaryl, and heterocyclyl, and

5 wherein aryl denotes phenyl or naphthyl, and

wherein heteroaryl is a 5- or 6-membered aromatic ring which contains 1, 2,  
 3 or 4 heteroatoms independently of each other selected from N, O and S,  
 wherein the H-atom in one or more NH groups may be optionally replaced by  
 10  $R^N$ ; and

wherein heterocyclyl is a 4- to 7-membered unsaturated or saturated  
 carbocyclic ring in which 1 or 2 -CH<sub>2</sub>-groups independently of each other are  
 replaced by  $NR^N$ , O, -C(=O)-, S, -S(=O)- or -S(=O)<sub>2</sub>-, and/or in which a -CH-  
 15 group is replaced by N; and

wherein each aryl, heteroaryl or heterocyclyl group may be optionally  
 substituted with one or more substituents independently of each other  
 selected from  $L^A$ ; and

20  $X^1$ ,  $X^2$ ,  $X^3$  are independently selected from the group X-G1 consisting of C( $R^2$ )  
 and N, such that 0, 1 or 2 members of the group consisting of  $X^1$ ,  $X^2$ , and  $X^3$   
 have the meaning N; and

25  $R^2$  is selected from the group R<sup>2</sup>-G1 consisting of H, F, Cl, CN, OH, C<sub>1-4</sub>-alkyl,  
 C<sub>3-7</sub>-cycloalkyl-, F<sub>2</sub>HC, F<sub>3</sub>C, C<sub>1-4</sub>-alkyl-O-, F<sub>2</sub>HC-O-, F<sub>3</sub>C-O- and C<sub>3-7</sub>-  
 cycloalkyl-O-; and

n is an integer selected from 0, 1, 2, 3 or 4; and

30 m is an integer selected from 0, 1, or 2;

including any tautomers and stereoisomers thereof,

or a salt thereof

or a solvate or hydrate thereof.

5

In a further aspect the present invention relates to processes for preparing a compound of general formula I and to new intermediate compounds in these processes.

10 A further aspect of the invention relates to a salt of the compounds of general formula I according to this invention, in particular to a pharmaceutically acceptable salt thereof.

In a further aspect this invention relates to a pharmaceutical composition, comprising  
15 one or more compounds of general formula I or one or more pharmaceutically acceptable salts thereof according to the invention, optionally together with one or more inert carriers and/or diluents.

In a further aspect this invention relates to a method for treating diseases or  
20 conditions which are mediated by activating the G-protein-coupled receptor GPR119 in a patient in need thereof characterized in that a compound of general formula I or a pharmaceutically acceptable salt thereof is administered to the patient.

According to another aspect of the invention, there is provided a method for treating  
25 a metabolic disease or disorder in a patient in need thereof characterized in that a compound of general formula I or a pharmaceutically acceptable salt thereof is administered to the patient.

According to another aspect of the invention, there is provided the use of a  
30 compound of the general formula I or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for a therapeutic method as described hereinbefore and hereinafter.

According to another aspect of the invention, there is provided a compound of the general formula I or a pharmaceutically acceptable salt thereof for use in a therapeutic method as described hereinbefore and hereinafter.

- 5 In a further aspect this invention relates to a method for treating a disease or condition mediated by the activation of the G-protein-coupled receptor GPR119 in a patient that includes the step of administering to the patient in need of such treatment a therapeutically effective amount of a compound of the general formula I or a pharmaceutically acceptable salt thereof in combination with a therapeutically  
10 effective amount of one or more additional therapeutic agents.

- In a further aspect this invention relates to a use of a compound of the general formula I or a pharmaceutically acceptable salt thereof in combination with one or more additional therapeutic agents for the treatment of diseases or conditions which  
15 are mediated by the activation of the G-protein-coupled receptor GPR119.

- In a further aspect this invention relates to a pharmaceutical composition which comprises a compound according to general formula I or a pharmaceutically acceptable salt thereof and one or more additional therapeutic agents, optionally  
20 together with one or more inert carriers and/or diluents.

Other aspects of the invention become apparent to the one skilled in the art from the specification and the experimental part as described hereinbefore and hereinafter.

## 25 Detailed Description

- Unless otherwise stated, the groups, residues, and substituents, particularly A, R<sup>1</sup>, R<sup>2</sup>, T, R<sup>N</sup>, R<sup>NT1</sup>, R<sup>NT2</sup>, L<sup>A</sup>, L<sup>P</sup>, L<sup>Q</sup>, R<sup>C</sup>, X<sup>1</sup>, X<sup>2</sup>, X<sup>3</sup>, n, m are defined as above and hereinafter. If residues, substituents, or groups occur several times in a compound, as for example R<sup>N</sup>, L<sup>A</sup>, L<sup>P</sup> or L<sup>Q</sup>, they may have the same or different meanings.  
30 Some preferred meanings of individual groups and substituents of the compounds according to the invention will be given hereinafter. Any and each of these definitions may be combined with each other.

**R<sup>1</sup>:****R<sup>1</sup>-G1:**

The group R<sup>1</sup> is preferably selected from the group R<sup>1</sup>-G1 as defined hereinbefore and hereinafter.

**R<sup>1</sup>-G2:**

According to one embodiment the group R<sup>1</sup> is selected from the group R<sup>1</sup>-G2 consisting of a 5-membered heteroaromatic ring which contains 2 or 3 heteroatoms independently of each other selected from N, O and S and a 6-membered heteroaromatic ring which contains 1 or 2 N atoms; and wherein optionally a second ring may be condensed to said 5- and 6-membered heteroaromatic rings, wherein said second ring is unsaturated or aromatic and 5- or 6-membered and may contain 1 or 2 heteroatoms independently of each other selected from N, O and S, and wherein in said second ring 1 or 2 -CH<sub>2</sub>-groups may be optionally replaced by -N(R<sup>N</sup>)-, -C(=O)- or -S(=O)<sub>2</sub>-, and

wherein in said heteroaromatic ring and/or said second ring the H-atom in one or more NH groups may be optionally replaced by R<sup>N</sup>, and

wherein each of said heteroaromatic ring and/or second ring independently of each other may be optionally substituted with one or two substituents selected from L<sup>A</sup>; and

wherein said heteroaromatic ring or said second ring may be optionally substituted with a group R<sup>C</sup>.

**R<sup>1</sup>-G2a:**

According to one embodiment the group R<sup>1</sup> is selected from the group R<sup>1</sup>-G2a consisting of a 5-membered heteroaromatic ring which contains 2 or 3 heteroatoms independently of each other selected from N, O and S and a 6-membered heteroaromatic ring which contains 1 or 2 N atoms;

wherein in said heteroaromatic ring the H-atom in one or more NH groups may be

optionally replaced by  $R^N$ , and

wherein said heteroaromatic ring may be optionally substituted with one or two substituents selected from  $L^A$ ; and

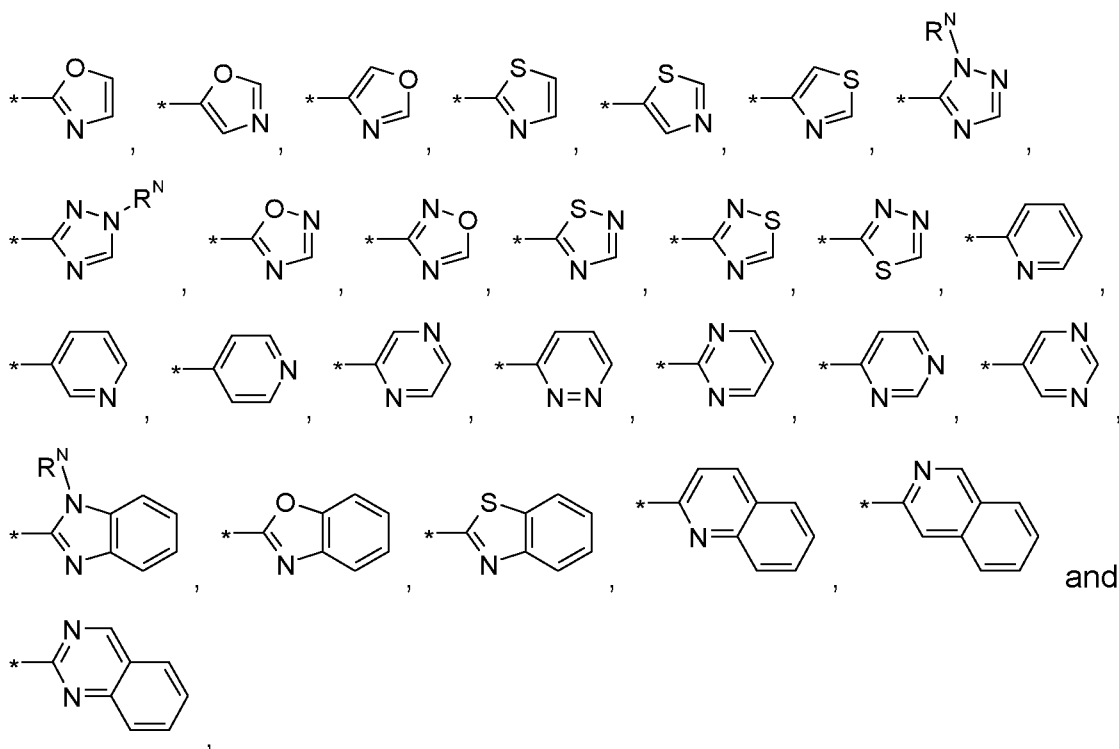
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wherein said heteroaromatic ring may be optionally substituted with a group  $R^C$ .

### $R^1$ -G3:

According to one embodiment the group  $R^1$  is selected from the group  $R^1$ -G3 consisting of:

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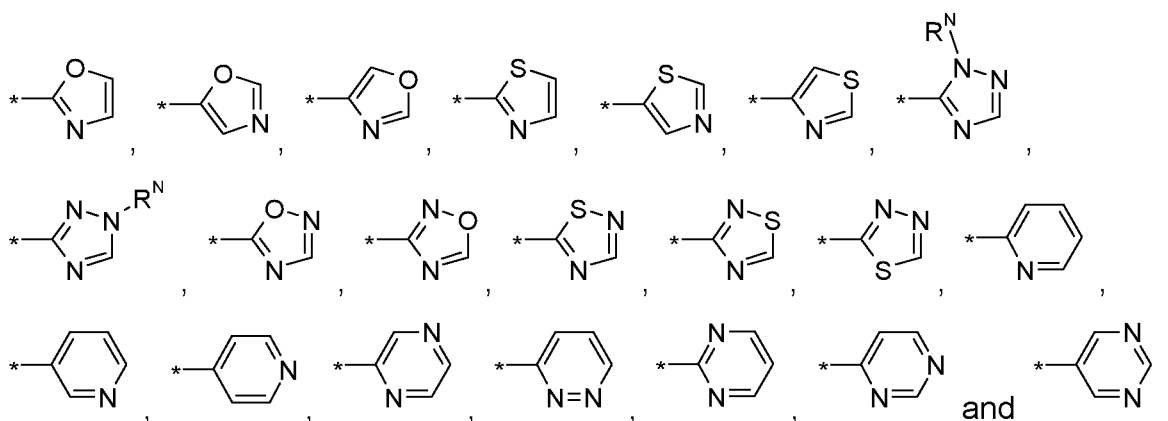
wherein  $R^N$  is as defined hereinbefore and hereinafter, and

wherein each ring may be optionally substituted with one substituent  $L^A$  and each group may be optionally substituted with one substituent  $R^C$ .

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### $R^1$ -G3a:

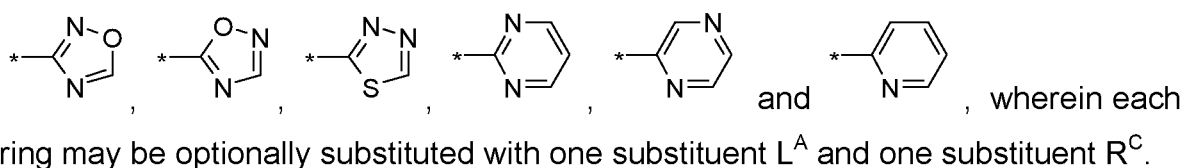
According to one embodiment the group  $R^1$  is selected from the group  $R^1$ -G3a consisting of:



- 5 wherein  $R^N$  is as defined hereinbefore and hereinafter, and wherein each group may be optionally substituted with one substituent  $L^A$  and one substituent  $R^C$ .

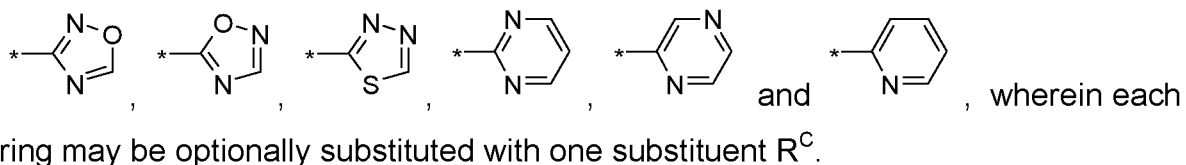
#### $R^1$ -G4:

- 10 In another embodiment the group  $R^1$  is selected from the group  $R^1$ -G4 consisting of



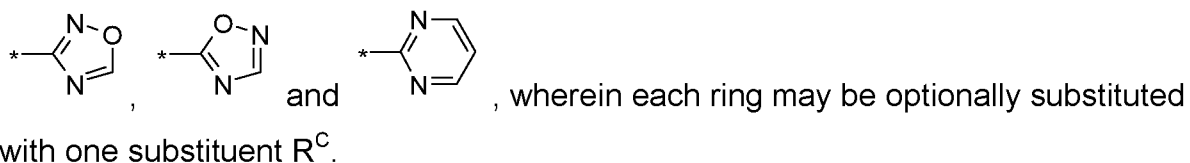
#### $R^1$ -G4a:

- 15 In another embodiment the group  $R^1$  is selected from the group  $R^1$ -G4a consisting of



#### $R^1$ -G5:

- 20 In another embodiment the group  $R^1$  is selected from the group  $R^1$ -G5 consisting of



#### $R^N$

**R<sup>N</sup>-G1:**

The group R<sup>N</sup> is preferably selected from the group R<sup>N</sup>-G1 as defined hereinbefore and hereinafter.

5 **R<sup>N</sup>-G2:**

In another embodiment the group R<sup>N</sup> is selected from the group R<sup>N</sup>-G2 consisting of H, methyl, ethyl, isopropyl, methylcarbonyl, and methylsulfonyl.

**R<sup>N</sup>-G3:**

10 In another embodiment the group R<sup>N</sup> is selected from the group R<sup>N</sup>-G3 consisting of H, methyl, methylcarbonyl, and methylsulfonyl.

**R<sup>N</sup>-G4:**

15 In another embodiment the group R<sup>N</sup> is selected from the group R<sup>N</sup>-G4 consisting of H and C<sub>1-3</sub>-alkyl.

**R<sup>N</sup>-G4a:**

In another embodiment the group R<sup>N</sup> is selected from the group R<sup>N</sup>-G4a consisting of H and methyl.

20

**R<sup>N</sup>-G4b:**

In another embodiment the group R<sup>N</sup> is selected from the group R<sup>N</sup>-G4b consisting of H.

25 **A:****A-G1:**

The group A is preferably selected from the group A-G1 as defined hereinbefore and hereinafter.

30 **A-G2:**

In one embodiment the group A is selected from the group A-G2 consisting of a phenyl ring, a 6-membered heteroaromatic ring which contains 1 or 2 N-atoms, and a 5-membered heteroaromatic ring which contains 1, 2 or 3 heteroatoms independently

of each other selected from N, O and S; and wherein optionally a second ring may be condensed to said phenyl ring or said heteroaromatic ring, wherein said second ring is unsaturated or aromatic and is 5- or 6-membered and may optionally contain 1 or 2 heteroatoms independently of each other selected from N, O and S, and wherein in  
5 said second ring 1 or 2 -CH<sub>2</sub>-groups may optionally be replaced by -N(R<sup>N</sup>)-, -C(=O)-, -S(=O)- or -S(=O)<sub>2</sub>-, and

wherein in said heteroaromatic rings and/or said second rings the H-atom in one or more NH groups may be optionally replaced by R<sup>N</sup>, and

10 wherein each of said phenyl ring, heteroaromatic rings and second rings may be optionally substituted independently of each other with one or more substituents selected from L<sup>A</sup>; and

15 wherein said phenyl ring, heteroaromatic rings or second rings may be optionally substituted with a group T; and

the group A-G2 further consists of 1,2,3,6-tetrahydropyridin-4-yl wherein the H of the NH group is replaced by C<sub>1-4</sub>-alkyl-S(=O)<sub>2</sub>-.

20 **A-G2a:**

In another embodiment the group A is selected from the group A-G2a consisting of a phenyl ring, a 6-membered heteroaromatic ring which contains 1 or 2 N-atoms and a 5-membered heteroaromatic ring which contains 1, 2 or 3 heteroatoms independently  
25 of each other selected from N, O and S; wherein said phenyl ring or heteroaromatic ring is substituted with a group T, and wherein said phenyl ring and heteroaromatic ring may be optionally substituted with one or more substituents independently of each other selected from L<sup>A</sup>,

30 wherein in said heteroaromatic rings the H-atom in one or more NH groups may be optionally replaced by R<sup>N</sup>.

**A-G2b:**

In another embodiment the group A is selected from the group A-G2b consisting of a phenyl ring and a 5- or 6-membered heteroaromatic ring which contains 1 or 2 heteroatoms independently of each other selected from N, O or S; and wherein a second ring is condensed to said phenyl ring or said heteroaromatic ring, wherein  
5 said second ring is unsaturated or aromatic and is 5- or 6-membered and may optionally contain 1 or 2 heteroatoms independently of each other selected from N, O and S, and wherein in said second ring 1 or 2 -CH<sub>2</sub>-groups may be optionally replaced by -N(R<sup>N</sup>)-, -C(=O)-, -S(=O)- or -S(=O)<sub>2</sub>-, and

10 wherein in said heteroaromatic ring and/or said second ring the H-atom in one or more NH groups may be optionally replaced by R<sup>N</sup>, and

wherein each of said phenyl ring, heteroaromatic ring and second ring may be optionally substituted with one or more substituents independently of each other  
15 selected from L<sup>A</sup>; and

wherein said phenyl ring, heteroaromatic ring or second ring may be optionally substituted with a group T.

20 **A-G2c:**

In another embodiment the group A is selected from the group A-G2c consisting of 1,2,3,6-tetrahydropyridin-4-yl wherein the H of the NH group is replaced by C<sub>1-4</sub>-alkyl-S(=O)<sub>2</sub>-.

25 **A-G3:**

In one embodiment the group A is selected from the group A-G3 consisting of the cyclic groups phenyl, pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, isoxazolyl, oxazolyl, oxadiazolyl, imidazolyl, pyrazolyl, thienyl and thiazolylring, and wherein optionally a second ring may be condensed to said cyclic groups, wherein said second ring is  
30 selected from the group consisting of cyclopentene, cyclohexene, dihydropyrrole, tetrahydropyridine, tetrahydropyrazine, dihydrooxazine, dihydrofuran, dihydropyran, [1,3]dioxol, dihydrodioxine, dihydropyrimidine, dihydropyrazine, dihydropyridazine, benzene, pyridine, pyrimidine, pyrazine, pyridazine, oxazole and thiazole, wherein in

said second ring 1 or 2 -CH<sub>2</sub>-groups may be optionally replaced by -C(=O)-, and wherein in said cyclic groups and/or second rings the H-atom in one or more -NH-groups may be replaced independently of each other by the substituent R<sup>N</sup>,

- 5 wherein each of the beforementioned rings may be optionally substituted with one or more substituents independently of each other selected from L<sup>A</sup>, and

wherein said cyclic group or second ring may be substituted with a group T; and

- 10 the group A-G3 further encompasses 1,2,3,6-tetrahydropyridin-4-yl wherein the H of the NH group is replaced by C<sub>1-3</sub>-alkyl-S(=O)<sub>2</sub>-.

#### **A-G3a:**

- In one embodiment the group A is selected from the group A-G3a consisting of a  
15 phenyl and a heteroaromatic carbocyclic ring selected from pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, isoxazolyl, oxazolyl, oxadiazolyl, imidazolyl, pyrazolyl, thienyl and thiazolylring, wherein said phenyl and heteroaromatic rings may be optionally substituted with one or more substituents independently of each other selected from L<sup>A</sup>, and wherein said phenyl or heteroaromatic ring is substituted with a group T.

20

#### **A-G3b:**

- In one embodiment the group A is selected from the group A-G3b consisting of a phenyl and a heteroaromatic ring selected from pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, isoxazolyl, oxazolyl, oxadiazolyl, imidazolyl, pyrazolyl, thienyl and  
25 thiazolyl ring, and wherein a second ring is condensed to said phenyl or heteroaromatic ring, wherein said second ring is selected from the group consisting of cyclopentene, cyclohexene, dihydropyrrole, tetrahydropyridine, tetrahydropyrazine, dihydrooxazine, dihydrofuran, dihydropyran, [1,3]dioxol, dihydrodioxine, dihydropyrimidine, dihydropyrazine, dihydropyridazine, benzene, pyridine, pyrimidine,  
30 pyrazine, pyridazine, oxazole and thiazole, wherein in said second ring 1 or 2 -CH<sub>2</sub>-groups may be optionally replaced by -C(=O)-, and wherein in said heteroaromatic ring and/or second ring the H-atom in one or more -NH-groups may be replaced independently of each other by the substituent R<sup>N</sup>,

wherein each of the beforementioned rings may be optionally substituted with one or more substituents independently of each other selected from  $L^A$ , and

- 5 wherein said phenyl ring, heteroaromatic ring or second ring may be optionally substituted with a group T.

**A-G3c:**

- 10 In another embodiment the group A is selected from the group A-G3c consisting of 1,2,3,6-tetrahydropyridin-4-yl wherein the H of the NH group is replaced by  $C_{1-3}$ -alkyl- $S(=O)_2$ -.

**A-G3d:**

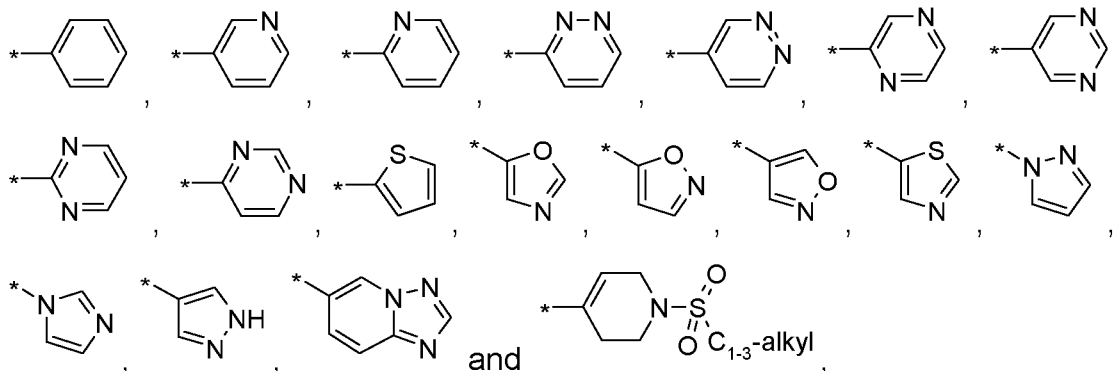
- 15 In another embodiment the group A is selected from the group A-G3c consisting of 1,2,3,6-tetrahydropyridin-4-yl wherein the H of the NH group is replaced by  $CH_3$ - $S(=O)_2$ -.

**A-G4:**

- 20 In one embodiment the group A is selected from the group A-G4 consisting of phenyl, pyridyl, pyrazinyl, pyridazinyl, pyrimidinyl, isoxazolyl, oxazolyl, imidazolyl, pyrazolyl, thienyl, thiazolyl, [1,2,4]triazolo[1,5-a]pyridinyl, benzooxazolyl, benzothiazolyl, indan-1-onyl, indolyl, 2,3-dihydro-indolyl, quinoxaliny, quinoliny, 3H-quinazolin-4-onyl, 2,3-dihydro-benzo[1,4]dioxinyl, 3,4-dihydro-1H-2-oxa-4a,9-diaza-fluorenyl, isoindole-1,3-dionyl, 1,3-dihydro-indol-2-onyl, 1H-indazolyl, indanyl, 2-oxo-2,3-dihydro-oxazolo[4,5-b]pyridinyl and isoxazolo[5,4-b]pyridinyl, wherein in the beforementioned groups in  
25 one or more -NH-groups the H-atom may be optionally replaced independently of each other by the substituent  $R^N$ , and wherein each ring may be optionally substituted with a group T and optionally with one or more substituents independently of each other selected from  $L^A$ , and  
30 the group A-G4 additionally consists of 1,2,3,6-tetrahydropyridin-4-yl wherein the H of the NH group is replaced by  $C_{1-3}$ -alkyl- $S(=O)_2$ -, preferably by  $CH_3$ - $S(=O)_2$ -.

**A-G5:**

In another embodiment the group A is selected from the group A-G5 consisting of:



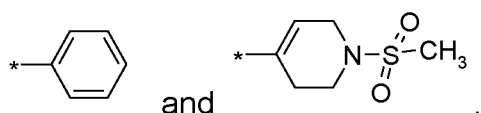
5

wherein in the above groups a H-atom in a -NH-group may be optionally replaced by the substituent  $R^N$ , and wherein each aromatic and heteroaromatic group is not substituted with a group T or is substituted with a group T, and each aromatic and heteroaromatic ring may be optionally substituted with one or more substituents independently of each other selected from  $L^A$ , and wherein the groups T and  $L^A$  are defined as hereinbefore and hereinafter.

10

#### A-G5a:

In another embodiment the group A is selected from the group A-G5a consisting of:



15

wherein the above-mentioned phenyl group is substituted with one  $C_{1-3}$ -alkyl-S(=O)<sub>2</sub>-,  $C_{1-3}$ -alkyl-S(=O)<sub>2</sub>-CH<sub>2</sub>- or -(CO)-NR<sup>NT1</sup>R<sup>NT2</sup>,

20 wherein R<sup>NT1</sup> and R<sup>NT2</sup> are as defined hereinbefore and hereinafter;

preferably R<sup>NT1</sup> is  $C_{1-6}$ -alkyl or tetrahydropyranyl,

wherein the alkyl group may be optionally substituted with one CN, OH, OCH<sub>3</sub>,  
25 tetrahydrofuryl, oxazolyl, [1,4]-dioxanyl or pyridinyl; and

R<sup>NT2</sup> is H or methyl, in particular R<sup>NT2</sup> is H;

or  $R^{NT1}$  and  $R^{NT2}$  together with the N atom to which they are attached form an azetidiny, pyrrolidiny, piperidiny or morpholiny group,

- 5 wherein each of the azetidiny, pyrrolidiny and piperidiny groups may be optionally substituted with one or two substituents independently selected from the group consisting of F, OH,  $CH_3$  and  $-OCH_3$ .

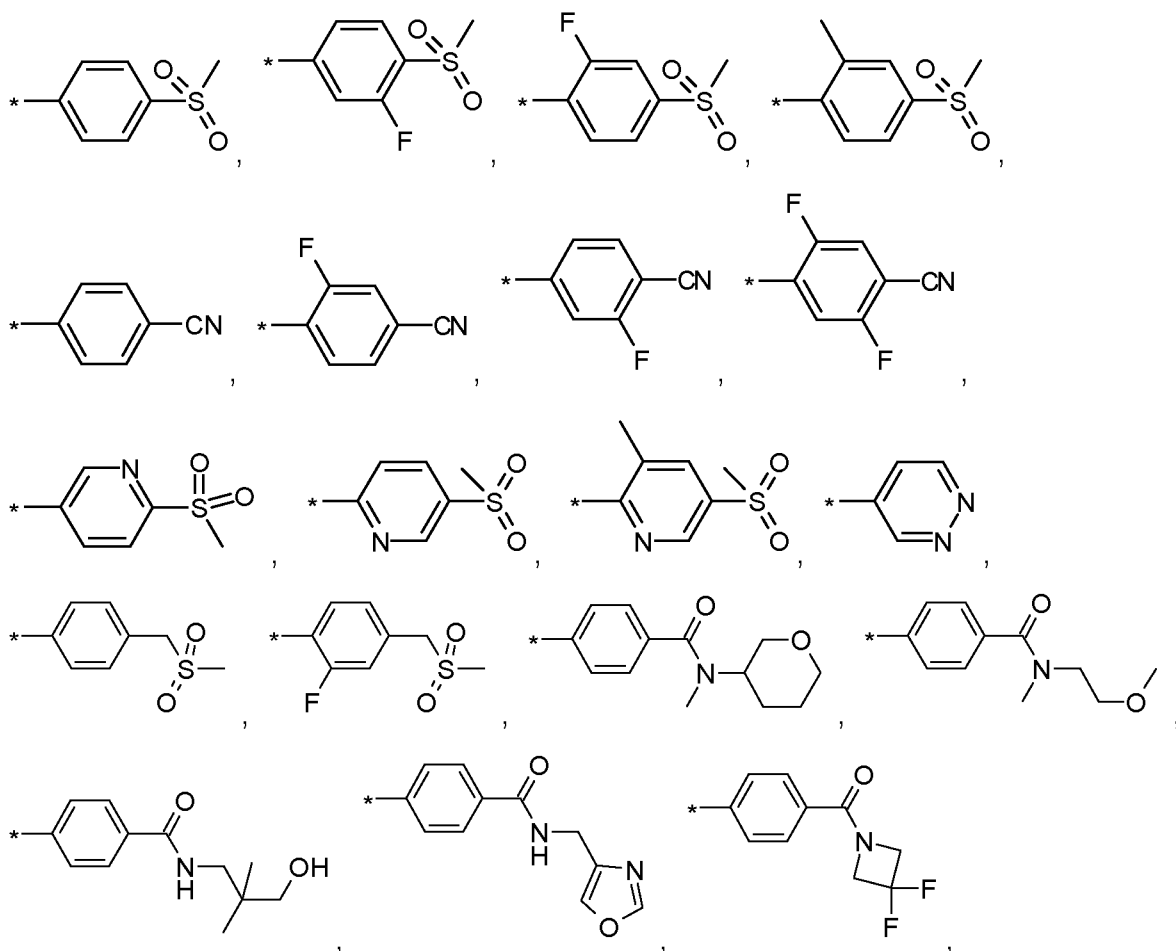
#### A-G5b:

- 10 In another embodiment the group A is selected from the group A-G5a, wherein the phenyl group is substituted in position 4.

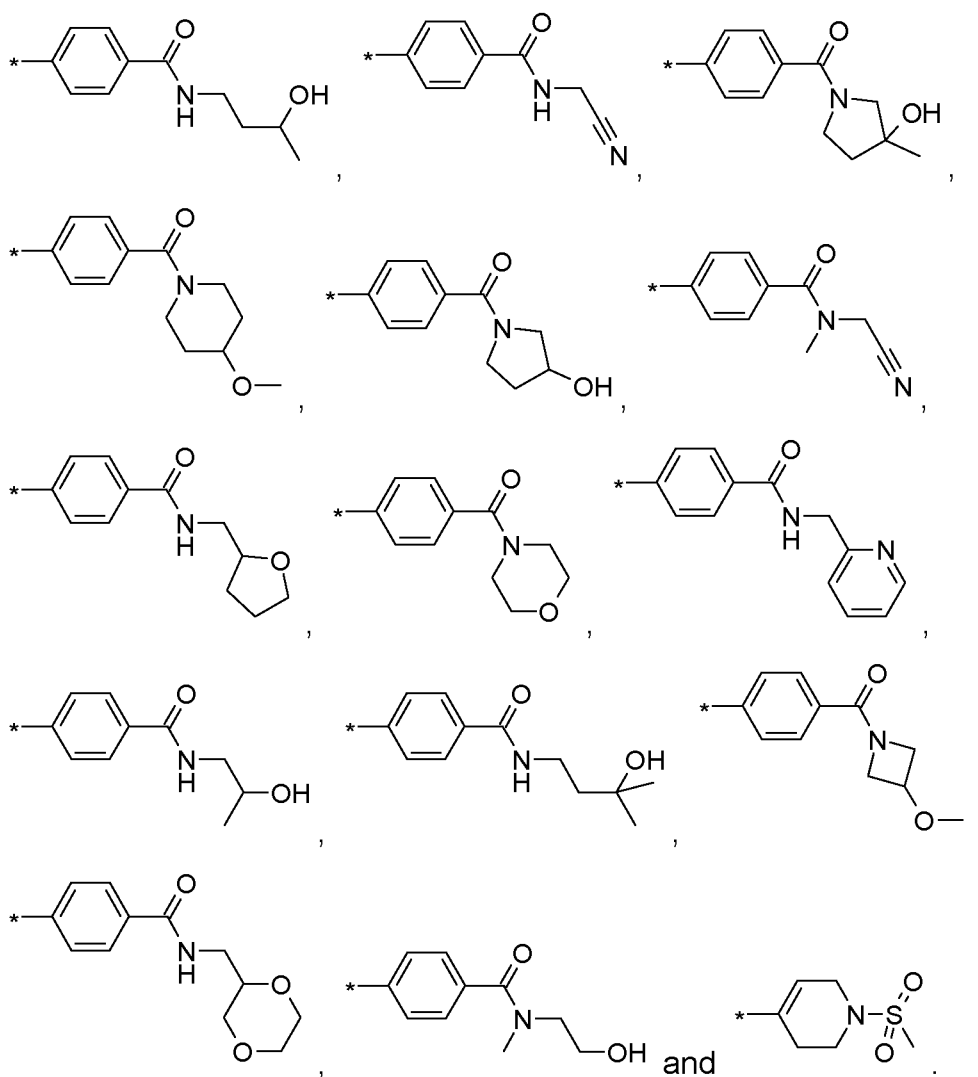
#### A-G6:

In another embodiment the group A is selected from the group A-G6 consisting of:

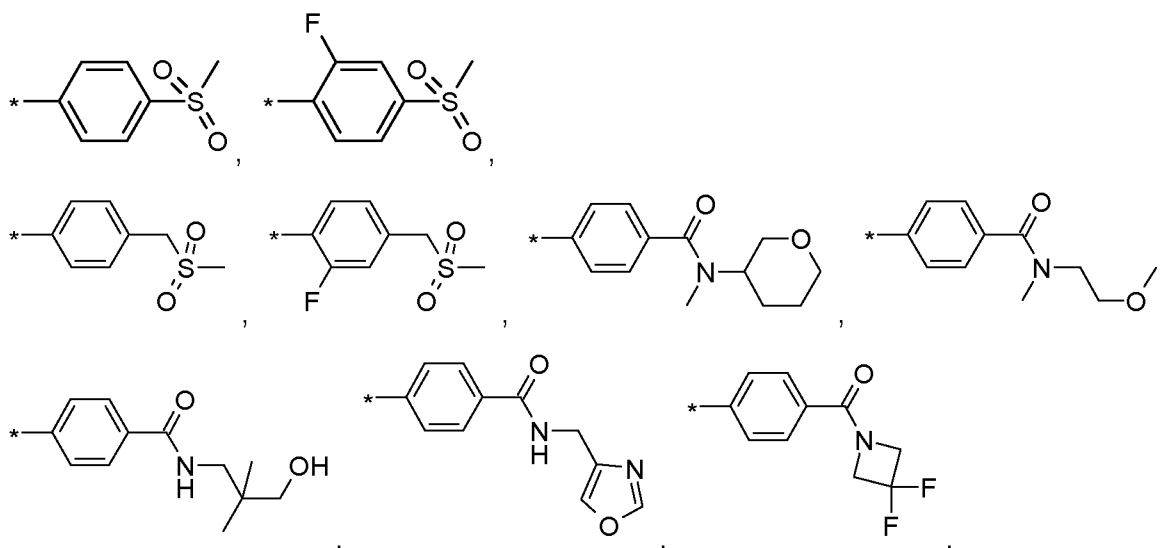
15



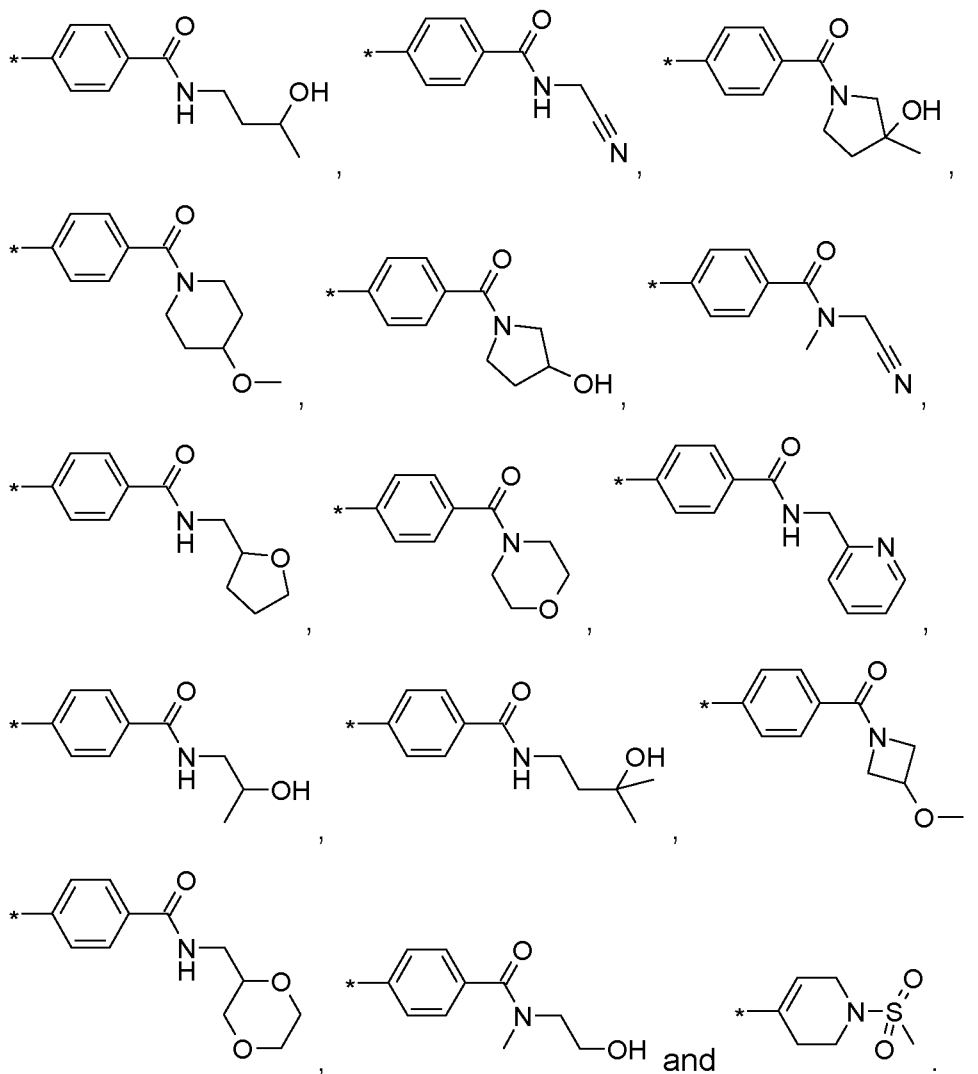
20

**A-G6a:**

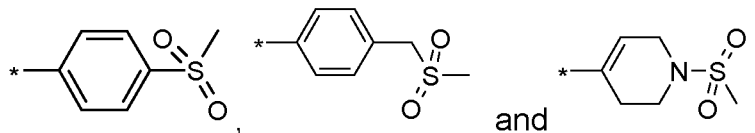
In another embodiment the group A is selected from the group A-G6a consisting of:



- 24 -

**A-G6b:**

In another embodiment the group A is selected from the group A-G6b consisting of:



10

**I****T-G1:**

The group T is preferably selected from the group T-G1 as defined hereinbefore and hereinafter.

15

**T-G2:**

According to one embodiment the group T is selected from the group T-G2 consisting of F, Cl, Br, CN, OH, NO<sub>2</sub>, C<sub>1-4</sub>-alkyl-, C<sub>1-4</sub>-alkyl-O-, C<sub>1-4</sub>-alkyl-O-C(=O)-, C<sub>1-4</sub>-alkyl-C(=O)-, C<sub>1-4</sub>-alkyl-S(=O), C<sub>1-4</sub>-alkyl-S(=O)<sub>2</sub>, C<sub>1-4</sub>-alkyl-S(=O)<sub>2</sub>-C<sub>1-4</sub>-alkyl-, R<sup>NT1</sup>R<sup>NT2</sup>N-C(=O)-, R<sup>NT1</sup>R<sup>NT2</sup>N-S(=O)<sub>2</sub>-, C<sub>1-4</sub>-alkyl-S(=O)<sub>2</sub>-(R<sup>N</sup>)N-, R<sup>NT1</sup>R<sup>NT2</sup>N, R<sup>NT1</sup>R<sup>NT2</sup>N-C(=O)-  
 5 C<sub>1-4</sub>-alkyl-, wherein each alkyl-group may be optionally substituted with one or more substituents independently of each other selected from F, Cl, CN, OH, aryl, heteroaryl, and heterocyclyl,

wherein heteroaryl is selected from the group consisting of pyridinyl, pyrimidinyl,  
 10 pyridazinyl, pyrazinyl, pyrazolyl, imidazolyl, [1,2,4]triazolyl and tetrazolyl; and

wherein heterocyclyl is azetidiny, pyrrolidinyl, piperidinyl, piperazinyl or morpholinyl, in which a -CH<sub>2</sub>-group may be optionally replaced by a group selected from -C(=O)- and -S(=O)<sub>2</sub>-, wherein heterocyclyl group may be optionally substituted with one or  
 15 more substituents independently of each other selected from C<sub>1-3</sub>-alkyl; and

wherein phenyl and heteroaryl may be optionally substituted independently of each other with one or more substituents L<sup>A</sup>.

#### 20 T-G3:

According to another embodiment the group T is selected from the group T-G3 consisting of CN, C<sub>1-4</sub>-alkyl-S(=O)<sub>2</sub>-CH<sub>2</sub>-, C<sub>1-4</sub>-alkyl-S(=O)<sub>2</sub>, R<sup>NT1</sup>R<sup>NT2</sup>N-S(=O)<sub>2</sub>-, R<sup>NT1</sup>R<sup>NT2</sup>N-C(=O)-, C<sub>1-4</sub>-alkyl-S(=O)<sub>2</sub>-(R<sup>N</sup>)N-, and R<sup>NT1</sup>R<sup>NT2</sup>N-.

#### 25 T-G4:

According to another embodiment the group T is selected from the group T-G4 consisting of C<sub>1-4</sub>-alkyl-S(=O)<sub>2</sub>-CH<sub>2</sub>-, C<sub>1-4</sub>-alkyl-S(=O)<sub>2</sub> and R<sup>NT1</sup>R<sup>NT2</sup>N-C(=O)-. Examples of the group T-G4 are CH<sub>3</sub>-S(=O)<sub>2</sub>-CH<sub>2</sub>-, and CH<sub>3</sub>-S(=O)<sub>2</sub>-.

#### 30 R<sup>NT1</sup>

#### R<sup>NT1</sup>-G1:

R<sup>NT1</sup> is preferably selected from the group R<sup>NT1</sup>-G1 as defined hereinbefore and hereinafter.

**R<sup>NT1</sup>-G2:**

In another embodiment R<sup>NT1</sup> is selected from the group R<sup>NT1</sup>-G2 consisting of H, C<sub>1-4</sub>-alkyl, C<sub>3-6</sub>-cycloalkyl, tetrahydropyranyl, wherein each alkyl and cycloalkyl group  
5 may be optionally substituted with one substituent selected from the group consisting of F, CH<sub>3</sub>, OH, C<sub>1-3</sub>-alkyl-O-, (R<sup>N</sup>)<sub>2</sub>N, CN, tetrahydrofuranyl, 1,4-dioxinyl, oxazolyl, and pyridyl.

**R<sup>NT1</sup>-G3:**

10 In another embodiment R<sup>NT1</sup> is selected from the group R<sup>NT1</sup>-G3 consisting of H, C<sub>1-4</sub>-alkyl and C<sub>3-6</sub>-cycloalkyl,  
wherein each alkyl and cycloalkyl group may be optionally substituted with one or two substituents independently of each other selected from the group consisting of F, CH<sub>3</sub>, OH and C<sub>1-3</sub>-alkyl-O-.

**R<sup>NT1</sup>-G4:**

15 In another embodiment R<sup>NT1</sup> is selected from the group R<sup>NT1</sup>-G4 consisting of H and C<sub>1-4</sub>-alkyl,  
wherein each alkyl and cycloalkyl group may be optionally substituted with one  
20 substituent selected from the group consisting of F, CH<sub>3</sub>, OH and C<sub>1-3</sub>-alkyl-O-.

**R<sup>NT2</sup>****R<sup>NT2</sup>-G1:**

R<sup>NT2</sup> is preferably selected from the group R<sup>NT2</sup>-G1 as defined hereinbefore and  
25 hereinafter.

**R<sup>NT2</sup>-G2:**

In another embodiment R<sup>NT2</sup> is selected from the group R<sup>NT2</sup>-G2 consisting of H and C<sub>1-3</sub>-alkyl.

**R<sup>NT2</sup>-G3:**

30 In another embodiment R<sup>NT2</sup> is selected from the group R<sup>NT2</sup>-G3 consisting of H and methyl.

**R<sup>NT2</sup>-G4:**

In another embodiment R<sup>NT2</sup> is selected from the group R<sup>NT2</sup>-G4 consisting of H.

5 **R<sup>NT1</sup>R<sup>NT2</sup>****R<sup>NT1</sup>R<sup>NT2</sup>-G1:**

According to one embodiment the groups R<sup>NT1</sup> and R<sup>NT2</sup> are linked and form a group which is selected from the group R<sup>NT1</sup>R<sup>NT2</sup>-G1 as defined hereinbefore and hereinafter.

10

**R<sup>NT1</sup>R<sup>NT2</sup>-G2:**

According to another embodiment the groups R<sup>NT1</sup> and R<sup>NT2</sup> are linked and together with the N-atom to which they are attached form a group which is selected from the group R<sup>NT1</sup>R<sup>NT2</sup>-G2 consisting of azetidiny, pyrrolidinyl, piperidinyl, morpholinyl,

15 piperazinyl, piperazin-2-onyl, N-C<sub>1-3</sub>-alkyl-piperazinyl, N-C<sub>1-3</sub>-alkyl-piperazin-2-onyl, and N-(C<sub>1-3</sub>-alkyl-C(=O))-piperazinyl, which may be optionally substituted with one or more substituents independently of each other selected from the group consisting of F, HO, C<sub>1-3</sub>-alkyl, C<sub>1-3</sub>-alkyl-O-, and (R<sup>N</sup>)<sub>2</sub>N.

20 **R<sup>NT1</sup>R<sup>NT2</sup>-G3:**

According to another embodiment the groups R<sup>NT1</sup> and R<sup>NT2</sup> are linked and together with the N-atom to which they are attached form a group which is selected from the group R<sup>NT1</sup>R<sup>NT2</sup>-G3 consisting of azetidiny, pyrrolidinyl, piperidinyl and morpholinyl,

25 of each other selected from the group consisting of F, OH, CH<sub>3</sub> and CH<sub>3</sub>-O-.

**L<sup>A</sup>:****L<sup>A</sup>-G1:**

The group L<sup>A</sup> is preferably selected from the group L<sup>A</sup>-G1 as defined hereinbefore and hereinafter.

30

**L<sup>A</sup>-G2:**

In another embodiment the group  $L^A$  is selected from the group  $L^A$ -G2 consisting of F, Cl, Br, CN, OH,  $C_{1-3}$ -alkyl-,  $C_{1-3}$ -alkyl-O-,  $H_2N$ -,  $C_{1-3}$ -alkyl-NH- and  $(C_{1-3}\text{-alkyl})_2N$ -, wherein the  $C_{1-3}$ -alkyl- and  $C_{1-3}$ -alkyl-O- group may be optionally substituted with one or more F-atoms.

5

 **$L^A$ -G3:**

In another embodiment the group  $L^A$  is selected from the group  $L^A$ -G3 consisting of F, Cl,  $C_{1-4}$ -alkyl- and  $CF_3$ .

10  **$R^C$ :** **$R^C$ -G1:**

The group  $R^C$  is preferably selected from the group  $R^C$ -G1 as defined hereinbefore and hereinafter.

15  **$R^C$ -G2:**

According to one embodiment the group  $R^C$  is selected from the group  $R^C$ -G2 consisting of F, Cl, Br, I, CN, OH,  $C_{1-6}$ -alkyl-,  $C_{1-6}$ -alkenyl-,  $C_{1-6}$ -alkynyl-,  $C_{3-6}$ -cycloalkyl,  $C_{1-6}$ -alkyl-O-,  $C_{3-6}$ -cycloalkyl-O-,  $C_{1-6}$ -alkyl-S-,  $C_{1-6}$ -alkyl-O-C(=O)-,  $C_{1-4}$ -alkyl-S(=O)-,  $C_{1-4}$ -alkyl-S(=O)- $C_{1-4}$ -alkyl-,  $C_{1-4}$ -alkyl-S(=O)<sub>2</sub>-,  $C_{1-4}$ -alkyl-S(=O)<sub>2</sub>- $C_{1-4}$ -alkyl-,  $R^{NT1}R^{NT2}N$ -,  $R^{NT1}R^{NT2}N$ - $C_{1-3}$ -alkyl-,  $R^{NT1}R^{NT2}N$ -C(=O)-,  $R^{NT1}R^{NT2}N$ -S(=O)<sub>2</sub>-,  $R^{NT1}R^{NT2}N$ -S(=O)<sub>2</sub>- $C_{1-4}$ -alkyl-,  $R^{NT1}R^{NT2}N$ -C(=O)- $C_{1-4}$ -alkyl-, heterocyclyl, heterocyclyl-O-, phenyl and heteroaryl, wherein each alkyl, alkenyl, alkynyl, and cycloalkyl group may be optionally substituted with one or more substituents independently of each other selected from F, Cl, CN, OH,  $C_{1-3}$ -alkyl,  $C_{3-6}$ -cycloalkyl,  $C_{1-3}$ -alkyl-O-, phenyl, heteroaryl, and heterocyclyl, and

wherein heteroaryl is selected from the group consisting of pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, pyrazolyl, imidazolyl, thiazolyl, and thienyl; and

25

wherein heterocyclyl is selected from the group consisting of pyrrolidin-2-onyl, piperidin-2-onyl, piperazin-2-onyl, morpholinyl, morpholin-3-onyl, oxetanyl, tetrahydrofuranyl, and tetrahydropyranyl, each of which may be optionally substituted with one or two substituents independently of each other selected from  $C_{1-3}$ -alkyl; and

30

wherein phenyl and heteroaryl may be optionally substituted independently of each other with one or more substituents  $L^A$ .

### **$R^C$ -G3:**

- 5 According to one embodiment the group  $R^C$  is selected from the group  $R^C$ -G3 consisting of F, Cl, CN,  $C_{1-6}$ -alkyl-,  $C_{3-6}$ -cycloalkyl,  $C_{1-6}$ -alkyl-O-,  $C_{3-6}$ -cycloalkyl-O-,  $C_{1-4}$ -alkyl-S(=O)-,  $C_{1-4}$ -alkyl-S(=O)<sub>2</sub>-,  $R^{NT1}R^{NT2}N$ -,  $R^{NT1}R^{NT2}N$ - $C_{1-3}$ -alkyl-,  $R^{NT1}R^{NT2}N$ -C(=O)-,  $R^{NT1}R^{NT2}N$ -S(=O)<sub>2</sub>-,  $R^{NT1}R^{NT2}N$ -C(=O)- $C_{1-4}$ -alkyl-, heterocyclyl, heterocyclyl-O-, phenyl and heteroaryl, wherein each alkyl and cycloalkyl group may be optionally substituted with one or more substituents independently of each other selected from F, H<sub>3</sub>C-, H<sub>3</sub>C-O-, phenyl, and heterocyclyl, and
- 10

wherein heteroaryl is selected from the group consisting of pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, and thienyl; and

15

wherein heterocyclyl is selected from the group consisting of oxetanyl, tetrahydrofuranyl and tetrahydropyranyl, each of which may be optionally substituted with one or two H<sub>3</sub>C- groups; and

- 20 wherein phenyl and heteroaryl may be optionally substituted with one substituent  $L^A$ .

### **$R^C$ -G4:**

- According to another embodiment the group  $R^C$  is selected from the group  $R^C$ -G4 consisting of F, Cl,  $C_{1-4}$ -alkyl, F<sub>3</sub>C-,  $C_{3-4}$ -cycloalkyl, phenyl, wherein the phenyl ring may be monosubstituted with F, Cl, CH<sub>3</sub>, CF<sub>3</sub>, or OCH<sub>3</sub> and the cycloalkyl groups may be monosubstituted with CH<sub>3</sub>.
- 25

### **$R^C$ -G4a:**

- According to another embodiment the group  $R^C$  is selected from the group  $R^C$ -G4a consisting of F, Cl,  $C_{1-4}$ -alkyl, F<sub>3</sub>C- and  $C_{3-4}$ -cycloalkyl, wherein the cycloalkyl groups may be monosubstituted with CH<sub>3</sub>.
- 30

### **$R^C$ -G4b:**

According to another embodiment the group  $R^C$  is selected from the group  $R^C$ -G4b consisting of F, Cl,  $C_{1-4}$ -alkyl,  $F_3C$ - and cyclopropyl, wherein the cyclopropyl group may be monosubstituted with  $CH_3$ .

5  **$R^C$ -G4c:**

According to another embodiment the group  $R^C$  is selected from the group  $R^C$ -G4a consisting of F, Cl,  $C_{1-4}$ -alkyl,  $F_3C$ -,  $C_{3-4}$ -cycloalkyl, and  $C_{1-3}$ -alkyl-O-, wherein the cycloalkyl groups may be monosubstituted with  $CH_3$ .

10  **$R^C$ -G5:**

According to another embodiment the group  $R^C$  is selected from the group  $R^C$ -G5 consisting of  $C_{1-4}$ -alkyl,  $F_3C$ -, cyclopropyl, cyclobutyl and phenyl, wherein the phenyl ring may be monosubstituted with F, Cl,  $CH_3$ ,  $CF_3$ , or  $OCH_3$ .

15  **$R^C$ -G5a:**

According to another embodiment the group  $R^C$  is selected from the group  $R^C$ -G5a consisting of  $C_{1-4}$ -alkyl and  $F_3C$ -.

Preferred examples of the group  $R^C$ -G5a are ethyl, n-propyl and isopropyl.

20

**$R^C$ -G5b:**

According to another embodiment the group  $R^C$  is selected from the group  $R^C$ -G5a consisting of  $C_{1-3}$ -alkyl,  $F_3C$ -, and  $H_3C$ -O-.

25  **$X^1, X^2, X^3$**

**X-G1:**

The group  $X^1, X^2, X^3$  is preferably selected from the group X-G1 as defined hereinbefore and hereinafter.

30 **X-G2:**

In another embodiment the group  $X^1, X^2, X^3$  is selected from the group X-G2 consisting of  $C(R^2)$ .

**X-G3:**

In another embodiment the group  $X^1$ ,  $X^2$ ,  $X^3$  is selected from the group X-G3 consisting of N and  $C(R^2)$ , such that 1 or 2 members of the group consisting of  $X^1$ ,  $X^2$  and  $X^3$  have the meaning N and the other members of said group have the meaning  $C(R^2)$ .

**X-G4:**

In another embodiment the group  $X^1$ ,  $X^2$ ,  $X^3$  is selected from the group X-G4 consisting of N and  $C(R^2)$ , such that 1 member of the group consisting of  $X^1$ ,  $X^2$  and  $X^3$  has the meaning N and the other members of said group have the meaning  $C(R^2)$ .

**X-G4a:**

In another embodiment  $X^1$ ,  $X^2$  and  $X^3$  are selected from the group X-G4a consisting of:

$X^1$  and  $X^3$  each being  $C(R^2)$ , and  $X^2$  having the meaning N.

**X-G5:**

In another embodiment the group  $X^1$ ,  $X^2$ ,  $X^3$  is selected from the group X-G5 consisting of N and  $C(R^2)$ , such that 2 members of the group consisting of  $X^1$ ,  $X^2$  and  $X^3$  have the meaning N and the other member of said group has the meaning  $C(R^2)$ .

**R<sup>2</sup>****R<sup>2</sup>-G1:**

The group  $R^2$  is preferably selected from the group  $R^2$ -G1 as defined hereinbefore and hereinafter.

**R<sup>2</sup>-G2:**

In another embodiment the group  $R^2$  is selected from the group  $R^2$ -G2 consisting of H, F, CN, OH,  $H_3C-$ ,  $F_2HC-$ ,  $F_3C-$ ,  $H_3C-O-$ ,  $F_2HC-O-$ , and  $F_3C-O-$ .

**R<sup>2</sup>-G3:**

In another embodiment the group  $R^2$  is selected from the group  $R^2$ -G3 consisting of H, F, and  $H_3C$ -.

 **$R^2$ -G4:**

- 5 In another embodiment the group  $R^2$  is selected from the group  $R^2$ -G4 consisting of H.

 **$L^P$ :** **$L^P$ -G1:**

- 10 The group  $L^P$  is preferably selected from the group  $L^P$ -G1 as defined hereinbefore and hereinafter.

 **$L^P$ -G2:**

- 15 In another embodiment the group  $L^P$  is selected from the group  $L^P$ -G2 consisting of F and methyl.

 **$L^Q$ :** **$L^Q$ -G1:**

- 20 The group  $L^Q$  is preferably selected from the group  $L^Q$ -G1 as defined hereinbefore and hereinafter.

 **$L^Q$ -G2:**

- 25 In another embodiment the group  $L^Q$  is selected from the group  $L^Q$ -G2 consisting of F and methyl.

**n:**

The index n is an integer selected from 0, 1, 2, 3 or 4.

According to one embodiment the index n is 0, 1 or 2, in particular 0 or 1.

30

According to another embodiment the index n is 0.

**m:**

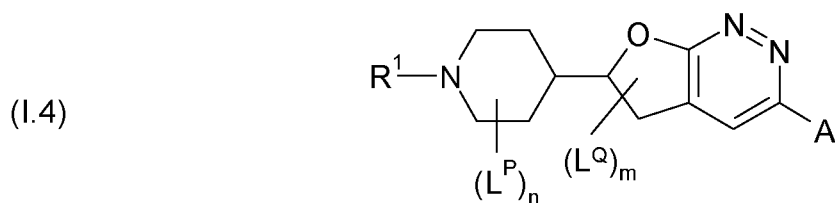
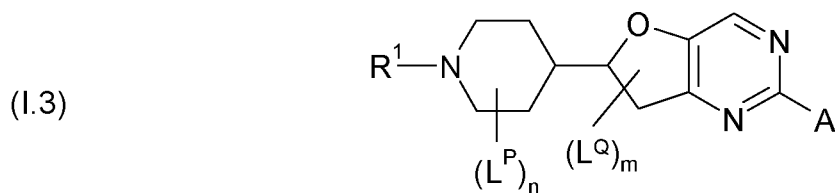
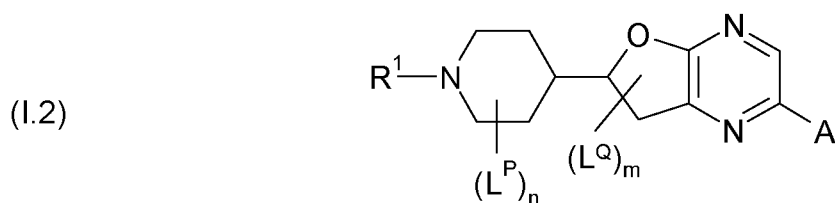
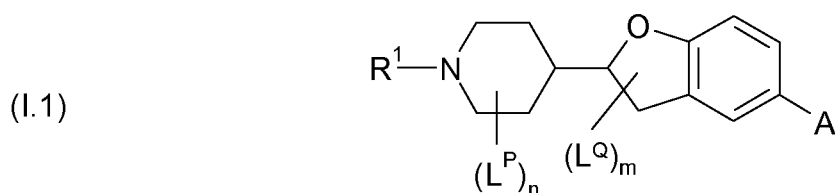
The index m is an integer selected from 0, 1 or 2.

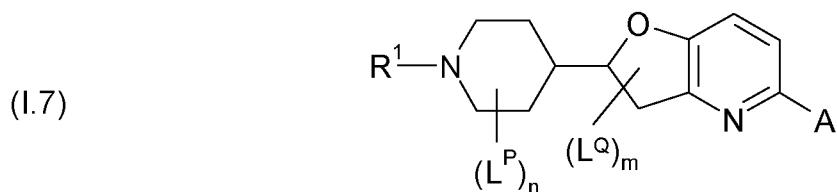
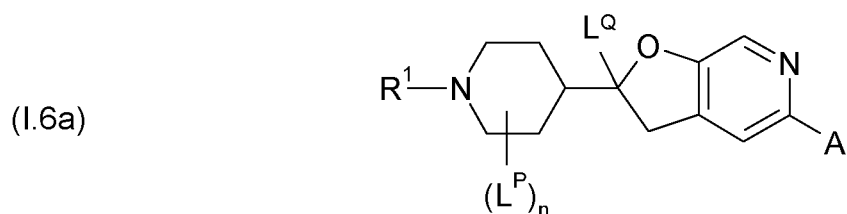
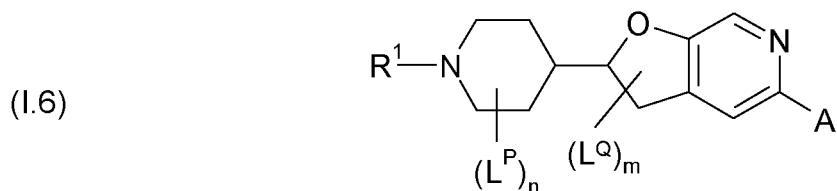
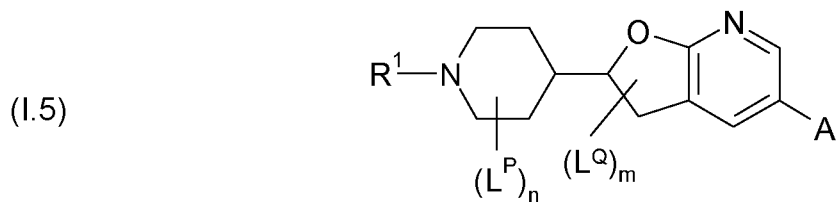
According to one embodiment the index m is 0, 1 or 2, in particular 0 or 1.

- 5 According to another embodiment the index m is 1.

According to another embodiment the index m is 0.

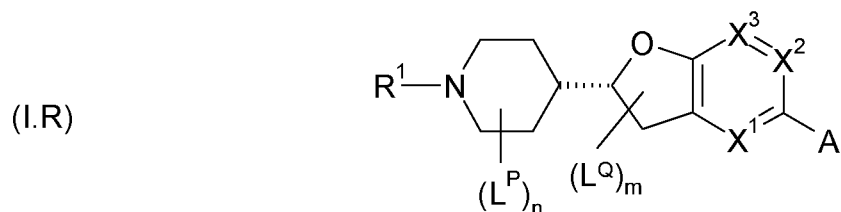
10 The following preferred embodiments of compounds of the formula I are described using generic formulas (I.1) to (I.7), wherein any tautomers and stereoisomers, solvates, hydrates and salts thereof, in particular the pharmaceutically acceptable salts thereof, are encompassed.

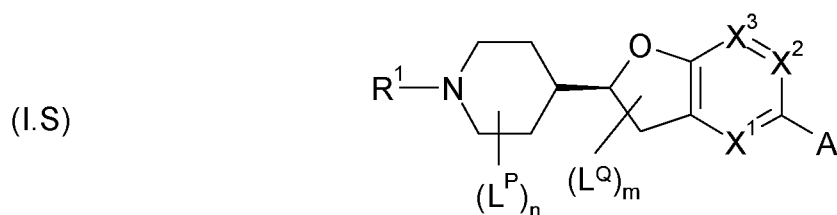




wherein in each of the above formulas (I.1) to (I.7), the groups  $R^1$ ,  $L^P$ ,  $L^Q$ ,  $n$ ,  $m$  and  $A$  are defined as hereinbefore and hereinafter.

- 5 Further preferred embodiments of compounds of the formula I are described by generic formulas (I.R) and (I.S), wherein any tautomers and stereoisomers, solvates, hydrates and salts thereof, in particular the pharmaceutically acceptable salts thereof, are encompassed.





wherein in each of the above formulas (I.R) and (I.S), the groups R<sup>1</sup>, L<sup>P</sup>, L<sup>Q</sup>, n, m, X<sup>1</sup>, X<sup>2</sup>, X<sup>3</sup>, and A are defined as hereinbefore and hereinafter.

- 5 Examples of preferred subgeneric embodiments according to the present invention are set forth in the following table, wherein each substituent group of each embodiment is defined according to the definitions set forth hereinbefore and wherein all other substituents of the formula I are defined according to the definitions set forth hereinbefore:

10

| Embodi-<br>ment | Formula | R <sup>1</sup> -   | A-    |
|-----------------|---------|--------------------|-------|
| E-1             | I       | R <sup>1</sup> -G1 | A-G1  |
| E-2             | I       | R <sup>1</sup> -G2 | A-G2a |
| E-3             | I       | R <sup>1</sup> -G2 | A-G2b |
| E-4             | I       | R <sup>1</sup> -G2 | A-G4  |
| E-5             | I       | R <sup>1</sup> -G2 | A-G5  |
| E-6             | I.R     | R <sup>1</sup> -G1 | A-G1  |
| E-7             | I.R     | R <sup>1</sup> -G2 | A-G2a |
| E-8             | I.R     | R <sup>1</sup> -G2 | A-G2b |
| E-9             | I.R     | R <sup>1</sup> -G2 | A-G4  |
| E-10            | I.R     | R <sup>1</sup> -G2 | A-G5  |
| E-11            | I.S     | R <sup>1</sup> -G1 | A-G1  |
| E-12            | I.S     | R <sup>1</sup> -G2 | A-G2a |
| E-13            | I.S     | R <sup>1</sup> -G2 | A-G2b |
| E-14            | I.S     | R <sup>1</sup> -G2 | A-G4  |
| E-15            | I.S     | R <sup>1</sup> -G2 | A-G5  |
| E-16            | I.1     | R <sup>1</sup> -G1 | A-G1  |
| E-17            | I.1     | R <sup>1</sup> -G2 | A-G2a |

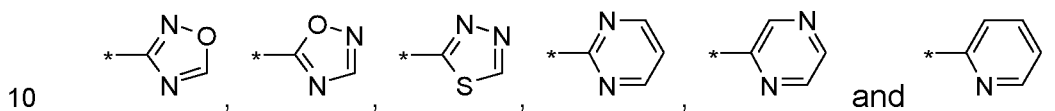
| Embodi-<br>ment | Formula | R <sup>1</sup> -   | A-    |
|-----------------|---------|--------------------|-------|
| E-18            | I.1     | R <sup>1</sup> -G2 | A-G2b |
| E-19            | I.1     | R <sup>1</sup> -G2 | A-G4  |
| E-20            | I.1     | R <sup>1</sup> -G2 | A-G5  |
| E-21            | I.2     | R <sup>1</sup> -G1 | A-G1  |
| E-22            | I.2     | R <sup>1</sup> -G2 | A-G2a |
| E-23            | I.2     | R <sup>1</sup> -G2 | A-G2b |
| E-24            | I.2     | R <sup>1</sup> -G2 | A-G4  |
| E-25            | I.2     | R <sup>1</sup> -G2 | A-G5  |
| E-26            | I.3     | R <sup>1</sup> -G1 | A-G1  |
| E-27            | I.3     | R <sup>1</sup> -G2 | A-G2a |
| E-28            | I.3     | R <sup>1</sup> -G2 | A-G2b |
| E-29            | I.3     | R <sup>1</sup> -G2 | A-G4  |
| E-30            | I.3     | R <sup>1</sup> -G2 | A-G5  |
| E-31            | I.4     | R <sup>1</sup> -G1 | A-G1  |
| E-32            | I.4     | R <sup>1</sup> -G2 | A-G2a |
| E-33            | I.4     | R <sup>1</sup> -G2 | A-G2b |
| E-34            | I.4     | R <sup>1</sup> -G2 | A-G4  |
| E-35            | I.4     | R <sup>1</sup> -G2 | A-G5  |
| E-36            | I.5     | R <sup>1</sup> -G1 | A-G1  |
| E-37            | I.5     | R <sup>1</sup> -G2 | A-G2a |
| E-38            | I.5     | R <sup>1</sup> -G2 | A-G2b |
| E-39            | I.5     | R <sup>1</sup> -G2 | A-G4  |
| E-40            | I.5     | R <sup>1</sup> -G2 | A-G5  |
| E-41            | I.6     | R <sup>1</sup> -G1 | A-G1  |
| E-42            | I.6     | R <sup>1</sup> -G2 | A-G2a |
| E-43            | I.6     | R <sup>1</sup> -G2 | A-G2b |
| E-44            | I.6     | R <sup>1</sup> -G2 | A-G4  |
| E-45            | I.6     | R <sup>1</sup> -G2 | A-G5  |
| E-46            | I.7     | R <sup>1</sup> -G1 | A-G1  |
| E-47            | I.7     | R <sup>1</sup> -G2 | A-G2a |
| E-48            | I.7     | R <sup>1</sup> -G2 | A-G2b |
| E-49            | I.7     | R <sup>1</sup> -G2 | A-G4  |

| Embodi-<br>ment | Formula | R <sup>1</sup> -   | A-   |
|-----------------|---------|--------------------|------|
| E-50            | I.7     | R <sup>1</sup> -G2 | A-G5 |

Preferred are those compounds of formula I, wherein

- 5 X<sup>1</sup> is CH;  
X<sup>2</sup> is CH or N;  
X<sup>3</sup> is CH;

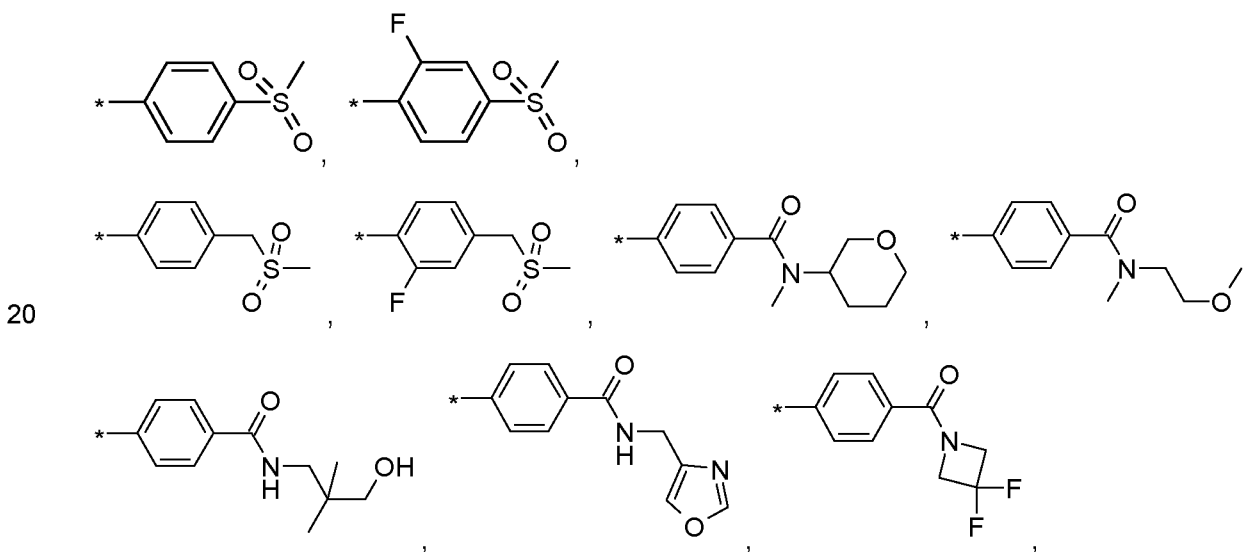
R<sup>1</sup> is selected from the group consisting of:

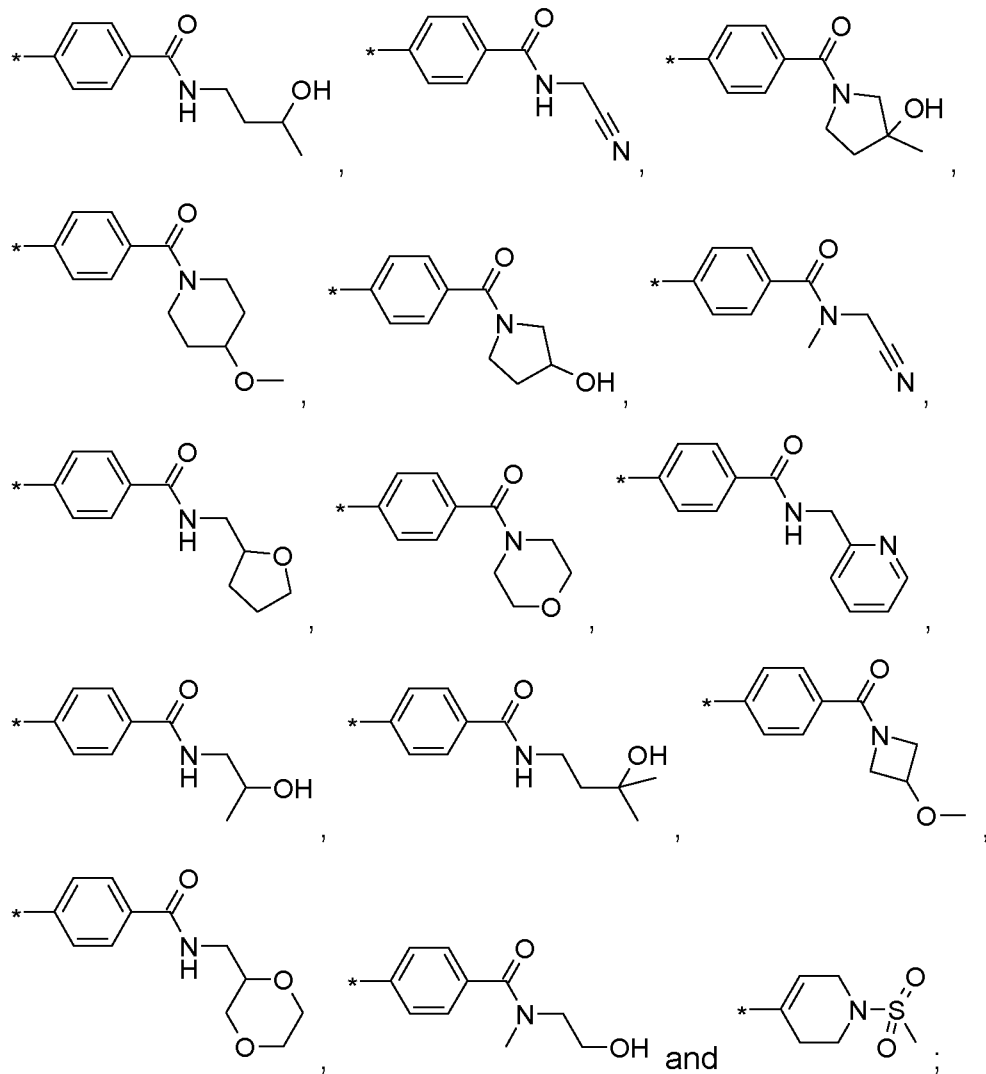


wherein each ring may be optionally substituted with one F and/or with one substituent R<sup>C</sup>;

- 15 R<sup>C</sup> is selected from the group consisting of F, Cl, C<sub>1-4</sub>-alkyl, F<sub>3</sub>C- and cyclopropyl, wherein the cyclopropyl group may be monosubstituted with CH<sub>3</sub>;

A is selected from the group consisting of:





$L^Q$  is  $CH_3$ ;

$n$  is 0;

$m$  is 0 or 1;

10 and the pharmaceutically acceptable salts thereof.

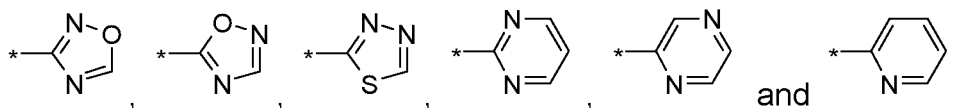
More preferred are those compounds of formula I, wherein

$X^1$  is CH;

15  $X^2$  is N;

$X^3$  is CH;

$R^1$  is selected from the group consisting of:

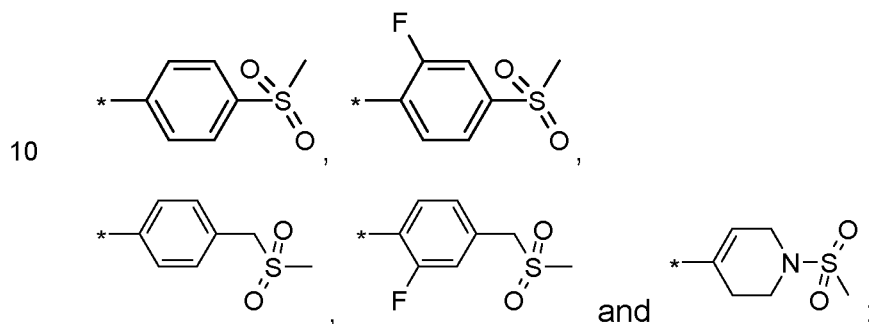


wherein each ring may be optionally substituted with one F and/or with one substituent  $R^C$ ;

5

$R^C$  is selected from the group consisting of F, Cl,  $C_{1-4}$ -alkyl,  $F_3C$ - and cyclopropyl, wherein the cyclopropyl group may be monosubstituted with  $CH_3$ ;

A is selected from the group consisting of:



10

$L^Q$  is  $CH_3$ ;

n is 0;

15 m is 0 or 1;

and the pharmaceutically acceptable salts thereof.

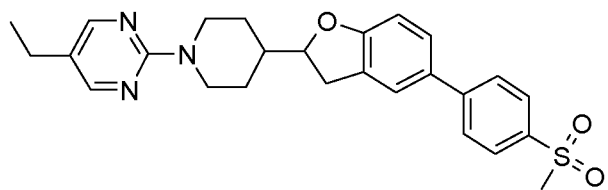
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Particularly preferred compounds, including their tautomers and stereoisomers, the salts thereof, or any solvates or hydrates thereof, are described in the experimental section hereinafter.

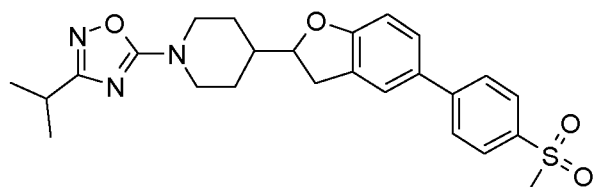
The following compounds are mentioned as examples of compounds according to the invention:

Example    Structure

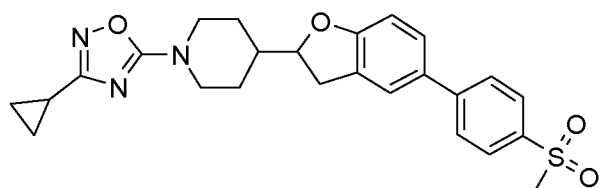
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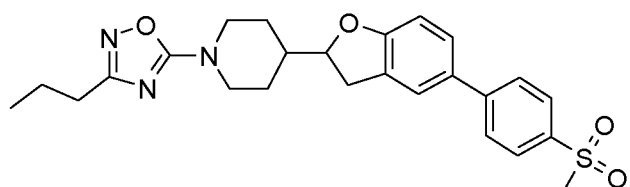
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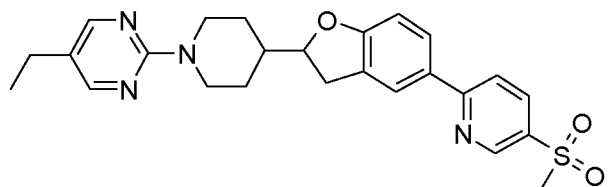
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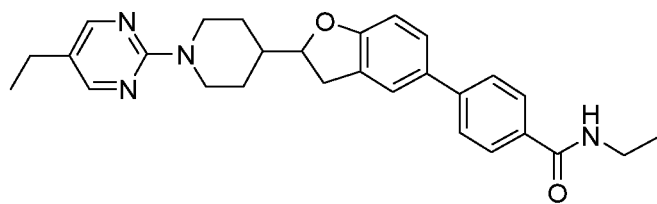
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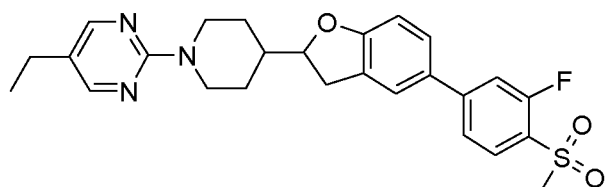
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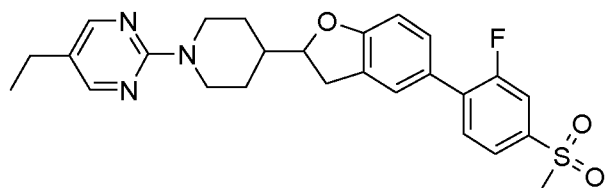
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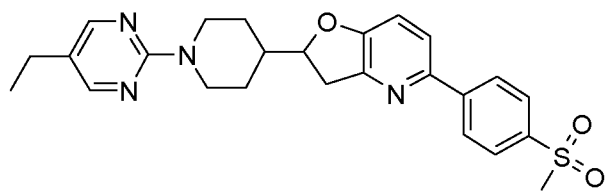
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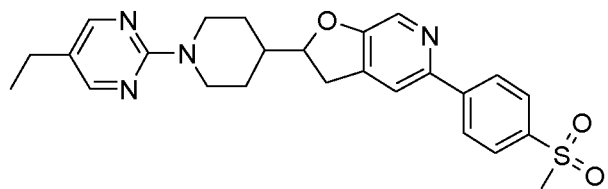
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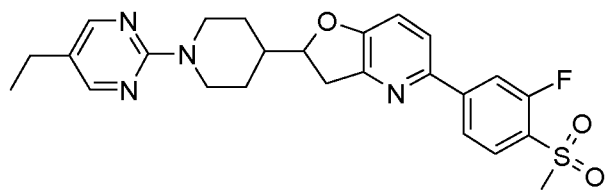
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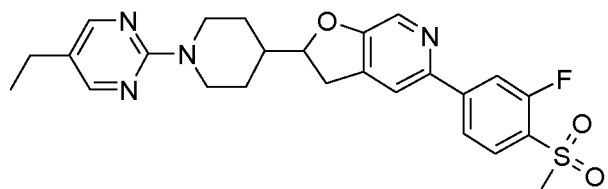
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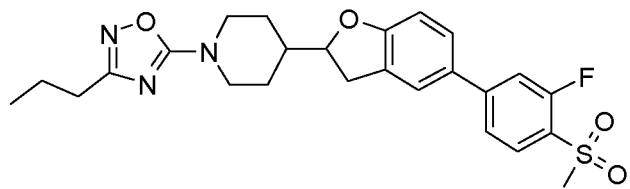
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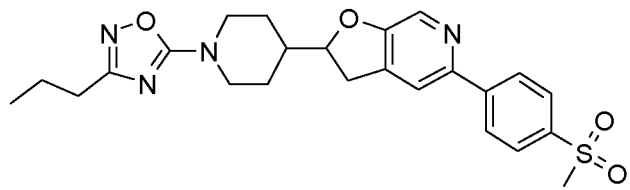
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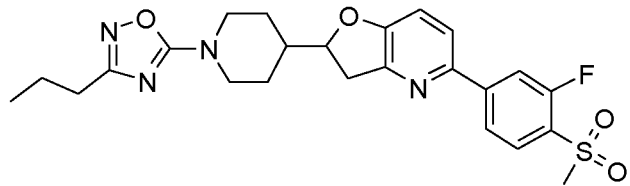
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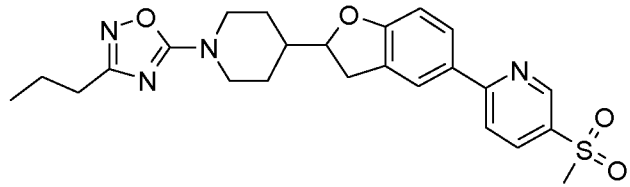
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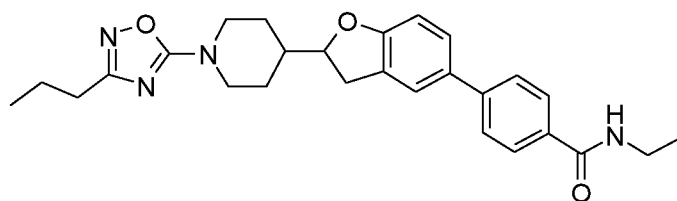
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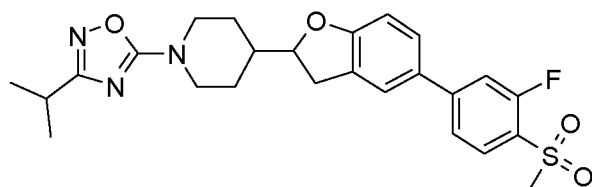
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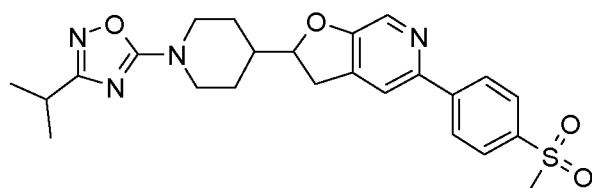
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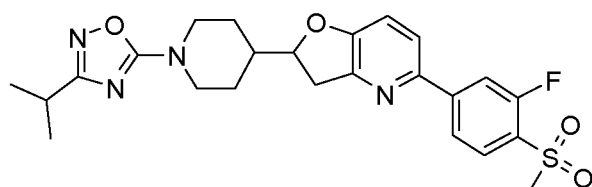
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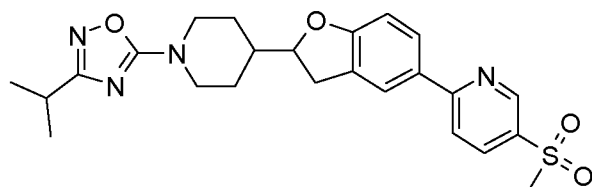
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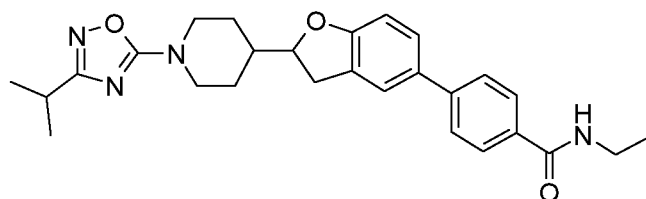
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including any tautomers and stereoisomers thereof, or a salt thereof or a solvate or hydrate thereof.

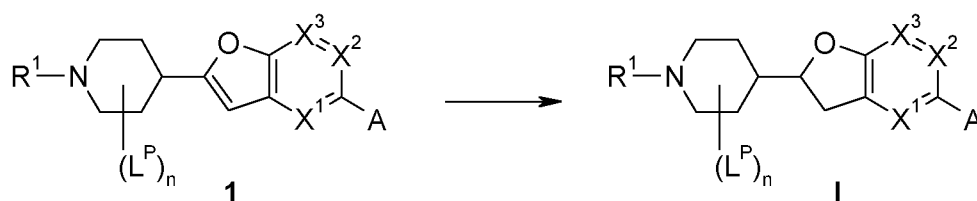
- 5 The compounds according to the invention and their intermediates may be obtained using methods of synthesis which are known to the one skilled in the art and described in the literature of organic synthesis. Preferably the compounds are obtained analogously to the methods of preparation explained more fully hereinafter, in particular as described in the experimental section. In some cases the sequence

adopted in carrying out the reaction schemes may be varied. Variants of these reactions that are known to the skilled man but are not described in detail here may also be used. The general processes for preparing the compounds according to the invention will become apparent to the skilled man on studying the schemes that follow. Starting compounds are commercially available or may be prepared by methods that are described in the literature or herein, or may be prepared in an analogous or similar manner. Before the reaction is carried out any corresponding functional groups in the compounds may be protected using conventional protecting groups. These protecting groups may be cleaved again at a suitable stage within the reaction sequence using methods familiar to the skilled man.

Compounds of the invention **I** are accessible using the synthetic route sketched in Scheme 1;  $R^1$ ,  $L^P$ ,  $n$ ,  $X^1$ ,  $X^2$ ,  $X^3$ , and  $A$  have the meanings as defined hereinbefore and hereinafter. Starting with compound **1** the target compounds are obtained upon partial reduction of the benzofuran. The reaction is preferably conducted with hydrogen as the reducing agent in the presence of a transition metal catalyst. Suited transition metals may be derived from Ni, Pd, Pt, Ir, and Rh, such as Raney nickel, Pd on carbon, Pt on carbon, Rh on carbon,  $PtO_2$ , and  $Rh_2O_3$ . The reduction is preferably carried out in tetrahydrofuran, acetone, ethyl acetate, alcohol, e.g. methanol, ethanol, or isopropanol, acetic acid, or mixtures thereof, at hydrogen pressures of 1 to 100 bar, at 0 to 120 °C. Alternatively, formic acid or a formate instead of hydrogen may be used as reducing agent.

The reduction may also be accomplished with a silane or sodium amalgam as reducing agent. Reduction using a silane is for example conducted with triethylsilane and trifluoroacetic acid in dichloromethane, chloroform, acetonitrile, mixtures thereof, or without a solvent in trifluoroacetic acid, at -20 to 120 °C. Sodium amalgam is frequently employed in an aqueous solution with sodium hydroxide or sodium bicarbonate.

Scheme 1

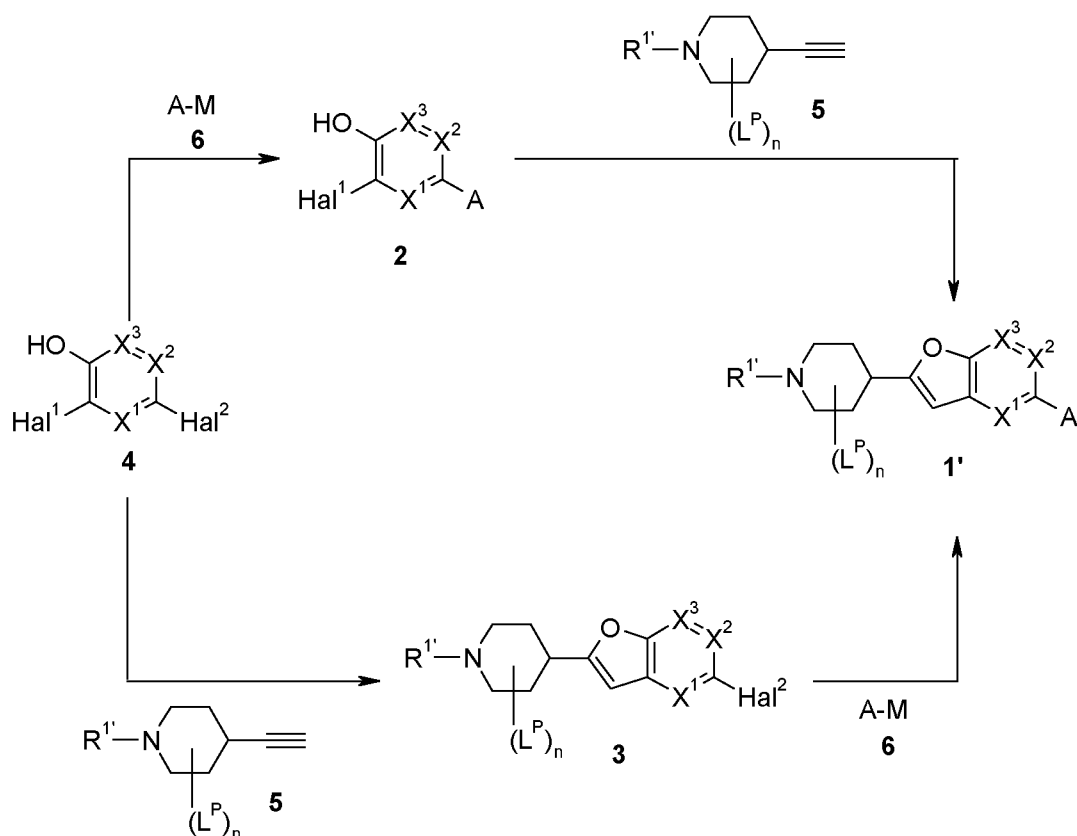


Compound **1**, in turn, may be obtained from compound **4**, bearing two replaceable halogen or pseudo-halogen groups, as described in Scheme 2;  $R^1$ ,  $L^P$ ,  $n$ ,  $X^1$ ,  $X^2$ ,  $X^3$ , and  $A$  have the meanings as defined hereinbefore and hereinafter. Depending on the reactivity of the two carbon atoms bearing the halogen or pseudo-halogen groups, the two coupling partners, **6** and **5**, are introduced following the sequence depicted on the top or bottom of the scheme. Both residues are preferably attached via a transition metal catalyzed reaction, preferably mediated by a palladium, nickel, copper, or iron species. The active catalyst may be derived from an elemental form of the transition metal, such as palladium on carbon or nanoparticles of iron or palladium, or a salt of the transition metal, such as fluoride, chloride, bromide, acetate, triflate, or trifluoroacetate, which are preferably combined with ligands, such as phosphines, e.g. tri-*tert*-butylphosphine, tricyclohexylphosphine, optionally substituted biphenyl-dicyclohexyl-phosphines, optionally substituted biphenyl-di-*tert*-butyl-phosphines, 1,1'-bis(diphenylphosphino)-ferrocene, triphenylphosphine, tritolyphosphine, or trifurylphosphine, phosphites, 1,3-disubstituted imidazole carbenes, 1,3-disubstituted imidazolidine carbenes, dibenzylideneacetone, allyl, or nitriles.  $A-M$  is preferably a boronic acid, trifluoroborate, boronic ester, zinc halide, or magnesium halide of  $A$  and alkyne **5** is preferably used as is or zinc acetylide.

Depending on the nucleophiles the reactions are preferably conducted in benzene, toluene, ether, tetrahydrofuran, 1,2-dimethoxyethane, 1,4-dioxane,  $N,N$ -dimethylformamide,  $N,N$ -dimethylacetamide,  $N$ -methylpyrrolidinone, alcohol, water, or mixtures thereof, at  $-10$  to  $160$  °C. Additives such as halide salts, e.g. lithium chloride, potassium fluoride, tetrabutylammonium fluoride, hydroxide sources, such as potassium hydroxide, potassium carbonate, amines, such as triethylamine, diisopropylamine, and ethyldiisopropylamine, silver salts, such as silver oxide or triflate, and/or copper salts, such as copper iodide or chloride or copper thiophene-2-carboxylate, may be beneficial or even essential for the reaction to proceed. The conditions for the coupling of alkyne **5** with one of the electrophiles, **2** or **4**, may bring about the subsequent cyclization as well and thus provide the benzofuran. For instance, with  $Pd(PPh_3)_2Cl_2$ ,  $CuI$ , and triethylamine in  $N,N$ -dimethylformamide at  $20$  to  $140$  °C the benzofuran may be obtained directly. If the intermediate alkyne is obtained the benzofuran may be formed in a separate step using, for example,  $Bu_4NF$  in tetrahydrofuran at  $50$  to  $70$  °C,  $NaOH$  in aqueous solution at elevated

temperature, CuI or CuCN, optionally in the presence of NEt<sub>3</sub>, in N,N-dimethylformamide at elevated temperature, AuCl(PPh<sub>3</sub>) and AgOSO<sub>2</sub>CF<sub>3</sub> in CH<sub>2</sub>Cl<sub>2</sub> or tetrahydrofuran, AgOSO<sub>2</sub>CF<sub>3</sub>, optionally in the presence of trifluoroacetic acid, in CH<sub>2</sub>Cl<sub>2</sub>, Pd, e.g. PdCl<sub>2</sub>, or other transition metals such as Rh. The benzofuran may also be assembled from a constellation in which the oxygen to cyclize (oxygen at the carbon atom next to the carbon atom bearing the alkynyl group) is embedded in an amide group of an aza-heterocyclic group provided that the additional group on the amide N is cleavable under the reaction conditions (see e.g. *Synthesis* **2007**, 3117). The reactivities of the reaction partners (reacting carbons) described may be reversed, i.e. compounds **2**, **3**, and **4** are the nucleophile bearing M and compounds **5** and **6** are the electrophile bearing Hal<sup>1</sup> or Hal<sup>2</sup>, providing the same products under the same or similar conditions.

Scheme 2



R<sup>1'</sup> = R<sup>1</sup>, protective group, e.g., -CO<sub>2</sub>tBu

Hal<sup>1</sup>, Hal<sup>2</sup> = halogen or pseudohalogen, e.g., Cl, Br, I, OSO<sub>2</sub>CF<sub>3</sub>, OSO<sub>2</sub>Me, OSO<sub>2</sub>aryl

M = metal residue, e.g., B(OH)<sub>2</sub>, BF<sub>3</sub>K, B(OCMe<sub>2</sub>CMe<sub>2</sub>O), ZnCl/Br/I, MgCl/Br/I

Another viable route to synthesize compounds of the invention employs benzofuran derivative **7** as origin (Scheme 3);  $R^1$ ,  $L^P$ ,  $n$ ,  $X^1$ ,  $X^2$ ,  $X^3$ , and  $A$  have the meanings as defined hereinbefore and hereinafter. Compound **7** and piperidine **11** are preferably combined by a transition metal catalyzed process as described above for Scheme 2.

5 The reactivity of the 2-position of the benzofuran **7** determines the suited piperidine **11** for the coupling reaction. Benzofurans bearing Cl, Br, or I at the 2-position are preferably matched with, e.g., tetrahydropyridines bearing for  $Z$   $B(OH)_2$ ,

$B(OCMe_2CMe_2O)$ , or  $BF_3K$ . Reversing the reactivity of **7**, i.e. **7** is the nucleophilic partner bearing  $M$ , e.g.  $B(OH)_2$  or  $B(OCMe_2CMe_2O)$ , demands a piperidine of

10 opposite reactivity, i.e. tetrahydropyridines bearing for  $Z$ , e.g.,  $OSO_2CF_3$  or Cl.

Moreover, piperidin-4-ones ( $Z = =O$ ) may be coupled with electrophilic benzofurans **7** ( $Y = Cl, Br, I$ ) using tosylhydrazone, a base such as  $LiOtBu$ , and a Pd catalyst in a solvent such as 1,4-dioxane (see e.g. *Chem. Eur. J.* **2008**, *14*, 4792-5, and *Org. Lett.* **2010**, *12*, 4042-5, and references quoted therein). The additional double-bond in the

15 product due to the use of a tetrahydropyridine may be reduced along with the

benzofuran in the next reaction step as described above for Scheme 1. Halogenation with Cl, Br, or I of compound **9** delivers compound **10**. Chlorination is accomplished with, for example, *N*-chlorosuccinimide, chlorine, or sulfuryl chloride. *N*-chlorosuccinimide is preferably used in the presence of a Lewis acid, e.g.  $ZrCl_4$  or HCl, in

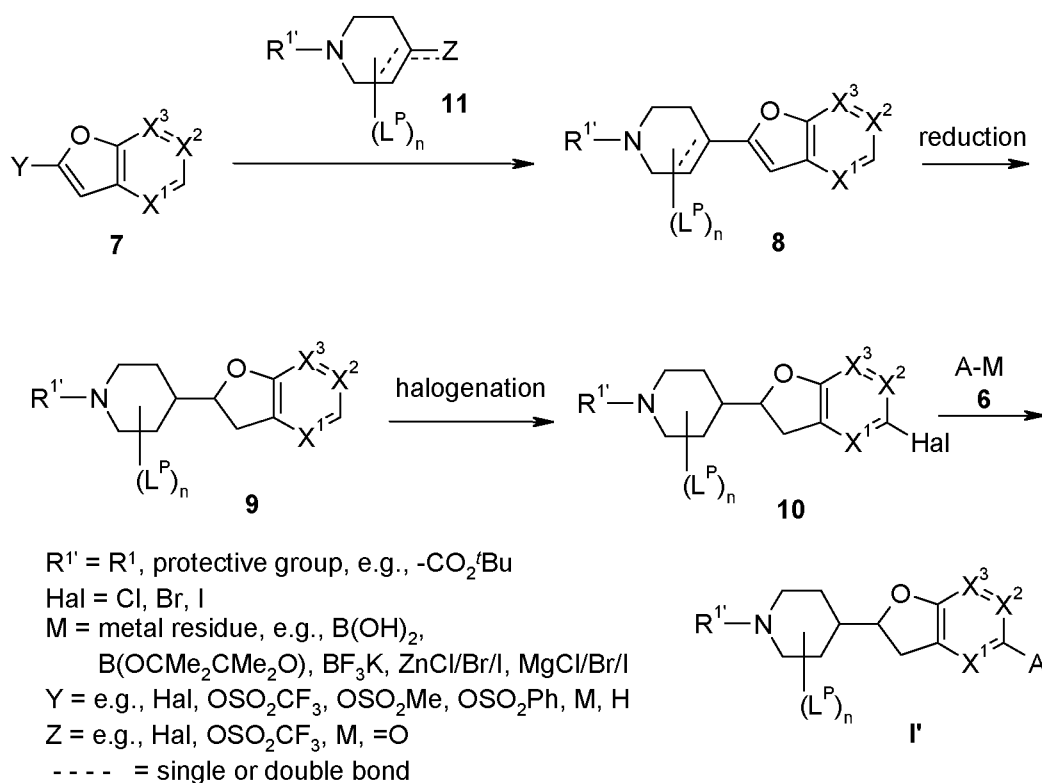
20 dichloromethane, acetonitrile, *N,N*-dimethylformamide, methanol, water, or acetic acid; chlorine is preferably employed in chloroform or acetic acid, and sulfuryl

chloride in dichloromethane and chloroform. Bromination is preferably achieved using bromine or *N*-bromosuccinimide in dichloromethane, acetonitrile, or acetic acid,

optionally in the presence of a Lewis acid. Iodine may be introduced with, e.g., iodine combined with silver nitrate, iodine in sulfuric acid, *N*-iodosuccinimide combined with

25 indium triflate, or iodine chloride in acetic acid or dichloromethane. The concluding step in Scheme 3, transition metal catalyzed coupling of **10** and **6**, may be carried out in analogy to the proceeding described above.

Scheme 3

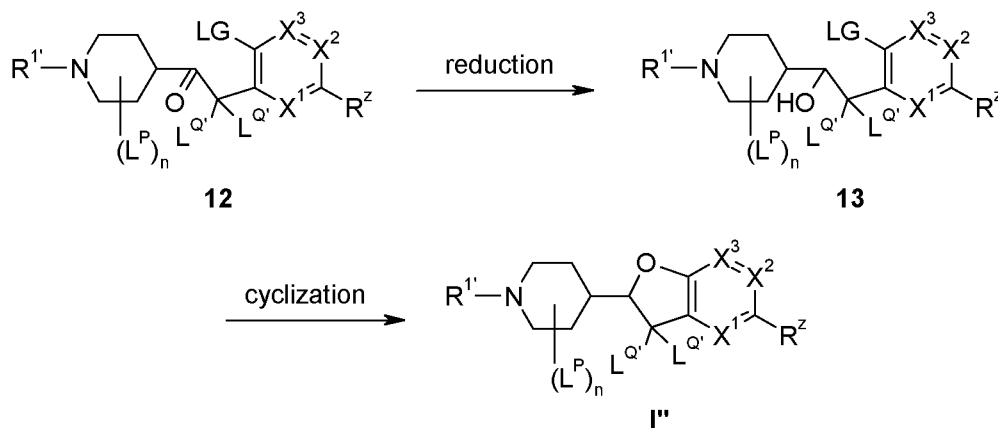


Scheme 4 shows another way of synthesis of compounds of the invention;  $R^1$ ,  $L^P$ ,  $L^Q$ ,  
 5  $n$ ,  $X^1$ ,  $X^2$ ,  $X^3$ , and  $A$  have the meanings as defined hereinbefore and hereinafter. The  
 sequence commences with reduction of ketone **12** to obtain alcohol **13**. The  
 reduction is preferably conducted with a complex metal hydride, such as sodium  
 borohydride, lithium borohydride, lithium triethylborohydride, diisobutylaluminum  
 hydride, or lithium aluminum hydride. Sodium borohydride is usually used in aqueous  
 10 or alcoholic solutions at  $-20$  to  $100^\circ\text{C}$ , while the other reagents are preferably  
 employed in dichloromethane, 1,2-dichloroethane, hexanes, ether, 1,4-dioxane,  
 tetrahydrofuran, N-methylpyrrolidone, benzene, toluene, or mixtures thereof, at  $-80$  to  
 $60^\circ\text{C}$ . The reduction may also be conducted in a stereoselective fashion to access  
 only one enantiomer using, e.g., the conditions of the Corey-Bakshi-Shibata (CBS)  
 15 reduction (also called Corey-Itsuno reduction).

Intramolecular substitution of the leaving group LG with oxygen provides target  
 compound **1'**. For LG equals F,  $\text{SO}_2\text{C}_{1-4}\text{-alkyl}$ ,  $\text{SO}_2\text{-aryl}$ , or  $\text{NO}_2$ , the reaction is  
 preferably carried out in the presence of a base, such as NaH,  $\text{CaH}_2$ , BuLi,  $\text{KO}^t\text{Bu}$ , or  
 KOH, in toluene, tetrahydrofuran, 1,4-dioxane, N,N-dimethylformamide, N,N-  
 20 dimethylacetamide, N-methylpyrrolidone, or mixtures thereof, at  $20$  to  $200^\circ\text{C}$ . For LG

is Cl, Br, I, the reaction is preferably conducted in the presence of a transition metal catalyst, such as a Pd or Cu species.

Scheme 4



LG = leaving group, e.g., F, Cl, Br, I, OSO<sub>2</sub>C<sub>1-4</sub>-alkyl, SO<sub>2</sub>-aryl, NO<sub>2</sub>  
 R<sup>Z</sup> = A or group that allows introduction of A, e.g., as described above  
 R' = R<sup>1</sup>, protective group, e.g., -CO<sub>2</sub><sup>t</sup>Bu  
 L<sup>Q'</sup> = L<sup>Q</sup>, H

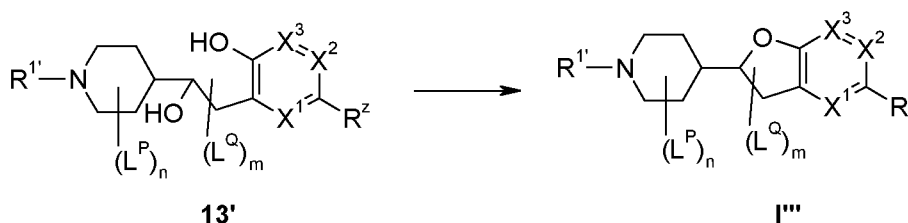
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The dihydrofuran ring may also be formed from compound 13', bearing an additional hydroxy group on the aromatic ring. Intramolecular substitution of the aliphatic OH group with the aromatic O group may be accomplished using a phosphine and an azodicarboxylic ester or amide in tetrahydrofuran, 1,4-dioxane, diethyl ether, toluene, benzene, dichloromethane, or mixtures thereof at -30 to 100 °C (Mitsunobu reaction). Triphenylphosphine or tributylphosphine combined with dimethyl azodicarboxylate, diethyl azodicarboxylate, diisopropyl azodicarboxylate, di-(4-chlorobenzyl) azodicarboxylate, dibenzyl azodicarboxylate, di-tert-butyl azodicarboxylate, azodicarboxylic acid bis-(dimethylamide), azodicarboxylic acid dipiperidide, or azodicarboxylic acid dimorpholide are common combinations for this transformation. Alternatively, the aliphatic OH group may be transformed into a leaving group, such as Cl, Br, I, OSO<sub>2</sub>CH<sub>3</sub>, and OSO<sub>2</sub>Ph, and then displaced with the aromatic O under basic conditions. Suited bases may be, for instance, carbonates, e.g. Cs<sub>2</sub>CO<sub>3</sub> and K<sub>2</sub>CO<sub>3</sub>, hydrides, e.g. NaH, alcoholates, e.g. NaOMe and KO<sup>t</sup>Bu, hydroxides, e.g. KOH and NaOH, that are preferably employed in toluene, tetrahydrofuran, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidinone, dimethyl sulfoxide, alcohol, water, and mixtures thereof. The reaction may be carried out such

that the aliphatic hydroxy group is substituted with complete inversion of configuration delivering an enantiomerically enriched or pure product provided an enantiomerically enriched or pure starting compound is used.

5

Scheme 5



$R^{1'} = R^1$ , protective group, e.g.,  $-\text{CO}_2^t\text{Bu}$

$R^z = \text{A}$  or group that allows introduction of A, e.g., as described above

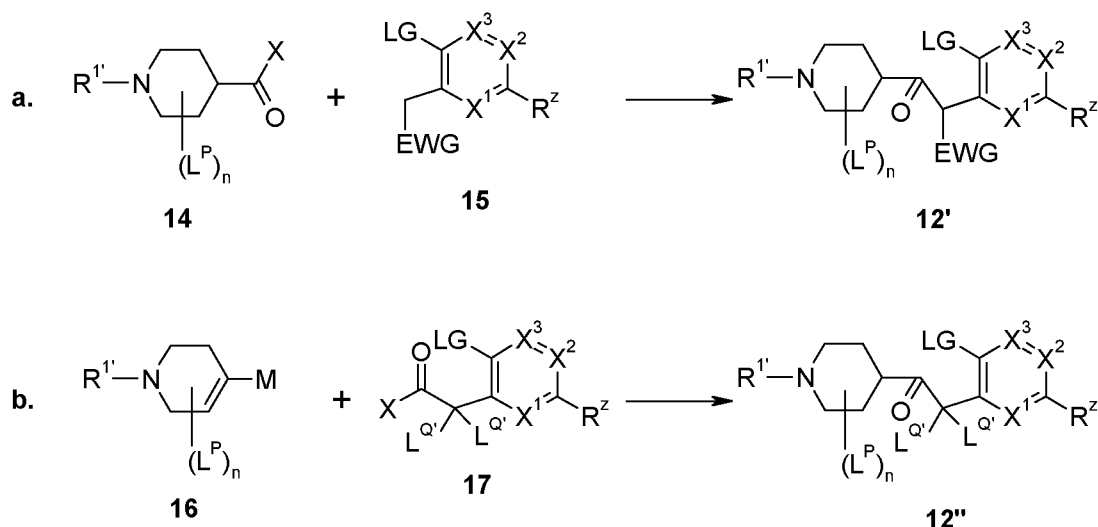
Intermediate **12** may be accessed as delineated in Scheme 6;  $R^1$ ,  $L^P$ ,  $L^Q$ ,  $n$ ,  $X^1$ ,  $X^2$ ,  $X^3$ , and A have the meanings as defined hereinbefore and hereinafter. A carboxylic acid derivative **14** can be merged with an aromatic compound **15**, that bears an anionic carbon center attached to the aromatic ring, to provide intermediate **12'** (route **a.**). Suited carboxylic acid derivatives may be e.g. carboxylic halides, carboxylic esters, carboxylic anhydrides, and carboxylic amides, while suited nucleophile precursors **15** preferably bear an electron-withdrawing group (EWG) at the carbon center to generate the negative charge more easily; preferred EWG are carboxylic esters and cyano. The reaction is mediated by a base that deprotonates compound **15** to generate the anion which, in turn, adds to the carboxylic function of **14** to give **12'**; the anion generating step may be carried out in the presence or prior to the addition of compound **14**. Most preferred bases are selected from alcoholates, e.g.  $\text{KO}^t\text{Bu}$  and  $\text{NaOMe}$ , amines, e.g. triethylamine and 1,8-diazabicyclo[5.4.0]undec-7-ene, carbonates, e.g.  $\text{Cs}_2\text{CO}_3$  and  $\text{K}_2\text{CO}_3$ , hydroxides, e.g.  $\text{NaOH}$  and  $\text{KOH}$ , and amides, e.g.  $\text{LiN}(\text{SiMe}_3)_2$  and  $\text{LiN}^i\text{Pr}_2$ , that, depending on their reactivity and compatibility, may be used in solvents such as toluene, tetrahydrofuran, 1,4-dioxane, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidinone, dimethyl sulfoxide, alcohol, or mixtures thereof. For example, a compound **14** bearing an ester function ( $X = \text{O}-\text{C}_{1-4}\text{-alkyl}$ ) may be combined with a compound **15** bearing a cyano or ester group ( $\text{EWG} = \text{CN}$  or  $\text{C}(=\text{O})\text{OC}_{1-4}\text{-alkyl}$ ) using  $\text{KO}^t\text{Bu}$  or  $\text{NaOEt}$  as base and tetrahydrofuran, N-methylpyrrolidinon, or ethanol as solvent. The product **12'** may be

transformed into intermediate **12** by hydrolysis of the ester or cyano group followed by decarboxylation of the resulting carboxylic acid function. EWG groups such as nitro or sulfonyl can be removed as well.

Combination of compounds **16** and **17** is another way of synthesis for intermediate

- 5 **12** (route **b.**). Depending on the reactivity of the coupling partners, the reaction is best conducted in the presence of a transition metal catalyst or without an additive. For example, compound **16** bearing a boronic acid ( $M = B(OH)_2$ ) and compound **17** having a carboxylic chloride ( $X = Cl$ ) may be coupled using a Pd catalyst, e.g.  $Pd(PPh_3)_4$ , and a base, e.g.  $K_3PO_4$ , in a solvent, e.g. toluene or 1,4-dioxane, at 60 to
- 10 120 °C. A compound **16** with  $M = Li$  or  $MgCl$  may be matched with an electrophile **17** bearing a carboxamide group ( $X = N(OMe)Me$ ). The reaction is commonly conducted in tetrahydrofuran, 1,4-dioxane, ether, toluene, or mixtures thereof, at -70 to 40 °C, optionally in the presence of an additive such as  $CeCl_3$ . Compound **12''** may be converted to intermediate **12** by reduction of the double bond with hydrogen or a
- 15 formate in the presence of a transition metal, e.g. Pd on carbon, or a hydride, e.g.  $[CuH(PPh_3)]_6$ .

Scheme 6



$R^{1'} = R^1$ , protective group, e.g.,  $-\text{CO}_2^t\text{Bu}$

$R^z = \text{A}$  or group that allows introduction of A, e.g., as described above

$L^{Q'} = \text{H}$ ,  $L^Q$

EWG = H or electron withdrawing group, e.g.,  $\text{CO}_2\text{C}_{1-4}\text{-alkyl}$ , CN,  $\text{SO}_2\text{C}_{1-4}\text{-alkyl}$ ,  $\text{NO}_2$

LG = leaving group, e.g., F, Cl, Br, I,  $\text{SO}_2\text{C}_{1-4}\text{-alkyl}$ ,  $\text{SO}_2\text{-aryl}$ ,  $\text{NO}_2$

M = metal residue, e.g.,  $\text{B}(\text{OH})_2$ ,  $\text{BF}_3\text{K}$ ,  $\text{B}(\text{OCMe}_2\text{CMe}_2\text{O})$ ,  $\text{ZnCl}/\text{Br}/\text{I}$ ,  $\text{MgCl}/\text{Br}/\text{I}$ ,  $\text{CeCl}_2$

X = leaving group, e.g., Cl,  $\text{OC}_{1-4}\text{-alkyl}$ ,  $\text{N}(\text{OMe})\text{Me}$

The general way of attaching residue  $R^1$  to the N atom of the piperidine of the compounds of the invention or an intermediate towards them is sketched in Scheme

7;  $R^1$ ,  $L^P$ , and n have the meanings as defined hereinbefore and hereinafter. The

reaction may be conducted as a classical nucleophilic substitution on a

heteroaromatic bearing a leaving group, such as F, Cl, Br,  $\text{SO}_2\text{C}_{1-4}\text{-alkyl}$ ,  $\text{SO}_2\text{aryl}$ , and  $\text{NO}_2$ . The reaction partners are preferably coupled in the presence of a mild base, e.g.  $\text{Na}_2\text{CO}_3$ ,  $\text{K}_2\text{CO}_3$ , or  $\text{Cs}_2\text{CO}_3$ , pyridine, 4-dimethylaminopyridine,

triethylamine, ethyldiisopropylamine, 1,8-diazabicyclo[5.4.0]undec-7-ene, in toluene, tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane, acetonitrile, N,N-

dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidinone, water, methanol, ethanol, isopropanol, dimethyl sulfoxide, or mixtures thereof, at 20 to 220 °C by conventional or microwave heating. Alternatively, the piperidine **18** may be

transformed into the corresponding metal piperidide by deprotonation with a strong base, e.g. butyl lithium, NaH, or KH, prior to the addition of the electrophile **19**.

In certain cases the use of transition metals as catalysts for the coupling may be beneficial or even essential. The leaving group X in compound **19** is then preferably Cl, Br, I,  $\text{OSO}_2\text{CH}_3$ ,  $\text{OSO}_2\text{tolyl}$ , and  $\text{OSO}_2\text{CF}_3$ . The reactions are preferably

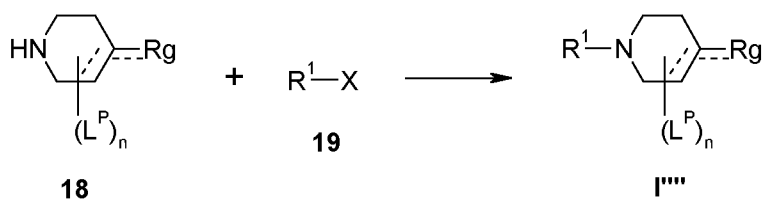
conducted with a transition metal derived catalyst which is preferably based on copper or palladium. The catalyst may be an elemental form of the transition metal, such as palladium on charcoal or nanoparticles of palladium, a salt of the transition metal, such as CuCl, CuBr, CuI, Cu(O<sub>3</sub>SCF<sub>3</sub>)<sub>2</sub>, Cu(O<sub>2</sub>CCH<sub>3</sub>)<sub>2</sub>, PdCl<sub>2</sub>, PdBr<sub>2</sub>,

- 5 Pd(O<sub>2</sub>CCH<sub>3</sub>)<sub>2</sub>, and Pd(O<sub>2</sub>CCF<sub>3</sub>)<sub>2</sub>, or a complex of the transition metal, such as Pd<sub>2</sub>(dibenzylideneacetone)<sub>3</sub>, all of which may optionally be combined with additional ligands, such as phosphines, e.g. triphenylphosphine, tritolylphosphine, tri-cyclohexylphosphine, tri-tert-butylphosphine, 1,1'-bis(diphenylphosphino)ferrocene, optionally substituted biphenyl-di-tert-butylphosphines or biphenyl-dicyclohexyl-phosphines, 2,2'-bis(diphenylphosphinyl)-1,1'-binaphthyl, 1,3-disubstituted imidazole or imidazolidine carbenes, phosphites, 1,3-diketones, nitriles, or alkenes. The coupling reaction is preferably conducted in the presence of a base, such as NaOtBu, KOtBu, LiN(SiMe<sub>3</sub>)<sub>2</sub>, K<sub>2</sub>CO<sub>3</sub>, Cs<sub>2</sub>CO<sub>3</sub>, or K<sub>3</sub>PO<sub>4</sub>, in toluene, benzene, tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane, N,N-dimethylformamide, N,N-
- 10 dimethylacetamide, N-methylpyrrolidinone, dimethyl sulfoxide, tBuOH, or mixtures thereof, at 0 to 180 °C.

Alternatively, particular residues R<sup>1</sup> such as [1,2,4]oxadiazoles and [1,2,4]triazoles may be assembled from the corresponding cyanamide of compound **18** and N-hydroxyamidine or N-aminoamidine, respectively, as described in the experimental

20 part.

Scheme 7



Rg = group that allows attachment of or is missing residue to obtain compounds of general formula I, e.g., see respective compounds outlined above

X = leaving group, e.g., F, Cl, Br, I, OSO<sub>2</sub>CF<sub>3</sub>, OSO<sub>2</sub>C<sub>1-4</sub>-alkyl, OSO<sub>2</sub>-aryl, SO<sub>2</sub>C<sub>1-4</sub>-alkyl, NO<sub>2</sub>

- - - = single or double bond

- 25 The synthetic routes presented may rely on the use of protecting groups. For example, potentially reactive groups present, such as hydroxy, carbonyl, carboxy, amino, alkylamino, or imino, may be protected during the reaction by conventional

protecting groups which are cleaved again after the reaction. Suitable protecting groups for the respective functionalities and their removal are well known to the one skilled in the art and are described in the literature of organic synthesis.

- 5 The compounds of general formula I may be resolved into their enantiomers and/or diastereomers as mentioned before. Thus, for example, *cis/trans* mixtures may be resolved into their *cis* and *trans* isomers and racemic compounds may be separated into their enantiomers.
- 10 The *cis/trans* mixtures may be resolved, for example, by chromatography into the *cis* and *trans* isomers thereof. The compounds of general formula I which occur as racemates may be separated by methods known *per se* into their optical antipodes and diastereomeric mixtures of compounds of general formula I may be resolved into their diastereomers by taking advantage of their different physico-chemical properties
- 15 using methods known *per se*, e.g. chromatography and/or fractional crystallization; if the compounds obtained thereafter are racemates, they may be resolved into the enantiomers as mentioned above.

The racemates are preferably resolved by column chromatography on chiral phases

20 or by crystallization from an optically active solvent or by reacting with an optically active substance which forms salts or derivatives such as esters or amides with the racemic compound. Salts may be formed with enantiomerically pure acids for basic compounds and with enantiomerically pure bases for acidic compounds.

Diastereomeric derivatives are formed with enantiomerically pure auxiliary

25 compounds, e.g. acids, their activated derivatives, or alcohols. Separation of the diastereomeric mixture of salts or derivatives thus obtained may be achieved by taking advantage of their different physico-chemical properties, e.g. differences in solubility; the free antipodes may be released from the pure diastereomeric salts or derivatives by the action of suitable agents. Optically active acids in common use for

30 such a purpose are e.g. the D- and L-forms of tartaric acid, dibenzoyltartaric acid, ditoluoyltartaric acid, malic acid, mandelic acid, camphorsulfonic acid, glutamic acid, aspartic acid, or quinic acid. Optically active alcohols applicable as auxiliary residues may be, for example, (+) or (-)-menthol and optically active acyl groups in amides may be, for example, (+)- or (-)-menthyloxycarbonyl.

As mentioned above, the compounds of formula I may be converted into salts, particularly for pharmaceutical use into the pharmaceutically acceptable salts. As used herein, "pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof.

The compounds according to the invention are advantageously also obtainable using the methods described in the examples that follow, which may also be combined for this purpose with methods known to the skilled man from the literature.

### Terms and definitions

Terms not specifically defined herein should be given the meanings that would be given to them by one of skill in the art in light of the disclosure and the context. As used in the specification, however, unless specified to the contrary, the following terms have the meaning indicated and the following conventions are adhered to.

The terms "compound(s) according to this invention", "compound(s) of formula (I)", "compound(s) of the invention" and the like denote the compounds of the formula (I) according to the present invention including their tautomers, stereoisomers and mixtures thereof and the salts thereof, in particular the pharmaceutically acceptable salts thereof, and the solvates and hydrates of such compounds, including the solvates and hydrates of such tautomers, stereoisomers and salts thereof.

The terms "treatment" and "treating" embraces both preventative, i.e. prophylactic, or therapeutic, i.e. curative and/or palliative, treatment. Thus the terms "treatment" and "treating" comprise therapeutic treatment of patients having already developed said condition, in particular in manifest form. Therapeutic treatment may be symptomatic treatment in order to relieve the symptoms of the specific indication or causal treatment in order to reverse or partially reverse the conditions of the indication or to stop or slow down progression of the disease. Thus the compositions and methods of the present invention may be used for instance as therapeutic treatment over a period of time as well as for chronic therapy. In addition the terms "treatment" and

"treating" comprise prophylactic treatment, i.e. a treatment of patients at risk to develop a condition mentioned hereinbefore, thus reducing said risk.

When this invention refers to patients requiring treatment, it relates primarily to treatment in mammals, in particular humans.

The term "therapeutically effective amount" means an amount of a compound of the present invention that (i) treats or prevents the particular disease or condition, (ii) attenuates, ameliorates, or eliminates one or more symptoms of the particular disease or condition, or (iii) prevents or delays the onset of one or more symptoms of the particular disease or condition described herein.

The terms "modulated" or "modulating", or "modulate(s)", as used herein, unless otherwise indicated, refers to the activation of the G-protein-coupled receptor GPR119 with one or more compounds of the present invention.

The terms "mediated" or "mediating" or "mediate", as used herein, unless otherwise indicated, refers to the (i) treatment, including prevention of the particular disease or condition, (ii) attenuation, amelioration, or elimination of one or more symptoms of the particular disease or condition, or (iii) prevention or delay of the onset of one or more symptoms of the particular disease or condition described herein.

The term "substituted" as used herein, means that any one or more hydrogens on the designated atom, radical or moiety is replaced with a selection from the indicated group, provided that the atom's normal valence is not exceeded, and that the substitution results in an acceptably stable compound.

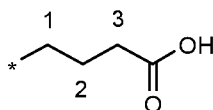
In the groups, radicals, or moieties defined below, the number of carbon atoms is often specified preceding the group, for example, C<sub>1-6</sub>-alkyl means an alkyl group or radical having 1 to 6 carbon atoms. In general, for groups comprising two or more subgroups, the last named subgroup is the radical attachment point, for example, the substituent "aryl-C<sub>1-3</sub>-alkyl-" means an aryl group which is bound to a C<sub>1-3</sub>-alkyl-group, the latter of which is bound to the core or to the group to which the substituent is attached.

In case a compound of the present invention is depicted in form of a chemical name and as a formula in case of any discrepancy the formula shall prevail.

- 5 An asterisk is may be used in sub-formulas to indicate the bond which is connected to the core molecule as defined.

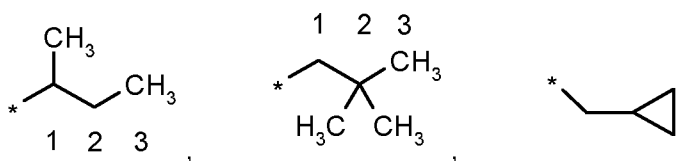
The numeration of the atoms of a substituent starts with the atom which is closest to the core or to the group to which the substituent is attached.

- 10 For example, the term "3-carboxypropyl-group" represents the following substituent:



wherein the carboxy group is attached to the third carbon atom of the propyl group.

The terms "1-methylpropyl-", "2,2-dimethylpropyl-" or "cyclopropylmethyl-" group represent the following groups:



15

The asterisk may be used in sub-formulas to indicate the bond which is connected to the core molecule as defined.

- 20 In a definition of a group the term "wherein each X, Y and Z group is optionally substituted with" and the like denotes that each group X, each group Y and each group Z either each as a separate group or each as part of a composed group may be substituted as defined. For example a definition "R<sup>ex</sup> denotes H, C<sub>1-3</sub>-alkyl, C<sub>3-6</sub>-cycloalkyl, C<sub>3-6</sub>-cycloalkyl-C<sub>1-3</sub>-alkyl or C<sub>1-3</sub>-alkyl-O-, wherein each alkyl group is
- 25 optionally substituted with one or more L<sup>ex</sup>." or the like means that in each of the beforementioned groups which comprise the term alkyl, i.e. in each of the groups C<sub>1-3</sub>-alkyl, C<sub>3-6</sub>-cycloalkyl-C<sub>1-3</sub>-alkyl and C<sub>1-3</sub>-alkyl-O-, the alkyl moiety may be substituted with L<sup>ex</sup> as defined.

- 30 In the following the term bicyclic includes spirocyclic.

Unless specifically indicated, throughout the specification and the appended claims, a given chemical formula or name shall encompass tautomers and all stereo, optical and geometrical isomers (e.g. enantiomers, diastereomers, E/Z isomers etc...) and  
5 racemates thereof as well as mixtures in different proportions of the separate enantiomers, mixtures of diastereomers, or mixtures of any of the foregoing forms where such isomers and enantiomers exist, as well as salts, including pharmaceutically acceptable salts thereof and solvates thereof such as for instance hydrates including solvates of the free compounds or solvates of a salt of the  
10 compound.

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of  
15 human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, and commensurate with a reasonable benefit/risk ratio.

As used herein, "pharmaceutically acceptable salts" refer to derivatives of the  
20 disclosed compounds wherein the parent compound is modified by making acid or base salts thereof.

Salts of other acids than those mentioned above which for example are useful for purifying or isolating the compounds of the present invention (e.g. trifluoro acetate  
25 salts) also comprise a part of the invention.

The term halogen generally denotes fluorine, chlorine, bromine and iodine.

The term "C<sub>1-n</sub>-alkyl", wherein n is an integer from 1 to n, either alone or in  
30 combination with another radical denotes an acyclic, saturated, branched or linear hydrocarbon radical with 1 to n C atoms. For example the term C<sub>1-5</sub>-alkyl embraces the radicals H<sub>3</sub>C-, H<sub>3</sub>C-CH<sub>2</sub>-, H<sub>3</sub>C-CH<sub>2</sub>-CH<sub>2</sub>-, H<sub>3</sub>C-CH(CH<sub>3</sub>)-, H<sub>3</sub>C-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-, H<sub>3</sub>C-CH<sub>2</sub>-CH(CH<sub>3</sub>)-, H<sub>3</sub>C-CH(CH<sub>3</sub>)-CH<sub>2</sub>-, H<sub>3</sub>C-C(CH<sub>3</sub>)<sub>2</sub>-, H<sub>3</sub>C-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-, H<sub>3</sub>C-CH<sub>2</sub>-CH<sub>2</sub>-CH(CH<sub>3</sub>)-, H<sub>3</sub>C-CH<sub>2</sub>-CH(CH<sub>3</sub>)-CH<sub>2</sub>-, H<sub>3</sub>C-CH(CH<sub>3</sub>)-CH<sub>2</sub>-CH<sub>2</sub>-, H<sub>3</sub>C-

$\text{CH}_2\text{-C}(\text{CH}_3)_2\text{-}$ ,  $\text{H}_3\text{C-C}(\text{CH}_3)_2\text{-CH}_2\text{-}$ ,  $\text{H}_3\text{C-CH}(\text{CH}_3)\text{-CH}(\text{CH}_3)\text{-}$  and  $\text{H}_3\text{C-CH}_2\text{-CH}(\text{CH}_2\text{CH}_3)\text{-}$ .

The term " $\text{C}_{1-n}$ -alkylene" wherein n is an integer 1 to n, either alone or in combination  
 5 with another radical, denotes an acyclic, straight or branched chain divalent alkyl radical containing from 1 to n carbon atoms. For example the term  $\text{C}_{1-4}$ -alkylene includes  $\text{-(CH}_2\text{)-}$ ,  $\text{-(CH}_2\text{-CH}_2\text{)-}$ ,  $\text{-(CH(CH}_3\text{))}-$ ,  $\text{-(CH}_2\text{-CH}_2\text{-CH}_2\text{)-}$ ,  $\text{-(C(CH}_3\text{)}_2\text{)-}$ ,  $\text{-(CH(CH}_2\text{CH}_3\text{))}-$ ,  $\text{-(CH(CH}_3\text{)-CH}_2\text{)-}$ ,  $\text{-(CH}_2\text{-CH(CH}_3\text{))}-$ ,  $\text{-(CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{)-}$ ,  $\text{-(CH}_2\text{-CH}_2\text{-CH(CH}_3\text{))}-$ ,  $\text{-(CH(CH}_3\text{)-CH}_2\text{-CH}_2\text{)-}$ ,  $\text{-(CH}_2\text{-CH(CH}_3\text{)-CH}_2\text{)-}$ ,  $\text{-(CH}_2\text{-C(CH}_3\text{)}_2\text{)-}$ ,  $\text{-(C(CH}_3\text{)}_2\text{-CH}_2\text{)-}$ ,  $\text{-(CH(CH}_3\text{)-CH(CH}_3\text{))}-$ ,  $\text{-(CH}_2\text{-CH(CH}_2\text{CH}_3\text{))}-$ ,  $\text{-(CH(CH}_2\text{CH}_3\text{)-CH}_2\text{)-}$ ,  $\text{-(CH(CH}_2\text{CH}_2\text{CH}_3\text{))}-$ ,  $\text{-(CHCH(CH}_3\text{)}_2\text{)-}$  and  $\text{-C(CH}_3\text{)(CH}_2\text{CH}_3\text{)-}$ .

The term " $\text{C}_{2-n}$ -alkenyl", is used for a group as defined in the definition for " $\text{C}_{1-n}$ -alkyl" with at least two carbon atoms, if at least two of those carbon atoms of said group  
 15 are bonded to each other by a double bond. For example the term  $\text{C}_{2-3}$ -alkenyl includes  $\text{-CH=CH}_2$ ,  $\text{-CH=CH-CH}_3$ ,  $\text{-CH}_2\text{-CH=CH}_2$ .

The term " $\text{C}_{2-n}$ -alkenylene" is used for a group as defined in the definition for " $\text{C}_{1-n}$ -alkylene" with at least two carbon atoms, if at least two of those carbon atoms  
 20 of said group are bonded to each other by a double bond. For example the term  $\text{C}_{2-3}$ -alkenylene includes  $\text{-CH=CH-}$ ,  $\text{-CH=CH-CH}_2\text{-}$ ,  $\text{-CH}_2\text{-CH=CH-}$ .

The term " $\text{C}_{2-n}$ -alkynyl", is used for a group as defined in the definition for " $\text{C}_{1-n}$ -alkyl" with at least two carbon atoms, if at least two of those carbon atoms of said group  
 25 are bonded to each other by a triple bond. For example the term  $\text{C}_{2-3}$ -alkynyl includes  $\text{-C}\equiv\text{CH}$ ,  $\text{-C}\equiv\text{C-CH}_3$ ,  $\text{-CH}_2\text{-C}\equiv\text{CH}$ .

The term " $\text{C}_{2-n}$ -alkynylene" is used for a group as defined in the definition for " $\text{C}_{1-n}$ -alkylene" with at least two carbon atoms, if at least two of those carbon atoms  
 30 of said group are bonded to each other by a triple bond. For example the term  $\text{C}_{2-3}$ -alkynylene includes  $\text{-C}\equiv\text{C-}$ ,  $\text{-C}\equiv\text{C-CH}_2\text{-}$ ,  $\text{-CH}_2\text{-C}\equiv\text{C-}$ .

The term " $\text{C}_{3-n}$ -carbocyclyl" as used either alone or in combination with another radical, denotes a monocyclic, bicyclic or tricyclic, saturated or unsaturated

hydrocarbon radical with 3 to n C atoms. The hydrocarbon radical is preferably nonaromatic. Preferably the 3 to n C atoms form one or two rings. In case of a bicyclic or tricyclic ring system the rings may be attached to each other via a single bond or may be fused or may form a spirocyclic or bridged ring system. For example  
5 the term C<sub>3-10</sub>-carbocyclyl includes C<sub>3-10</sub>-cylcoalkyl, C<sub>3-10</sub>-cycloalkenyl, octahydropentalenyl, octahydroindenyl, decahydronaphthyl, indanyl, tetrahydronaphthyl. Most preferably the term C<sub>3-n</sub>-carbocyclyl denotes C<sub>3-n</sub>-cylcoalkyl, in particular C<sub>3-7</sub>-cycloalkyl.

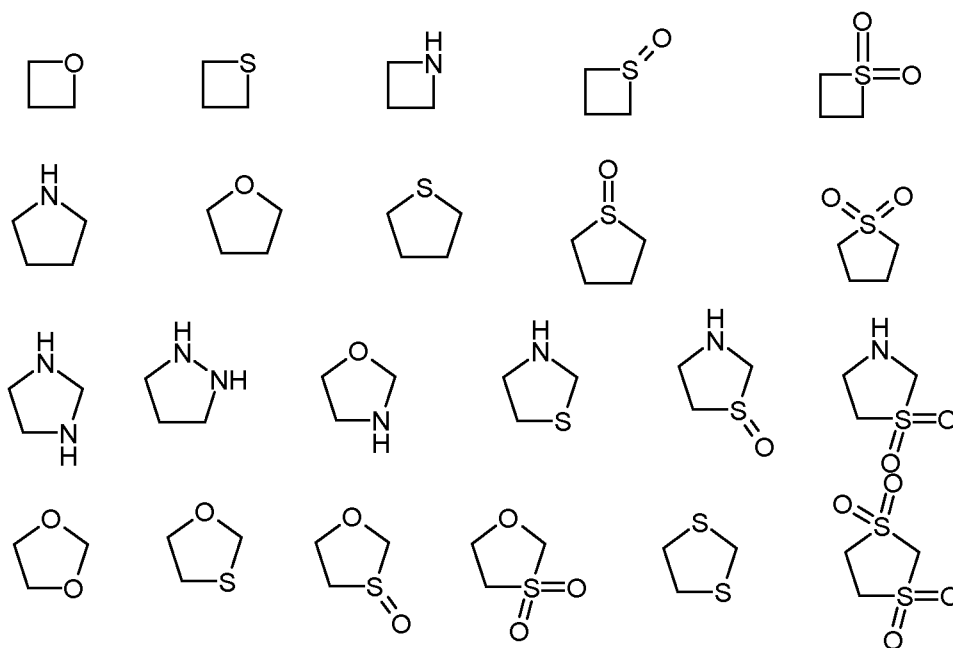
10 The term "C<sub>3-n</sub>-cycloalkyl", wherein n is an integer 4 to n, either alone or in combination with another radical denotes a cyclic, saturated, unbranched hydrocarbon radical with 3 to n C atoms. The cyclic group may be mono-, bi-, tri- or spirocyclic, most preferably monocyclic. Examples of such cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl,  
15 cyclododecyl, bicyclo[3.2.1.]octyl, spiro[4.5]decyl, norpinyl, norbonyl, norcaryl, adamantyl, etc.

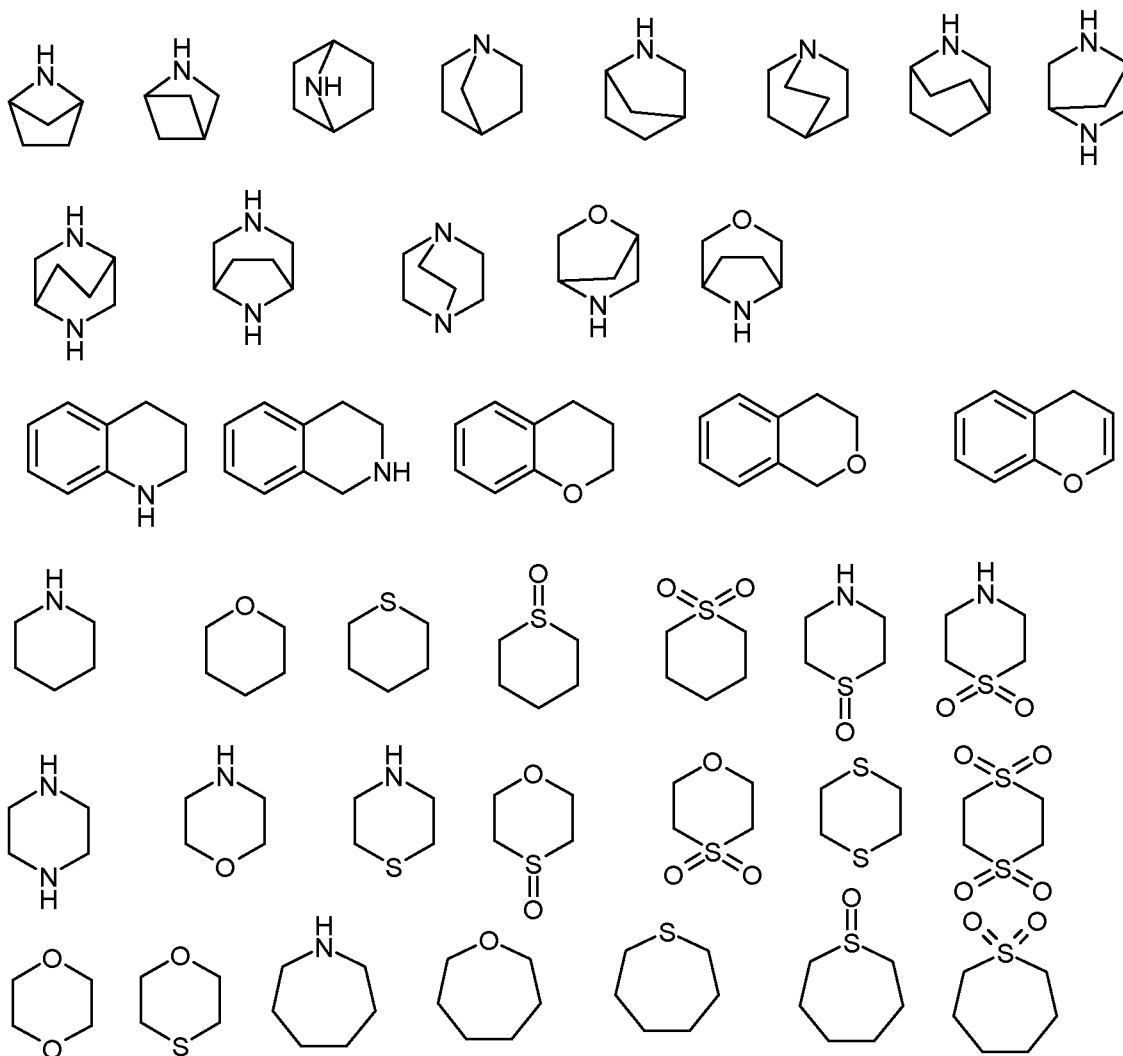
The term "C<sub>3-n</sub>-cycloalkenyl", wherein n is an integer 3 to n, either alone or in combination with another radical, denotes a cyclic, unsaturated but nonaromatic,  
20 unbranched hydrocarbon radical with 3 to n C atoms, at least two of which are bonded to each other by a double bond. For example the term C<sub>3-7</sub>-cycloalkenyl includes cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclopentadienyl, cyclohexenyl, cyclohexadienyl, cycloheptenyl, cycloheptadienyl and cycloheptatrienyl.

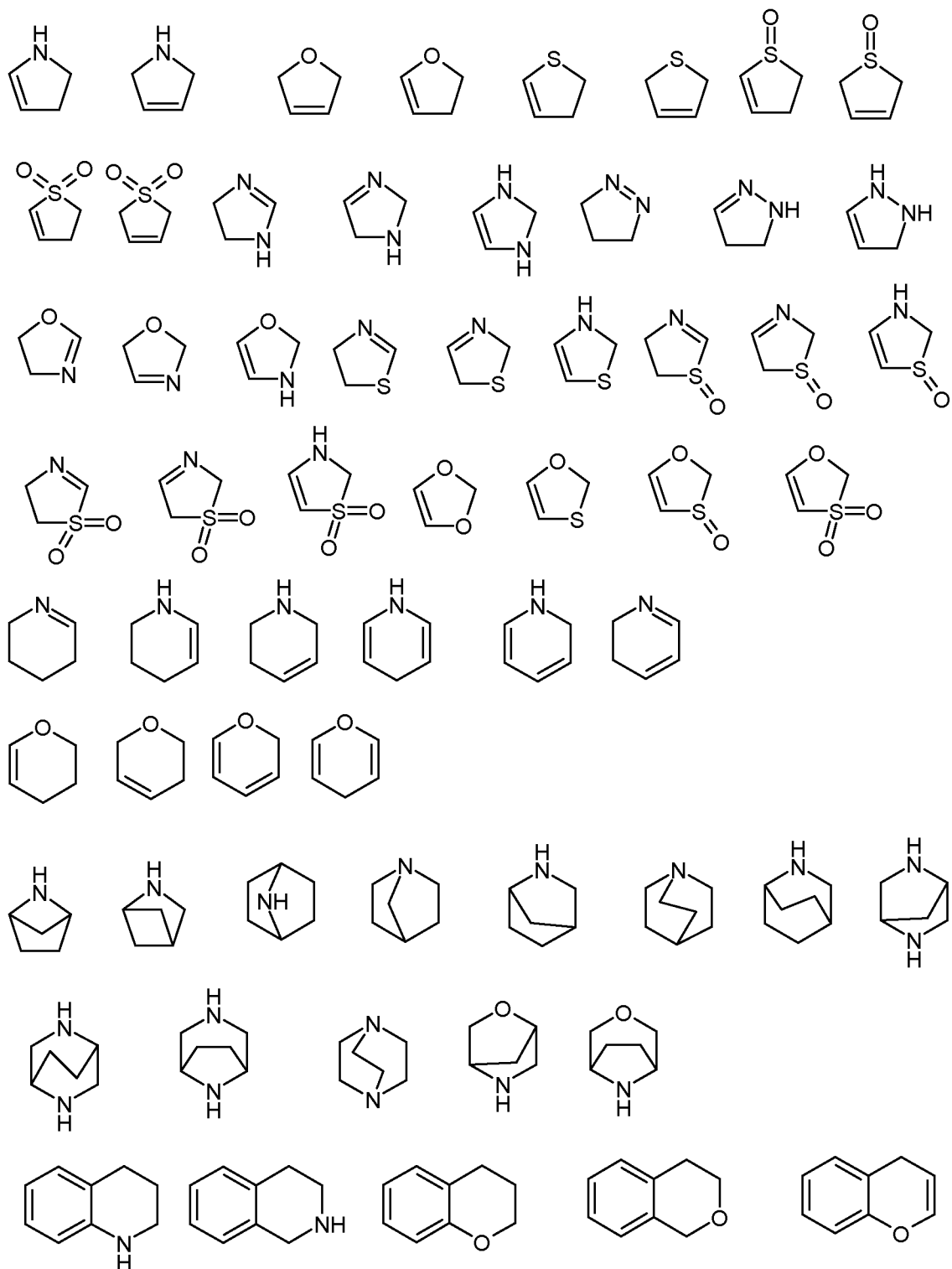
25 The term "aryl" as used herein, either alone or in combination with another radical, denotes a carbocyclic aromatic monocyclic group containing 6 carbon atoms which may be further fused to a second 5- or 6-membered carbocyclic group which may be aromatic, saturated or unsaturated. Aryl includes, but is not limited to, phenyl, indanyl, indenyl, naphthyl, anthracenyl, phenanthrenyl, tetrahydronaphthyl and  
30 dihydronaphthyl. More preferably the term "aryl" as used herein, either alone or in combination with another radical, denotes phenyl or naphthyl, most preferably phenyl.

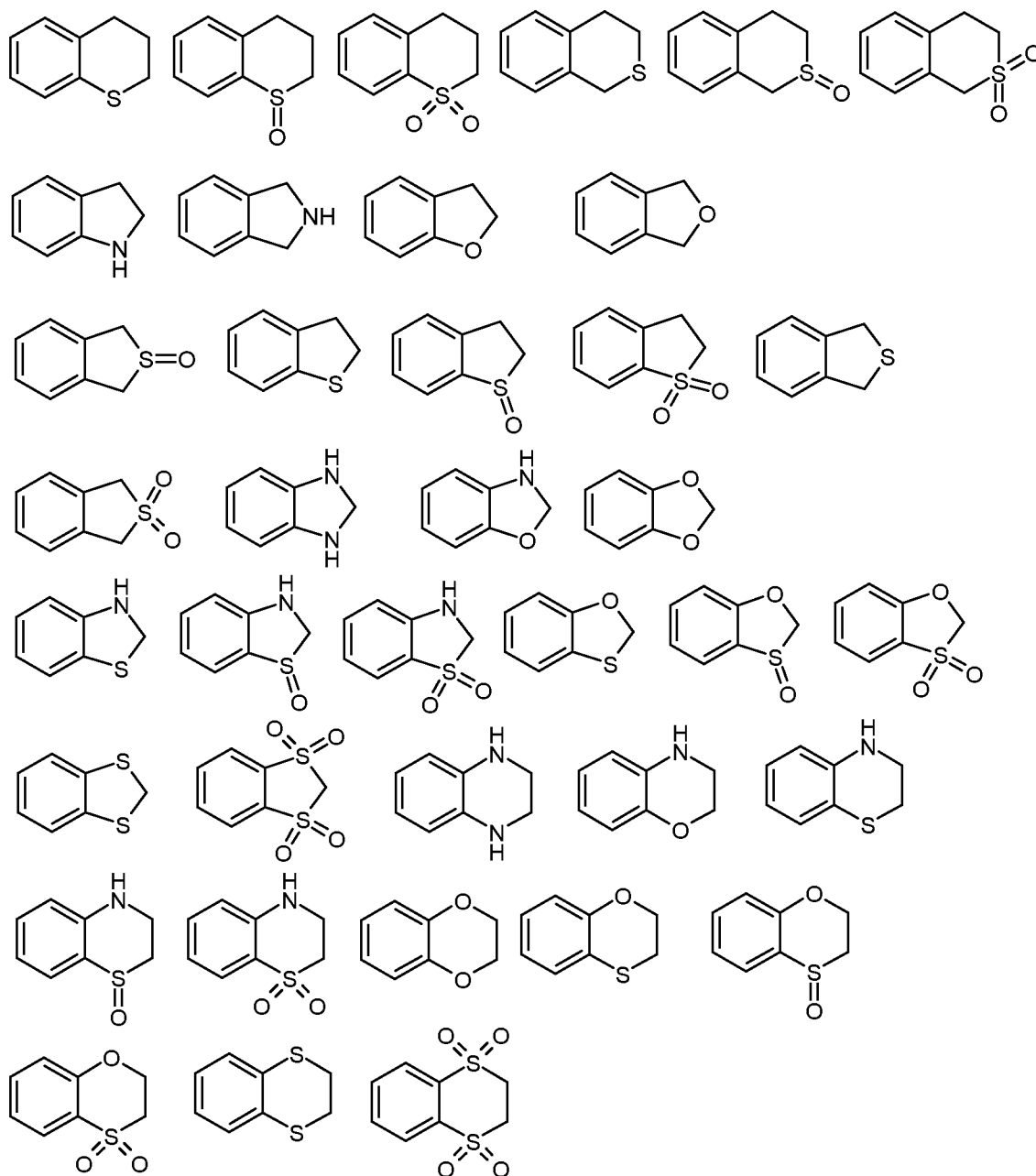
The term "heterocyclyl" means a saturated or unsaturated mono-, bi-, tri- or spirocarbocyclic, preferably mono-, bi- or spirocyclic-ring system containing one or more heteroatoms selected from N, O or S(O)<sub>r</sub> with r=0, 1 or 2, which in addition may have a carbonyl group. More preferably the term "heterocyclyl" as used herein, either  
 5 alone or in combination with another radical, means a saturated or unsaturated, even more preferably a saturated mono-, bi- or spirocyclic-ring system containing 1, 2, 3 or 4 heteroatoms selected from N, O or S(O)<sub>r</sub> with r=0, 1 or 2 which in addition may have a carbonyl group. The term "heterocyclyl" is intended to include all the possible isomeric forms. Examples of such groups include aziridinyl, oxiranyl, azetidiny,  
 10 oxetanyl, pyrrolidinyl, tetrahydrofuranyl, piperidinyl, tetrahydropyranyl, azepanyl, piperazinyl, morpholinyl, tetrahydrofuranonyl, tetrahydropyranonyl, pyrrolidinonyl, piperidinonyl, piperazinonyl, morpholinonyl.

Thus, the term "heterocyclyl" includes the following exemplary structures which are  
 15 not depicted as radicals as each form may be attached through a covalent bond to any atom so long as appropriate valences are maintained:









The term "heteroaryl" means a mono- or polycyclic, preferably mono- or bicyclic-ring system containing one or more heteroatoms selected from N, O or S(O)<sub>r</sub> with r=0, 1 or 2 wherein at least one of the heteroatoms is part of an aromatic ring, and wherein said ring system may have a carbonyl group. More preferably the term "heteroaryl" as used herein, either alone or in combination with another radical, means a mono- or bicyclic-ring system containing 1, 2, 3 or 4 heteroatoms selected from N, O or S(O)<sub>r</sub> with r=0, 1 or 2 wherein at least one of the heteroatoms is part of an aromatic ring, and wherein said ring system may have a carbonyl group. The term "heteroaryl" is intended to include all the possible isomeric forms.



Many of the terms given above may be used repeatedly in the definition of a formula or group and in each case have one of the meanings given above, independently of one another.

## 5 Pharmacological Activity

The activity of the compounds of the invention may be demonstrated using the following assay:

10 The compounds of formula I according to the invention modulate the activity of the G-protein-coupled receptor GPR119. The effect of the compounds on the activation of GPR119 and on the stimulation of intracellular cAMP concentration is determined using the AlphaScreen cAMP Assay Kit (Cat.No.# 6760625R) made by PerkinElmer.

15 MIN6 cells [Miyazaki J et al. Endocrinology. 1990 Jul;127(1):126-32] are stably transfected with an expression vector for human GPR119 cDNA (Acc. No. NP\_848566). Min-6 /hGPR119 cells are cultured in DMEM, 10% FBS, 50µM β-mercaptoethanol, 0.3mg/mL Genitacin, 2mM GlutaMAX at 37°C 5% CO<sub>2</sub>. For the assay, the cells are seeded in Optiplates (white, 384-well, 160W- barcoded, TC, sterile with lid, Cat.No.# 6007688 (Perkin Elmer); 10000 cells/well; 50µl). The plates  
20 covered with lids are then incubated for 24 hours at 37°C / 5% CO<sub>2</sub>. After the medium is aspirated from the wells completely, 10 µl of the test compound are added, the compounds are diluted using stimulating buffer (140mM NaCl, 3.6mM KCl, 0.5mM NaH<sub>2</sub>PO<sub>4</sub>, 0.5mM MgSO<sub>4</sub>, 1.5mM CaCl<sub>2</sub>, 10mM Hepes, 5mM NaHCO<sub>3</sub>; pH 7.4. 0.5mM IBMX and 0.1% BSA, the final DMSO concentration is 1%). After 45 minutes  
25 incubation at room temperature (approx. 20°C), the cAMP concentrations are determined using the AlphaScreen cAMP Assay Kit (Cat.No.# 6760625R from PerkinElmer). 10 µl of Biotin-cAMP (final concentration 1U/well in lysing buffer (5mM Hepes (pH 7.4), 0.1% BSA, 0.5% Tween) and 10µL Bead solution (final concentration 1 U/well in lysing buffer) are added. The plates are incubated for  
30 another 2 hours at room temperature. The cAMP concentrations are calculated using a cAMP standard curve from the Alpha Screen Counts. The data analysis is carried out by calculating the EC<sub>50</sub> value and the maximum value based on a positive control, using suitable software (Graphpad Prism). The compounds according to the invention increase the intracellular cAMP level in the range of 3-5.

The compounds according to the invention typically have EC<sub>50</sub> values in the range from about 1 nM to about 10 µM, preferably from 1 nM to 2 µM, preferably less than 1 µM, particularly preferably less than 500 nM, most particularly preferably less than 100 nM.

EC<sub>50</sub> values for compounds according to the invention are shown in the following Table. The number of the compound corresponds to the number of the Example in the experimental section.

| Example | EC <sub>50</sub><br>[nM] | Example | EC <sub>50</sub><br>[nM] | Example | EC <sub>50</sub><br>[nM] | Example | EC <sub>50</sub> [nM] |
|---------|--------------------------|---------|--------------------------|---------|--------------------------|---------|-----------------------|
| 1       | 21                       | 2       | 27                       | 3       | 71                       | 4       | 52                    |
| 5       | 12                       | 6       | 32                       | 7       | 35                       | 8       | 11                    |
| 9       | 12                       | 10      | 152                      | 11      | 59                       | 12      | 22                    |
| 13      | 28                       | 14      | 29                       | 15      | 38                       | 16      | 17                    |
| 17      | 21                       | 18      | 2                        | 19      | 25                       | 20      | 16                    |
| 21      | 28                       | 22      | 6                        | 23      | 7                        | 24      | 60                    |
| 25      | 62                       | 26      | 9                        | 27      | 15                       | 28      | 22                    |
| 29      | 51                       | 30      | 4                        | 31      | 3                        | 32      | 29                    |
| 33      | 6                        | 34      | 18                       | 35      | 3                        | 36      | 5                     |
| 37      | 6                        | 38      | 14                       | 39      | 8                        | 40      | 2                     |
| 41      | 6                        | 42      | 11                       | 43      | 9                        | 44      | 6                     |
| 45      | 13                       | 46      | 18                       | 47      | 6                        | 48      | 12                    |
| 49      | 25                       | 50      | 5                        | 51      | 7                        | 52      | 19                    |
| 53      | 20                       | 55      | 16                       | 57      | 36                       | 60      | 11                    |
| 61      | 47                       | 62      | 20                       | 63      | 112                      | 64      | 33                    |
| 65      | 228                      | 66      | 63                       | 67      | 141                      | 68      | 60                    |
| 69      | 48                       | 70      | 108                      | 71      | 16                       | 72      | 12                    |
| 73      | 19                       | 74      | 52                       | 75      | 81                       | 76      | 59                    |
| 77      | 19                       | 78      | 39                       | 79      | 3                        | 80      | 5                     |
| 81      | 10                       | 82      | 3                        | 83      | 3                        | 84      | 2                     |

| Example | EC <sub>50</sub><br>[nM] | Example | EC <sub>50</sub><br>[nM] | Example | EC <sub>50</sub><br>[nM] | Example | EC <sub>50</sub> [nM] |
|---------|--------------------------|---------|--------------------------|---------|--------------------------|---------|-----------------------|
| 85      | 7                        | 86      | 12                       | 87      | 13                       | 88      | 59                    |
| 89      | 16                       | 90      | 60                       | 91      | 3                        | 92      | 10                    |
| 93      | 10                       | 94      | 18                       |         |                          |         |                       |

In view of their ability to modulate the activity of the G-protein-coupled receptor GPR119, in particular an agonistic activity, the compounds of general formula (I) according to the invention, including the corresponding salts thereof, are theoretically  
5 suitable for the treatment of all those diseases or conditions which may be affected or which are mediated by the activation of the G-protein-coupled receptor GPR119.

Accordingly, the present invention relates to a compound of general formula (II) as a  
10 medicament.

Furthermore, the present invention relates to the use of a compound of general  
formula (II) or a pharmaceutical composition according to this invention for the  
treatment and/or prevention of diseases or conditions which are mediated by the  
activation of the G-protein-coupled receptor GPR119 in a patient, preferably in a  
15 human.

In yet another aspect the present invention relates to a method for treating a disease  
or condition mediated by the activation of the G-protein-coupled receptor GPR119 in  
a mammal that includes the step of administering to a patient, preferably a human, in  
20 need of such treatment a therapeutically effective amount of a compound or a  
pharmaceutical composition of the present invention.

Diseases and conditions mediated by agonists of the G-protein-coupled receptor  
GPR119 embrace metabolic diseases or conditions.

25 According to one aspect the compounds and pharmaceutical compositions of the  
present invention are particularly suitable for treating diabetes mellitus, in particular  
Type 2 diabetes, Type 1 diabetes, complications of diabetes (such as e.g.

retinopathy, nephropathy or neuropathies, diabetic foot, ulcers or macro-angiopathies), metabolic acidosis or ketosis, reactive hypoglycaemia, hyperinsulinaemia, glucose metabolic disorder, insulin resistance, metabolic syndrome, dyslipidaemias of different origins, atherosclerosis and related diseases,  
5 obesity, high blood pressure, chronic heart failure, oedema and hyperuricaemia.

The compounds and pharmaceutical compositions of the present invention are also suitable for preventing beta-cell degeneration such as e.g. apoptosis or necrosis of pancreatic beta cells. The compounds and pharmaceutical compositions of the  
10 present invention are also suitable for improving or restoring the functionality of pancreatic cells, and also for increasing the number and size of pancreatic beta cells.

Therefore according to another aspect the invention relates to compounds of formula I and pharmaceutical compositions according to the invention for use in preventing,  
15 delaying, slowing the progression of and/or treating metabolic diseases, particularly in improving the glycaemic control and/or beta cell function in the patient.

In another aspect the invention relates to compounds of formula I and pharmaceutical compositions according to the invention for use in preventing,  
20 delaying, slowing the progression of and/or treating type 2 diabetes, overweight, obesity, complications of diabetes and associated pathological conditions.

In addition the compounds and pharmaceutical compositions according to the invention are suitable for use in one or more of the following therapeutic processes:  
25 - for preventing, delaying, slowing the progression of or treating metabolic diseases, such as for example type 1 diabetes, type 2 diabetes, insufficient glucose tolerance, insulin resistance, hyperglycaemia, hyperlipidaemia, hypercholesterolaemia, dyslipidaemia, syndrome X, metabolic syndrome, obesity, high blood pressure, chronic systemic inflammation, retinopathy, neuropathy, nephropathy,  
30 atherosclerosis, endothelial dysfunction or bone-related diseases (such as osteoporosis, rheumatoid arthritis or osteoarthritis);  
- for improving glycaemic control and/or reducing fasting plasma glucose, postprandial plasma glucose and/or the glycosylated haemoglobin HbA1c;

- for preventing, delaying, slowing or reversing the progression of disrupted glucose tolerance, insulin resistance and/or metabolic syndrome to type 2 diabetes;
- for preventing, delaying, slowing the progression of or treating a condition or a disease selected from among the complications of diabetes, such as for example
- 5 retinopathy, nephropathy or neuropathies, diabetic foot, ulcers or macroangiopathies;
- for reducing weight or preventing weight gain or assisting weight loss;
- for preventing or treating the degradation of pancreatic beta cells and/or improving and/or restoring the functionality of pancreatic beta cells and/or restoring the functionality of pancreatic insulin secretion;
- 10 - for maintaining and/or improving insulin sensitivity and/or preventing or treating hyperinsulinaemia and/or insulin resistance.

In particular, the compounds and pharmaceutical compositions according to the invention are suitable for the treatment of obesity, diabetes (comprising type 1 and

15 type 2 diabetes, preferably type 2 diabetes mellitus) and/or complications of diabetes (such as for example retinopathy, nephropathy or neuropathies, diabetic foot, ulcers or macroangiopathies).

The compounds according to the invention are most particularly suitable for treating

20 type 2 diabetes mellitus.

The dose range of the compounds of general formula (I) applicable per day is usually from 0.001 to 10 mg per kg body weight, for example from 0.01 to 8 mg per kg body weight of the patient. Each dosage unit may conveniently contain from 0.1 to 1000

25 mg, for example 0.5 to 500 mg.

The actual therapeutically effective amount or therapeutic dosage will of course depend on factors known by those skilled in the art such as age and weight of the patient, route of administration and severity of disease. In any case the compound or

30 composition will be administered at dosages and in a manner which allows a therapeutically effective amount to be delivered based upon patient's unique condition.

The compounds, compositions, including any combinations with one or more additional therapeutic agents, according to the invention may be administered by oral, transdermal, inhalative, parenteral or sublingual route. Of the possible methods of administration, oral or intravenous administration is preferred.

5

### Pharmaceutical Compositions

Suitable preparations for administering the compounds of formula (I), optionally in  
10 combination with one or more further therapeutic agents, will be apparent to those with ordinary skill in the art and include for example tablets, pills, capsules, suppositories, lozenges, troches, solutions, syrups, elixirs, sachets, injectables, inhalatives and powders etc. Oral formulations, particularly solid forms such as e.g. tablets or capsules are preferred. The content of the pharmaceutically active  
15 compound(s) is advantageously in the range from 0.1 to 90 wt.-%, for example from 1 to 70 wt.-% of the composition as a whole.

Suitable tablets may be obtained, for example, by mixing one or more compounds according to formula (I) with known excipients, for example inert diluents, carriers,  
20 disintegrants, adjuvants, surfactants, binders and/or lubricants. The tablets may also consist of several layers. The particular excipients, carriers and/or diluents that are suitable for the desired preparations will be familiar to the skilled man on the basis of his specialist knowledge. The preferred ones are those that are suitable for the particular formulation and method of administration that are desired. The  
25 preparations or formulations according to the invention may be prepared using methods known *per se* that are familiar to the skilled man, such as for example by mixing or combining at least one compound of formula I according to the invention, or a pharmaceutically acceptable salt of such a compound, and one or more excipients, carriers and/or diluents.

30

### Combination Therapy

The compounds of the invention may further be combined with one or more, preferably one additional therapeutic agent. According to one embodiment the additional therapeutic agent is selected from the group of therapeutic agents useful in

the treatment of diseases or conditions described hereinbefore, in particular associated with metabolic diseases or conditions such as for example diabetes mellitus, obesity, diabetic complications, hypertension, hyperlipidemia. Additional therapeutic agents which are suitable for such combinations include in particular those which for example potentiate the therapeutic effect of one or more active substances with respect to one of the indications mentioned and/or which allow the dosage of one or more active substances to be reduced.

Therefore a compound of the invention may be combined with one or more additional therapeutic agents selected from the group consisting of antidiabetic agents, agents for the treatment of overweight and/or obesity and agents for the treatment of high blood pressure, heart failure and/or atherosclerosis.

Antidiabetic agents are for example metformin, sulphonylureas, nateglinide, repaglinide, thiazolidinediones, PPAR-(alpha, gamma or alpha/gamma) agonists or modulators, alpha-glucosidase inhibitors, DPPIV inhibitors, SGLT2-inhibitors, insulin and insulin analogues, GLP-1 and GLP-1 analogues or amylin and amylin analogues, cycloset, 11 $\beta$ -HSD inhibitors. Other suitable combination partners are inhibitors of protein tyrosinephosphatase 1, substances that affect deregulated glucose production in the liver, such as e.g. inhibitors of glucose-6-phosphatase, or fructose-1,6-bisphosphatase, glycogen phosphorylase, glucagon receptor antagonists and inhibitors of phosphoenol pyruvate carboxykinase, glycogen synthase kinase or pyruvate dehydrokinase, alpha2-antagonists, CCR-2 antagonists or glucokinase activators. One or more lipid lowering agents are also suitable as combination partners, such as for example HMG-CoA-reductase inhibitors, fibrates, nicotinic acid and the derivatives thereof, PPAR-(alpha, gamma or alpha/gamma) agonists or modulators, PPAR-delta agonists, ACAT inhibitors or cholesterol absorption inhibitors such as, bile acid-binding substances such as, inhibitors of ileac bile acid transport, MTP inhibitors, or HDL-raising compounds such as CETP inhibitors or ABC1 regulators.

Therapeutic agents for the treatment of overweight and/or obesity are for example antagonists of the cannabinoid1 receptor, MCH-1 receptor antagonists, MC4 receptor

agonists, NPY5 or NPY2 antagonists,  $\beta$  3-agonists, leptin or leptin mimetics, agonists of the 5HT2c receptor.

Therapeutic agents for the treatment of high blood pressure, chronic heart failure  
5 and/or atherosclerosis are for example A-II antagonists or ACE inhibitors, ECE  
inhibitors, diuretics,  $\beta$ -blockers, Ca-antagonists, centrally acting antihypertensives,  
antagonists of the alpha-2-adrenergic receptor, inhibitors of neutral endopeptidase,  
thrombocyte aggregation inhibitors and others or combinations thereof are suitable.  
Angiotensin II receptor antagonists are preferably used for the treatment or  
10 prevention of high blood pressure and complications of diabetes, often combined with  
a diuretic such as hydrochlorothiazide.

The dosage for the combination partners mentioned above is usually 1/5 of the  
lowest dose normally recommended up to 1/1 of the normally recommended dose.

15 Preferably, compounds of the present invention and/or pharmaceutical compositions  
comprising a compound of the present invention optionally in combination with one or  
more additional therapeutic agents are administered in conjunction with exercise  
and/or a diet.

20 Therefore, in another aspect, this invention relates to the use of a compound  
according to the invention in combination with one or more additional therapeutic  
agents described hereinbefore and hereinafter for the treatment of diseases or  
conditions which may be affected or which are mediated by the activation of the G-  
25 protein-coupled receptor GPR119, in particular diseases or conditions as described  
hereinbefore and hereinafter.

In yet another aspect the present invention relates a method for treating a disease or  
condition mediated by the activation of the G-protein-coupled receptor GPR119 in a  
30 patient that includes the step of administering to the patient, preferably a human, in  
need of such treatment a therapeutically effective amount of a compound of the  
present invention in combination with a therapeutically effective amount of one or  
more additional therapeutic agents described in hereinbefore and hereinafter,

The use of the compound according to the invention in combination with the additional therapeutic agent may take place simultaneously or at staggered times.

5 The compound according to the invention and the one or more additional therapeutic agents may both be present together in one formulation, for example a tablet or capsule, or separately in two identical or different formulations, for example as a so-called kit-of-parts.

10 Consequently, in another aspect, this invention relates to a pharmaceutical composition which comprises a compound according to the invention and one or more additional therapeutic agents described hereinbefore and hereinafter, optionally together with one or more inert carriers and/or diluents.

15 Other features and advantages of the present invention will become apparent from the following more detailed Examples which illustrate, by way of example, the principles of the invention.

### Examples

20 The terms "ambient temperature" and "room temperature" are used interchangeably and designate a temperature of about 20 °C.

#### Preliminary remarks:

25 As a rule, <sup>1</sup>H-NMR and/or mass spectra have been obtained for the compounds prepared. The R<sub>f</sub> values are determined using Merck silica gel 60 F<sub>254</sub> plates and UV light at 254 nm.

30 Compounds given with a specific configuration at a stereocenter are isolated as pure isomers. The configuration of the stereocenter is arbitrarily assigned. Any compound following a compound with an arbitrarily assigned configuration is given the analogous configuration.

Analytical HPLC parameters employed for characterization of products (TFA denotes trifluoroacetic acid):

|                        |                                               |    |     |                        |                                         |    |     |
|------------------------|-----------------------------------------------|----|-----|------------------------|-----------------------------------------|----|-----|
| <b><u>method 1</u></b> | Waters XBridge C18, 4.6 x 30 mm, 3.5 μm       |    |     | <b><u>method 2</u></b> | Waters XBridge C18, 4.6 x 30 mm, 3.5 μm |    |     |
| mobile phase           | A: water + 0.1% TFA<br>B: methanol + 0.1% TFA |    |     | mobile phase           | A: water + 0.1% TFA<br>B: methanol      |    |     |
|                        | TIME (min)                                    | A% | B%  |                        | TIME (min)                              | A% | B%  |
|                        | 0.0                                           | 95 | 5   |                        | 0.0                                     | 95 | 5   |
|                        | 0.20                                          | 95 | 5   |                        | 1.6                                     | 0  | 100 |
|                        | 1.5                                           | 0  | 100 |                        | 1.85                                    | 0  | 100 |
|                        | 1.75                                          | 0  | 100 |                        | 1.9                                     | 95 | 5   |
|                        | 1.85                                          | 95 | 5   |                        |                                         |    |     |
| flow rate              | 4.0 mL/min                                    |    |     | flow rate              | 4.8 mL/min                              |    |     |
| wavelength             | UV 220, 230, or 254 nm                        |    |     | wavelength             | UV 220, 230, or 254 nm                  |    |     |

|                        |                                               |    |     |                        |                                       |    |     |
|------------------------|-----------------------------------------------|----|-----|------------------------|---------------------------------------|----|-----|
| <b><u>method 3</u></b> | Waters XBridge C18, 4.6 x 30 mm, 3.5 μm       |    |     | <b><u>method 4</u></b> | Waters XBridge C18, 3 x 30 mm, 2.5 μm |    |     |
| mobile phase           | A: water + 0.1% TFA<br>B: methanol + 0.1% TFA |    |     |                        | A: water + 0.1% TFA<br>B: methanol    |    |     |
|                        | TIME (min)                                    | A% | B%  |                        | TIME (min)                            | A% | B%  |
|                        | 0.0                                           | 95 | 5   |                        | 0.0                                   | 95 | 5   |
|                        | 0.20                                          | 95 | 5   |                        | 0.05                                  | 95 | 5   |
|                        | 1.5                                           | 0  | 100 |                        | 1.40                                  | 0  | 100 |
|                        | 1.9                                           | 0  | 100 |                        | 1.80                                  | 0  | 100 |
|                        | 2.0                                           | 95 | 5   |                        |                                       |    |     |
| flow rate              | 4.0 mL/min                                    |    |     | flow rate              | 2.2 mL/min                            |    |     |
| wavelength             | UV 220, 230, or 254 nm                        |    |     | wavelength             | UV 220, 230, or 254 nm                |    |     |

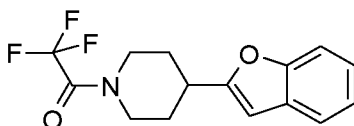
|                        |                                         |    |     |                        |                                         |    |     |
|------------------------|-----------------------------------------|----|-----|------------------------|-----------------------------------------|----|-----|
| <b><u>method 5</u></b> | Waters XBridge C18, 4.6 x 30 mm, 3.5 µm |    |     | <b><u>method 6</u></b> | Waters XBridge C18, 4,6 x 30 mm, 3.5 µm |    |     |
| mobile phase           | A: water + 0.1% TFA<br>B: methanol      |    |     | mobile phase           | A: water + 0.1% HCOOH<br>B: methanol    |    |     |
|                        | TIME (min)                              | A% | B%  |                        | TIME (min)                              | A% | B%  |
|                        | 0.0                                     | 95 | 5   |                        | 0.0                                     | 95 | 5   |
|                        | 1.6                                     | 0  | 100 |                        | 1.15                                    | 95 | 5   |
|                        | 1.85                                    | 0  | 100 |                        | 1.7                                     | 0  | 100 |
|                        | 1.9                                     | 95 | 5   |                        | 2.25                                    | 0  | 100 |
| flow rate              | 4.0 mL/min                              |    |     | flow rate              | 4.0 mL/min                              |    |     |
| wavelength             | UV 220, 230, or 254 nm                  |    |     | wavelength             | UV 220, 230, or 254 nm                  |    |     |

|                        |                                                   |    |     |                        |                                       |    |     |
|------------------------|---------------------------------------------------|----|-----|------------------------|---------------------------------------|----|-----|
| <b><u>method 7</u></b> | Waters XBridge C18, 3 x 30 mm, 2.5 µm             |    |     | <b><u>method 8</u></b> | Waters Sunfire C18, 3 x 30 mm, 2.5 µm |    |     |
| mobile phase           | A: water + 0.1% NH <sub>4</sub> OH<br>B: methanol |    |     | mobile phase           | A: water + 0.1% TFA<br>B: methanol    |    |     |
|                        | TIME (min)                                        | A% | B%  |                        | TIME (min)                            | A% | B%  |
|                        | 0.0                                               | 95 | 5   |                        | 0.00                                  | 95 | 5   |
|                        | 0.05                                              | 95 | 5   |                        | 1.25                                  | 95 | 5   |
|                        | 1.40                                              | 0  | 100 |                        | 1.70                                  | 0  | 100 |
|                        | 1.80                                              | 0  | 100 |                        | 1.75                                  | 0  | 100 |
|                        |                                                   |    |     |                        | 1.90                                  | 0  | 100 |
| flow rate              | 2.2 mL/min                                        |    |     | flow rate              | 1.8 mL/min                            |    |     |
| wavelength             | UV 220, 230, or 254 nm                            |    |     | wavelength             | UV 220, 230, or 254 nm                |    |     |

|                        |                                         |    |     |                         |                                                |    |     |
|------------------------|-----------------------------------------|----|-----|-------------------------|------------------------------------------------|----|-----|
| <b><u>method 9</u></b> | Waters Sunfire C18, 4.6 x 50 mm, 3.5 μm |    |     | <b><u>method 10</u></b> | Waters Sunfire C18, 4.6 x 30 mm, 3.5 μm, 60 °C |    |     |
| mobile phase           | A: water + 0.1% TFA<br>B: methanol      |    |     | mobile phase            | A: water + 0.1% HCOOH<br>B: methanol           |    |     |
|                        | TIME (min)                              | A% | B%  |                         | TIME (min)                                     | A% | B%  |
|                        | 0.00                                    | 80 | 20  |                         | 0.00                                           | 95 | 5   |
|                        | 1.70                                    | 0  | 100 |                         | 0.15                                           | 95 | 5   |
|                        | 2.50                                    | 0  | 100 |                         | 1.70                                           | 0  | 100 |
|                        | 2.60                                    | 80 | 20  |                         | 2.25                                           | 0  | 100 |
| flow rate              | 2.0 mL/min                              |    |     | flow rate               | 4.0 mL/min                                     |    |     |
| wavelength             | DAD 210 -500 nm                         |    |     | wavelength              | DAD 210-500 nm                                 |    |     |

**Intermediate 1**

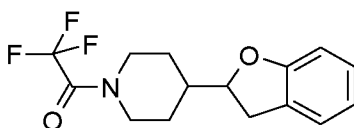
5 1-(4-Benzofuran-2-yl-piperidin-1-yl)-2,2,2-trifluoro-ethanone



Trifluoroacetic anhydride (9.41 mL) is added dropwise to a mixture of 4-benzofuran-2-yl-piperidine hydrochloride (8.00 g) and triethylamine (14.19 mL) in dichloromethane (80 mL) at 0 °C. The resulting mixture is warmed to room temperature, washed with water and aqueous NaHCO<sub>3</sub> solution, dried (MgSO<sub>4</sub>), and the solvent is evaporated. The crude product is used without further purification. LC (method 3): t<sub>R</sub> = 1.39 min; Mass spectrum (ESI<sup>+</sup>): m/z = 298 [M+H]<sup>+</sup>.

**Intermediate 2**

15 1-[4-(2,3-Dihydro-benzofuran-2-yl)-piperidin-1-yl]-2,2,2-trifluoro-ethanone



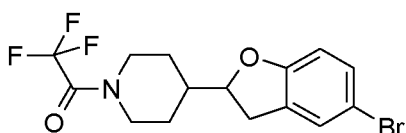
A mixture of 1-(4-benzofuran-2-yl-piperidin-1-yl)-2,2,2-trifluoro-ethanone (11.50 g), 10% palladium on carbon (1.15 g), ethyl acetate (135 mL) and methanol (15 mL) is

shaken under hydrogen atmosphere (3.5 bar) at room temperature for 24 h. The catalyst is then separated by filtration and the filtrate is concentrated to give an oil that is submitted to the next reaction without further purification. LC (method 2):  $t_R$  = 1.34 min.

5

### Intermediate 3

1-[4-(5-Bromo-2,3-dihydro-benzofuran-2-yl)-piperidin-1-yl]-2,2,2-trifluoro-ethanone



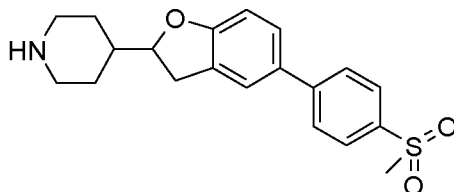
The title compound is prepared from 1-[4-(2,3-dihydro-benzofuran-2-yl)-piperidin-1-yl]-2,2,2-trifluoro-ethanone and N-bromo-succinimide following a procedure analogous to that described for Intermediate 1. LC (method 2):  $t_R$  = 1.47 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$  = 378 [M+H]<sup>+</sup>.

10

### Intermediate 4

15

4-[5-(4-Methanesulfonyl-phenyl)-2,3-dihydro-benzofuran-2-yl]-piperidine



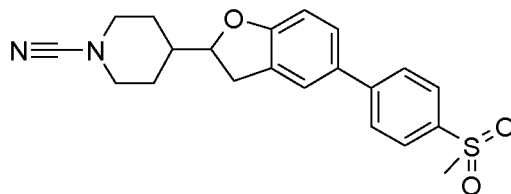
To a mixture of 1-[4-(5-bromo-2,3-dihydro-benzofuran-2-yl)-piperidin-1-yl]-2,2,2-trifluoro-ethanone (2.50 g) and 4-(methanesulfonyl)phenyl boronic acid (1.45 g) in N,N-dimethylformamide (25 mL) a 2 M aqueous Na<sub>2</sub>CO<sub>3</sub> solution (8.26 mL) is added. The mixture is sparged with argon for 10 min and PdCl<sub>2</sub>[1,1'-bis(diphenylphosphino)-ferrocene]·CH<sub>2</sub>Cl<sub>2</sub> complex (540 mg) is added. The resulting mixture is stirred over night at 90 °C. After cooling to room temperature, water (50 mL) and ethyl acetate (100 mL) are added and the aqueous phase is extracted with ethyl acetate. The organic phase is washed with water and brine, dried (MgSO<sub>4</sub>), and the solvent is evaporated. The residue is chromatographed on silica gel [dichloromethane/ (methanol/NH<sub>4</sub>OH 9:1) 90:10 - 80:20] to give the title compound, since the trifluoroacetyl group is removed under the reaction conditions. LC (method 1):  $t_R$  = 0.88 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$  = 358 [M+H]<sup>+</sup>.

20

25

**Intermediate 5**

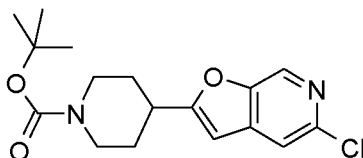
4-[5-(4-Methanesulfonyl-phenyl)-2,3-dihydro-benzofuran-2-yl]-piperidine-1-carbonitrile



- 5 Ethyldiisopropylamine (0.96 mL) and bromonitrile (175 mg) are added to a solution of 4-[5-(4-methanesulfonyl-phenyl)-2,3-dihydro-benzofuran-2-yl]-piperidine (400 mg) in dichloromethane (10 mL) and tetrahydrofuran (10 mL), and the reaction mixture is stirred over night at room temperature. Dichloromethane and water are added and the organic phase is separated and washed with water, 10% NH<sub>4</sub>Cl solution, and
- 10 brine, and dried over MgSO<sub>4</sub>. The solvent is evaporated and the residue is triturated with diethyl ether to give a brownish solid. Since this material still contains ethyldiisopropylamine hydrochloride, ethyl acetate and water are added. The organic phase is separated, dried over MgSO<sub>4</sub> and concentrated *in vacuo*. The residue is again triturated with diethyl ether to afford the title compound. LC (method 2): t<sub>R</sub> =
- 15 1.18 min; Mass spectrum (ESI<sup>+</sup>): m/z = 383 [M+H]<sup>+</sup>.

**Intermediate 6**

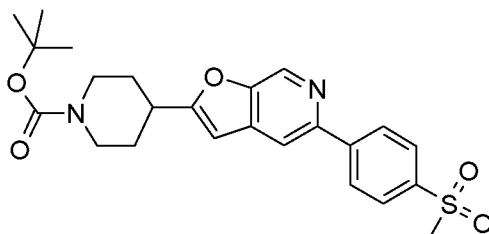
4-(5-Chloro-furo[2,3-c]pyridin-2-yl)-piperidine-1-carboxylic acid tert-butyl ester



- 20 Copper(I) iodide (25 mg) and bis-(triphenylphosphin)-palladium(II)-chloride (30 mg) are added to 6-chloro-4-iodo-pyridin-3-ol (200 mg) in N,N-dimethylformamide (3 mL) under an argon atmosphere. Triethylamine (110 µL) is added and the resulting mixture is stirred at room temperature for 1 h. A solution of 4-ethynyl-piperidine-1-carboxylic acid tert-butyl ester (175 mg) in N,N-dimethylformamide (2 mL) is added
- 25 dropwise and the reaction mixture is stirred at 55°C for 3 h. The solvent is evaporated and the residue is chromatographed on silica gel (cyclohexane/ethyl acetate 70:30) to give the title compound. LC (method 2): t<sub>R</sub> = 1.40 min; Mass spectrum (ESI<sup>+</sup>): m/z = 337 [M+H]<sup>+</sup>.

**Intermediate 7**

4-[5-(4-Methanesulfonyl-phenyl)-furo[2,3-c]pyridin-2-yl]-piperidine-1-carboxylic acid  
tert-butyl ester



5

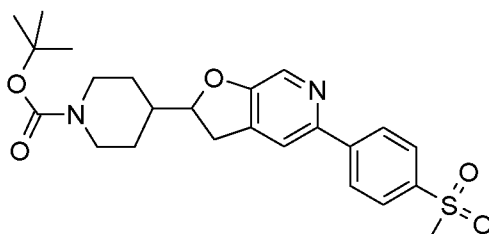
A mixture of 4-(5-chloro-furo[2,3-c]pyridin-2-yl)-piperidine-1-carboxylic acid tert-butyl ester (390 mg), 4-(methanesulfonyl)phenyl boronic acid (350 mg), aqueous Na<sub>2</sub>CO<sub>3</sub> solution (2 M; 1.50 mL), and dioxane (10 mL) is sparged with argon for 10 min and Pd(PPh<sub>3</sub>)<sub>4</sub> (100 mg) is added. The resulting mixture is heated to 170 °C in a microwave oven until the conversion is complete. The reaction mixture is concentrated *in vacuo*, diluted with water and extracted with ethyl acetate. The organic phase is washed with brine, dried over MgSO<sub>4</sub>, and the solvent is evaporated. The residue is chromatographed on silica gel (cyclohexane/ethyl acetate 60:40 → 40:60) to give the title compound. LC (method 5): t<sub>R</sub> = 1.32 min; Mass spectrum (ESI<sup>+</sup>): m/z = 457 [M+H]<sup>+</sup>.

10

15

**Intermediate 8**

4-[5-(4-Methanesulfonyl-phenyl)-2,3-dihydro-furo[2,3-c]pyridin-2-yl]-piperidine-1-  
carboxylic acid tert-butyl ester



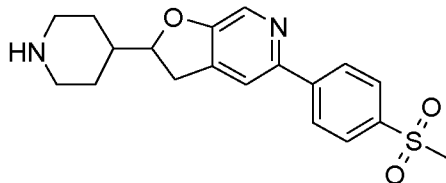
20

A mixture of 4-[5-(4-methanesulfonyl-phenyl)-furo[2,3-c]pyridin-2-yl]-piperidine-1-carboxylic acid tert-butyl ester (155 mg), acetic acid (4.0 mL) and 10% palladium on carbon (40 mg) in methanol (10 mL) is shaken under a hydrogen atmosphere (5 bar) at 50°C. The catalyst is filtered off and the filtrate is concentrated *in vacuo* to give the title compound. LC (method 5): t<sub>R</sub> = 1.32 min; Mass spectrum (ESI<sup>+</sup>): m/z = 459 [M+H]<sup>+</sup>.

25

**Intermediate 9**

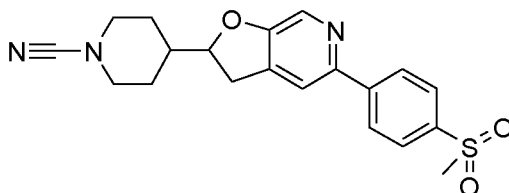
5-(4-Methanesulfonyl-phenyl)-2-piperidin-4-yl-2,3-dihydro-furo[2,3-c]pyridine



- 5 A mixture of 4-[5-(4-methanesulfonyl-phenyl)-2,3-dihydro-furo[2,3-c]pyridin-2-yl]-piperidine-1-carboxylic acid tert-butyl ester (190 mg) and trifluoro acetic acid (0.40 mL) in dichloromethane (3 mL) is stirred at room temperature for 2 h. The reaction mixture is diluted with dichloromethane and washed with aqueous Na<sub>2</sub>CO<sub>3</sub> solution. The aqueous phase is extracted dichloromethane and the combined organic phases
- 10 are washed with water, dried over MgSO<sub>4</sub>, and concentrated *in vacuo*. LC (method 5): t<sub>R</sub> = 0.62 min; Mass spectrum (ESI<sup>+</sup>): m/z = 359 [M+H]<sup>+</sup>.

**Intermediate 10**

4-[5-(4-Methanesulfonyl-phenyl)-2,3-dihydro-furo[2,3-c]pyridin-2-yl]-piperidine-1-  
carbonitrile

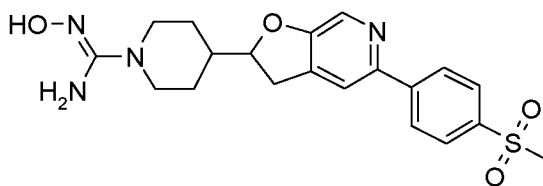


- The title compound is prepared from 5-(4-methanesulfonyl-phenyl)-2-piperidin-4-yl-2,3-dihydro-furo[2,3-c]pyridine and bromonitrile following a procedure analogous to that described for Intermediate 5. LC (method 5): t<sub>R</sub> = 0.91 min; Mass spectrum
- 20 (ESI<sup>+</sup>): m/z = 384 [M+H]<sup>+</sup>.

**Intermediate 11**

N-Hydroxy-4-[5-(4-methanesulfonyl-phenyl)-2,3-dihydro-furo[2,3-c]pyridin-2-yl]-  
piperidine-1-carboxamide

81

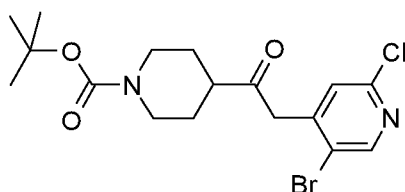


A mixture of 4-[5-(4-methanesulfonyl-phenyl)-2,3-dihydro-furo[2,3-c]pyridin-2-yl]-piperidine-1-carbonitrile (175 mg), hydroxylamine hydrochloride (50 mg), potassium carbonate (70 mg), ethanol (1 mL), and water (1.5 mL) is heated under reflux for 2h.

- 5 The reaction mixture is concentrated *in vacuo* and chromatographed on silica gel (dichloromethane/methanol 92:8 → 60:40) to give the title compound. LC (method 5):  $t_R = 0.65$  min; Mass spectrum ( $ESI^+$ ):  $m/z = 417$   $[M+H]^+$ .

### Intermediate 12

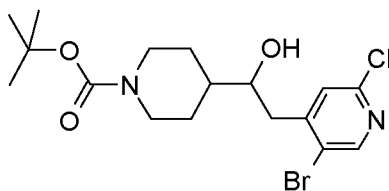
- 10 4-[2-(5-Bromo-2-chloro-pyridin-4-yl)-acetyl]-piperidine-1-carboxylic acid tert-butyl ester



- Lithium bis(trimethylsilyl)amide solution (1.0 M in tetrahydrofuran; 11.00 mL) is added drop wise to 5-bromo-2-chloro-4-picoline (950 mg) in tetrahydrofuran (15 mL) at -40°C under an argon atmosphere. The mixture is stirred for 2 h at -35°C to -45°C prior to the addition of piperidine-1,4-dicarboxylic acid 1-tert-butyl ester 4-ethyl ester (1.33 g), dissolved in tetrahydrofuran (15 mL). The reaction mixture is allowed to warm to room temperature over a period of 1 h. Ice cold water is added and the mixture is extracted with ethyl acetate. The combined extracts are washed with brine, dried over  $MgSO_4$ , and concentrated *in vacuo*. The residue is chromatographed on silica gel (cyclohexane/ethyl acetate 75:25 → 60:40) to give the title compound. LC (method 5):  $t_R = 1.43$  min; Mass spectrum ( $ESI^+$ ):  $m/z = 417, 419$   $[M+H]^+$ .

### Intermediate 13

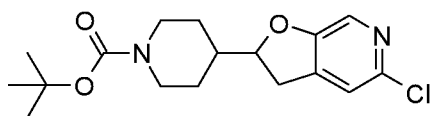
- 25 4-[2-(5-Bromo-2-chloro-pyridin-4-yl)-1-hydroxy-ethyl]-piperidine-1-carboxylic acid tert-butyl ester



Sodium borohydride (240 mg) is added to an ice-cooled solution of 4-[2-(5-bromo-2-chloro-pyridin-4-yl)-acetyl]-piperidine-1-carboxylic acid tert-butyl ester (1.65 g) in a mixture of tetrahydrofuran (40 mL) and water (10 mL). The resulting mixture stirred for 0.5 h. 2 N Citric acid is added and the mixture is extracted with ethyl acetate. The combined extracts are washed with aqueous NaHCO<sub>3</sub> solution and brine, dried over MgSO<sub>4</sub>, and concentrated *in vacuo*. The residue is chromatographed on silica gel (cyclohexane/ethyl acetate 65:35) to give the title compound. LC (method 5): t<sub>R</sub> = 1.48 min; Mass spectrum (ESI<sup>+</sup>): m/z = 419, 421 [M+H]<sup>+</sup>.

#### Intermediate 14

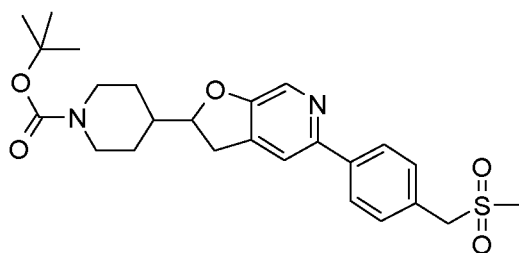
4-(5-Chloro-2,3-dihydro-furo[2,3-c]pyridin-2-yl)-piperidine-1-carboxylic acid tert-butyl ester



A mixture of 4-[2-(5-bromo-2-chloro-pyridin-4-yl)-1-hydroxy-ethyl]-piperidine-1-carboxylic acid tert-butyl ester (11.60 g), palladium acetate (500 mg), racemic 2-(di-tert-butylphosphino)-1,1'-binaphthyl (1.00 g), and cesium carbonate (14.00 g) in toluene (150 mL) is heated in an oil bath at 110°C under an argon atmosphere for 5 h. After cooling to room temperature ethyl acetate and water are added and the organic phase is separated, washed with brine, dried over MgSO<sub>4</sub>, and concentrated *in vacuo*. The residue is chromatographed on silica gel (cyclohexane/ethyl acetate 70:30 → 50:50) to give the title compound. LC (method 5): t<sub>R</sub> = 1.44 min; Mass spectrum (ESI<sup>+</sup>): m/z = 339 [M+H]<sup>+</sup>.

#### Intermediate 15

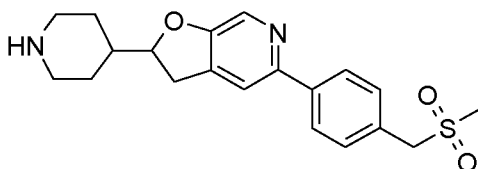
4-[5-(4-Methanesulfonylmethyl-phenyl)-2,3-dihydro-furo[2,3-c]pyridin-2-yl]-piperidine-1-carboxylic acid tert-butyl ester



The title compound is prepared from 4-(5-chloro-2,3-dihydro-furo[2,3-c]pyridin-2-yl)-piperidine-1-carboxylic acid tert-butyl ester and [4-[(methanesulfonyl)methyl]phenyl] boronic acid following a procedure analogous to that described for Intermediate 7. LC (method 6):  $t_R$  = 1.54 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$  = 473 [M+H]<sup>+</sup>.

### Intermediate 16

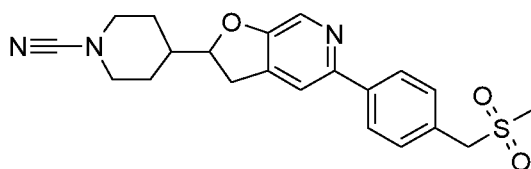
5-(4-Methanesulfonylmethyl-phenyl)-2-piperidin-4-yl-2,3-dihydro-furo[2,3-c]pyridine



The title compound is prepared from 4-[5-(4-methanesulfonylmethyl-phenyl)-2,3-dihydro-furo[2,3-c]pyridin-2-yl]-piperidine-1-carboxylic acid tert-butyl ester following a procedure analogous to that described for Intermediate 9. LC (method 6):  $t_R$  = 0.73 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$  = 373 [M+H]<sup>+</sup>.

### Intermediate 17

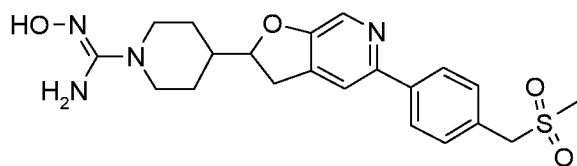
4-[5-(4-Methanesulfonylmethyl-phenyl)-2,3-dihydro-furo[2,3-c]pyridin-2-yl]-piperidine-1-carbonitrile



The title compound is prepared from 5-(4-methanesulfonylmethyl-phenyl)-2-piperidin-4-yl-2,3-dihydro-furo[2,3-c]pyridine and bromonitrile following a procedure analogous to that described for Intermediate 5. LC (method 6):  $t_R$  = 1.11 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$  = 398 [M+H]<sup>+</sup>.

### Intermediate 18

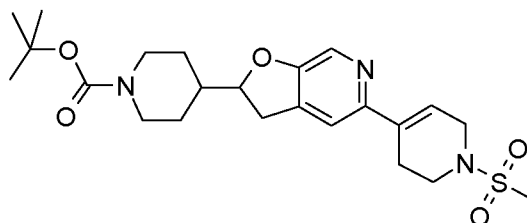
N-Hydroxy-4-[5-(4-methanesulfonylmethyl-phenyl)-2,3-dihydro-furo[2,3-c]pyridin-2-yl]-piperidine-1-carboxamide



The title compound is prepared from 4-[5-(4-methanesulfonylmethyl-phenyl)-2,3-dihydro-furo[2,3-c]pyridin-2-yl]-piperidine-1-carbonitrile and hydroxylamine hydrochloride following a procedure analogous to that described for Intermediate 11. LC (method 5):  $t_R = 0.83$  min; Mass spectrum (ESI<sup>+</sup>):  $m/z = 431$  [M+H]<sup>+</sup>.

**Intermediate 19**

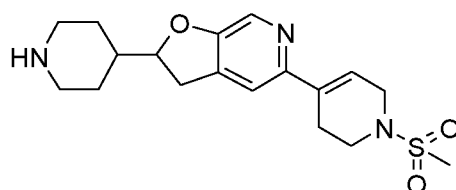
4-[5-(1-Methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-2,3-dihydro-furo[2,3-c]pyridin-2-yl]-piperidine-1-carboxylic acid tert-butyl ester



The title compound is prepared from 4-(5-chloro-2,3-dihydro-furo[2,3-c]pyridin-2-yl)-piperidine-1-carboxylic acid tert-butyl ester and 1-(methanesulfonyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,6-tetrahydropyridine following a procedure analogous to that described for Intermediate 7. LC (method 5):  $t_R = 1.12$  min; Mass spectrum (ESI<sup>+</sup>):  $m/z = 464$  [M+H]<sup>+</sup>.

**Intermediate 20**

5-(1-Methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-2-piperidin-4-yl-2,3-dihydro-furo[2,3-c]pyridine

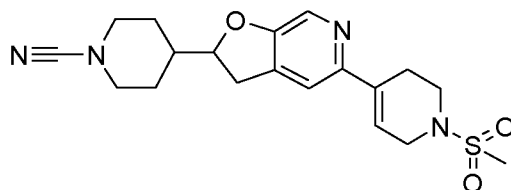


The title compound is prepared from 4-[5-(1-methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-2,3-dihydro-furo[2,3-c]pyridin-2-yl]-piperidine-1-carboxylic acid tert-butyl

ester following a procedure analogous to that described for Intermediate 9. LC (method 5):  $t_R = 0.44$  min; Mass spectrum (ESI<sup>+</sup>):  $m/z = 364$  [M+H]<sup>+</sup>.

### Intermediate 21

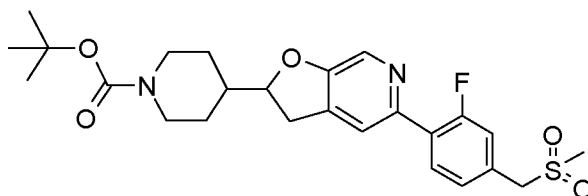
5 4-[5-(1-Methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-2,3-dihydro-furo[2,3-c]pyridine-2-yl]-piperidine-1-carbonitrile



The title compound is prepared from 5-(1-methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-2-piperidin-4-yl-2,3-dihydro-furo[2,3-c]pyridine and bromonitrile following a  
10 procedure analogous to that described for Intermediate 5. LC (method 5):  $t_R = 0.70$  min; Mass spectrum (ESI<sup>+</sup>):  $m/z = 389$  [M+H]<sup>+</sup>.

### Intermediate 22

15 4-[5-(2-Fluoro-4-methanesulfonylmethyl-phenyl)-2,3-dihydro-furo[2,3-c]pyridin-2-yl]-piperidine-1-carboxylic acid tert-butyl ester

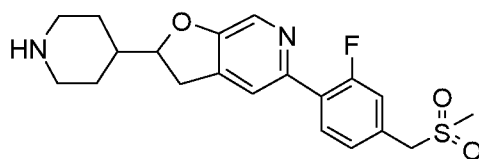


The title compound is prepared from 4-(5-chloro-2,3-dihydro-furo[2,3-c]pyridin-2-yl)-piperidine-1-carboxylic acid tert-butyl ester and 2-(2-fluoro-4-methanesulfonylmethyl-phenyl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane following a procedure analogous to  
20 that described for Intermediate 7. LC (method 6):  $t_R = 1.61$  min; Mass spectrum (ESI<sup>+</sup>):  $m/z = 491$  [M+H]<sup>+</sup>.

### Intermediate 23

25 5-(2-Fluoro-4-methanesulfonylmethyl-phenyl)-2-piperidin-4-yl-2,3-dihydro-furo[2,3-c]pyridine

86

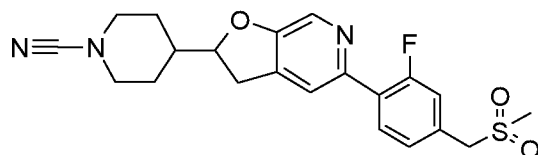


The title compound is prepared from 4-[5-(2-fluoro-4-methanesulfonylmethyl-phenyl)-2,3-dihydro-furo[2,3-c]pyridin-2-yl]-piperidine-1-carboxylic acid tert-butyl ester following a procedure analogous to that described for Intermediate 9. LC (method 6):

5  $t_R = 0.78$  min; Mass spectrum (ESI<sup>+</sup>):  $m/z = 391$  [M+H]<sup>+</sup>.

### Intermediate 24

4-[5-(2-Fluoro-4-methanesulfonylmethyl-phenyl)-2,3-dihydro-furo[2,3-c]pyridin-2-yl]-piperidine-1-carbonitrile



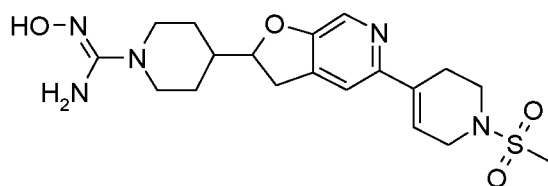
10

The title compound is prepared from 5-(2-fluoro-4-methanesulfonylmethyl-phenyl)-2-piperidin-4-yl-2,3-dihydro-furo[2,3-c]pyridine and bromonitrile following a procedure analogous to that described for Intermediate 5. LC (method 6):  $t_R = 1.21$  min; Mass spectrum (ESI<sup>+</sup>):  $m/z = 416$  [M+H]<sup>+</sup>.

15

### Intermediate 25

N-Hydroxy-4-[5-(1-methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-2,3-dihydro-furo[2,3-c]pyridin-2-yl]-piperidine-1-carboxamide



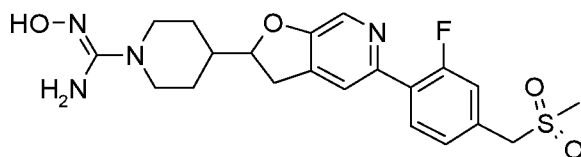
20

The title compound is prepared from 4-[5-(1-methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-2,3-dihydro-furo[2,3-c]pyridine-2-yl]-piperidine-1-carbonitrile and hydroxylamine hydrochloride following a procedure analogous to that described for Intermediate 11. LC (method 5):  $t_R = 0.54$  min; Mass spectrum (ESI<sup>+</sup>):  $m/z = 422$  [M+H]<sup>+</sup>.

25

### Intermediate 26

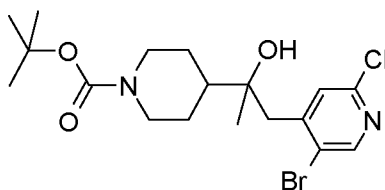
4-[5-(2-Fluoro-4-methanesulfonylmethyl-phenyl)-2,3-dihydro-furo[2,3-c]pyridin-2-yl]-  
N-hydroxy-piperidine-1-carboxamidine



The title compound is prepared from 4-[5-(2-fluoro-4-methanesulfonylmethyl-phenyl)-  
2,3-dihydro-furo[2,3-c]pyridin-2-yl]-piperidine-1-carbonitrile and hydroxylamine  
hydrochloride following a procedure analogous to that described for Intermediate 11.  
LC (method 6):  $t_R = 0.90$  min; Mass spectrum (ESI<sup>+</sup>):  $m/z = 449$  [M+H]<sup>+</sup>.

**Intermediate 27**

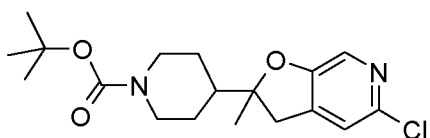
4-[2-(5-Bromo-2-chloro-pyridin-4-yl)-1-hydroxy-1-methyl-ethyl]-piperidine-1-carboxylic  
acid tert-butyl ester



A solution of 4-[2-(5-bromo-2-chloro-pyridin-4-yl)-acetyl]-piperidine-1-carboxylic acid  
tert-butyl ester (9.80 g) in tetrahydrofuran (6 mL) is added drop wise to an ice cooled  
solution of methyl magnesium bromide (1.4 M in toluene/tetrahydrofuran 75:25, 74  
mL). The reaction mixture is stirred for 30 min, warmed to room temperature and  
stirred for 1 h. The mixture is poured onto aqueous NH<sub>4</sub>Cl solution and extracted with  
ethyl acetate. The combined extracts are dried over MgSO<sub>4</sub> and concentrated *in vacuo*.  
Toluene is added to the residue and evaporated several times. Since the  
residue still contains a considerable amount of starting material, it is again treated  
with the Grignard reagent following the procedure described above. The crude  
product is purified by preparative HPLC (column: Waters X-Bridge C18; mobile  
phase: water+0.125 % NH<sub>4</sub>OH/methanol 90:10 → 100:0) to give the title compound.  
LC (method 4):  $t_R = 1.33$  min; Mass spectrum (ESI<sup>+</sup>):  $m/z = 433, 435$  [M+H]<sup>+</sup>.

**Intermediate 28**

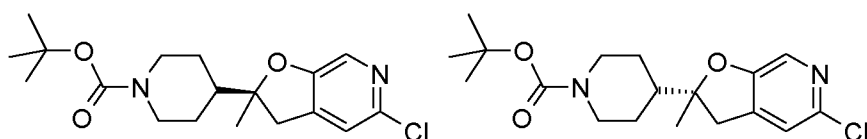
4-(5-Chloro-2-methyl-2,3-dihydro-furo[2,3-c]pyridin-2-yl)-piperidine-1-carboxylic acid  
tert-butyl ester



The title compound is prepared from 4-[2-(5-bromo-2-chloro-pyridin-4-yl)-1-hydroxy-1-methyl-ethyl]-piperidine-1-carboxylic acid tert-butyl ester following a procedure analogous to that described for Intermediate 14. LC (method 4):  $t_R$  = 1.29 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$  = 353 [M+H]<sup>+</sup>.

### Intermediate 29 and 30

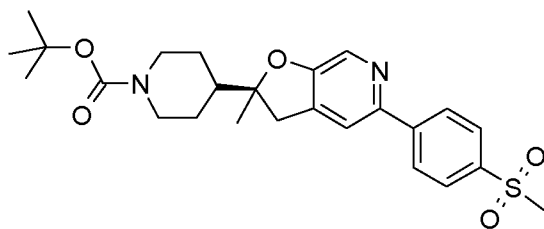
(S)-4-(5-Chloro-2-methyl-2,3-dihydro-furo[2,3-c]pyridin-2-yl)-piperidine-1-carboxylic acid tert-butyl ester and (R)-4-(5-Chloro-2-methyl-2,3-dihydro-furo[2,3-c]pyridin-2-yl)-piperidine-1-carboxylic acid tert-butyl ester



The title compounds are obtained in separate fractions upon SFC on chiral phase of racemic Intermediate 28 (column: Daicel IC, 250x20 mm; mobile phase: methanol containing 0.2% diethylamine/sc carbon dioxide 25:75; flow rate 60 ml/min). The configuration of the stereocenter is arbitrarily assigned; retention times on the SFC on chiral phase (Daicel IC, 250x4.6 mm; mobile phase: methanol containing 0.2% diethylamine/sc carbon dioxide 25:75; flow rate 4 ml/min): Intermediate 29:  $t_R$  = 3.77 min; Intermediate 30;  $t_R$  = 4.42 min.

### Intermediate 31

(S)-4-[5-(4-Methanesulfonyl-phenyl)-2-methyl-2,3-dihydro-furo[2,3-c]pyridin-2-yl]-piperidine-1-carboxylic acid tert-butyl ester



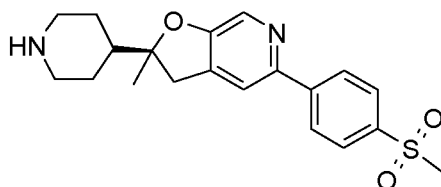
The title compound is prepared from (S)-4-(5-chloro-2-methyl-2,3-dihydro-furo[2,3-c]pyridin-2-yl)-piperidine-1-carboxylic acid tert-butyl ester (Intermediate 29; the configuration of the stereocenter is arbitrarily assigned) and 4-

(methanesulfonyl)phenylboronic acid following a procedure analogous to that described for Intermediate 7. LC (method 4):  $t_R = 1.19$  min; Mass spectrum (ESI<sup>+</sup>):  $m/z = 473$  [M+H]<sup>+</sup>.

5

**Intermediate 32**

(S)-5-(4-Methanesulfonyl-phenyl)-2-methyl-2-piperidin-4-yl-2,3-dihydro-furo[2,3-c]pyridine



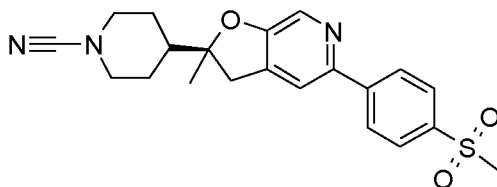
10

The title compound is prepared from (S)-4-[5-(4-methanesulfonyl-phenyl)-2-methyl-2,3-dihydro-furo[2,3-c]pyridin-2-yl]-piperidine-1-carboxylic acid tert-butyl ester (Intermediate 31; the configuration of the stereocenter is arbitrarily assigned) following a procedure analogous to that described for Intermediate 9. LC (method 7):  $t_R = 0.63$  min; Mass spectrum (ESI<sup>+</sup>):  $m/z = 373$  [M+H]<sup>+</sup>.

15

**Intermediate 33**

(S)-4-[5-(4-Methanesulfonyl-phenyl)-2-methyl-2,3-dihydro-furo[2,3-c]pyridin-2-yl]-piperidine-1-carbonitrile



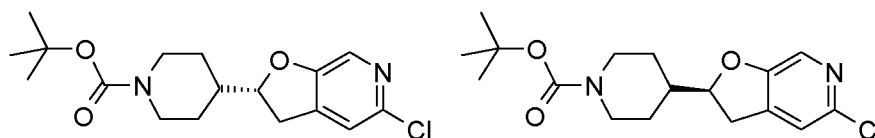
20

The title compound is prepared from (S)-5-(4-methanesulfonyl-phenyl)-2-methyl-2-piperidin-4-yl-2,3-dihydro-furo[2,3-c]pyridine (Intermediate 32; the configuration of the stereocenter is arbitrarily assigned) and bromonitrile following a procedure analogous to that described for Intermediate 5. LC (method 4):  $t_R = 0.87$  min; Mass spectrum (ESI<sup>+</sup>):  $m/z = 398$  [M+H]<sup>+</sup>.

25

**Intermediate 34 and 35**

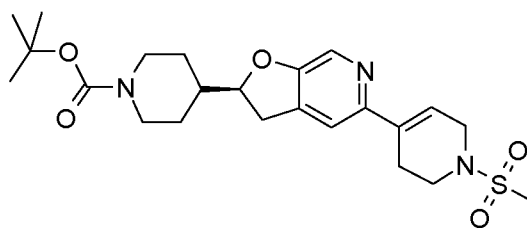
(R)-4-(5-Chloro-2,3-dihydro-furo[2,3-c]pyridin-2-yl)-piperidine-1-carboxylic acid tert-butyl ester and (S)-4-(5-Chloro-2,3-dihydro-furo[2,3-c]pyridin-2-yl)-piperidine-1-carboxylic acid tert-butyl ester



The title compounds are obtained in separate fractions upon SFC on chiral phase of racemic Intermediate 14 (column: Daicel IC, 250x20 mm; mobile phase: ethanol containing 0.2% diethylamine/sc carbon dioxide 25:75; flow rate 50 ml/min). The configuration of the stereocenter is arbitrarily assigned; retention times on the SFC on chiral phase (Daicel IC, 250x4.6 mm; mobile phase: ethanol containing 0.2% diethylamine/sc carbon dioxide 25:75; flow rate 4 ml/min): Intermediate 34:  $t_R$  = 1.64 min; Intermediate 35;  $t_R$  = 1.91 min.

### Intermediate 36

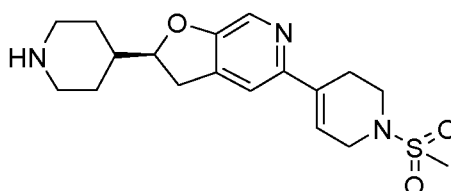
(S)-4-[5-(1-Methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-2,3-dihydro-furo[2,3-c]pyridin-2-yl]-piperidine-1-carboxylic acid tert-butyl ester



The title compound is prepared from (S)-4-(5-chloro-2,3-dihydro-furo[2,3-c]pyridin-2-yl)-piperidine-1-carboxylic acid tert-butyl ester (Intermediate 35, the configuration of the stereocenter is arbitrarily assigned) and 1-(methanesulfonyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,6-tetrahydropyridine following a procedure analogous to that described for Intermediate 7. LC (method 5):  $t_R$  = 1.10 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$  = 464 [M+H]<sup>+</sup>.

### Intermediate 37

(S)-5-(1-Methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-2-piperidin-4-yl-2,3-dihydro-furo[2,3-c]pyridine

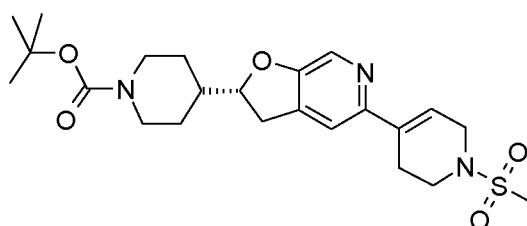


The title compound is prepared from (S)-4-[5-(1-methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-2,3-dihydro-furo[2,3-c]pyridin-2-yl]-piperidine-1-carboxylic acid tert-butyl ester (Intermediate 36, the configuration of the stereocenter is arbitrarily assigned) following a procedure analogous to that described for Intermediate 9. LC (method 5):

5  $t_R = 0.44$  min; Mass spectrum (ESI<sup>+</sup>):  $m/z = 364$  [M+H]<sup>+</sup>.

### Intermediate 38

(R)-4-[5-(1-Methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-2,3-dihydro-furo[2,3-c]pyridin-2-yl]-piperidine-1-carboxylic acid tert-butyl ester



10

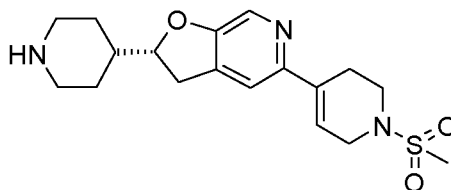
The title compound is prepared from (R)-4-(5-chloro-2,3-dihydro-furo[2,3-c]pyridin-2-yl)-piperidine-1-carboxylic acid tert-butyl ester (Intermediate 34, the configuration of the stereocenter is arbitrarily assigned) and 1-(methanesulfonyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,6-tetrahydropyridine following a procedure analogous to that described for Intermediate 7. LC (method 5):  $t_R = 1.10$  min; Mass spectrum (ESI<sup>+</sup>):  $m/z = 464$  [M+H]<sup>+</sup>.

15

### Intermediate 39

(R)-5-(1-Methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-2-piperidin-4-yl-2,3-dihydro-furo[2,3-c]pyridine

20



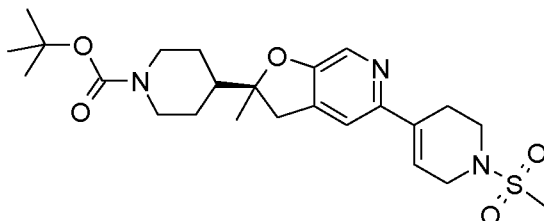
The title compound is prepared from (R)-4-[5-(1-methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-2,3-dihydro-furo[2,3-c]pyridin-2-yl]-piperidine-1-carboxylic acid tert-butyl ester (Intermediate 38, the configuration of the stereocenter is arbitrarily assigned)

25

following a procedure analogous to that described for Intermediate 9. LC (method 5):  $t_R = 0.44$  min; Mass spectrum (ESI<sup>+</sup>):  $m/z = 364$  [M+H]<sup>+</sup>.

**Intermediate 40**

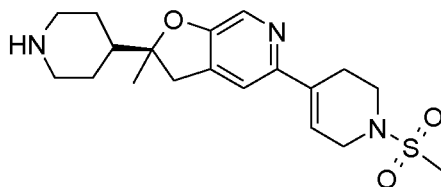
(S)-4-[5-(1-Methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-2-methyl-2,3-dihydro-furo[2,3-c]pyridin-2-yl]-piperidine-1-carboxylic acid tert-butyl ester



- 5 The title compound is prepared from (S)-4-(5-chloro-2-methyl-2,3-dihydro-furo[2,3-c]pyridin-2-yl)-piperidine-1-carboxylic acid tert-butyl ester (Intermediate 29; the configuration of the stereocenter is arbitrarily assigned) and 1-(methylsulfonyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,6-tetrahydropyridine following a procedure analogous to that described for Intermediate 7. LC (method 4):  $t_R = 1.02$
- 10 min; Mass spectrum (ESI<sup>+</sup>):  $m/z = 478 [M+H]^+$ .

**Intermediate 41**

(S)-5-(1-Methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-2-methyl-2-piperidin-4-yl-2,3-dihydro-furo[2,3-c]pyridine

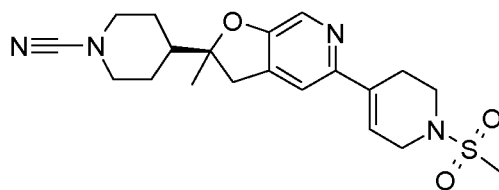


15

- The title compound is prepared from (S)-4-[5-(1-methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-2-methyl-2,3-dihydro-furo[2,3-c]pyridin-2-yl]-piperidine-1-carboxylic acid tert-butyl ester (Intermediate 40; the configuration of the stereocenter is arbitrarily assigned) following a procedure analogous to that described for Intermediate 9. LC
- 20 (method 7):  $t_R = 0.48$  min; Mass spectrum (ESI<sup>+</sup>):  $m/z = 378 [M+H]^+$ .

**Intermediate 42**

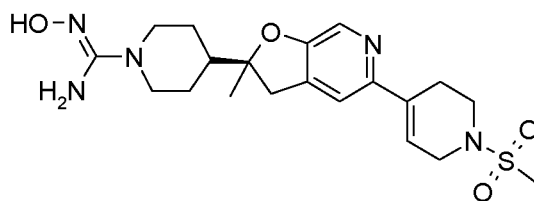
(S)-4-[5-(1-Methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-2-methyl-2,3-dihydro-furo[2,3-c]pyridin-2-yl]-piperidine-1-carbonitrile



The title compound is prepared from (S)-5-(1-methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-2-methyl-2-piperidin-4-yl-2,3-dihydro-furo[2,3-c]pyridine (Intermediate 41; the configuration of the stereocenter is arbitrarily assigned) and bromonitrile  
 5 following a procedure analogous to that described for Intermediate 5. LC (method 4):  $t_R = 0.68$  min; Mass spectrum (ESI<sup>+</sup>):  $m/z = 403$  [M+H]<sup>+</sup>.

### Intermediate 43

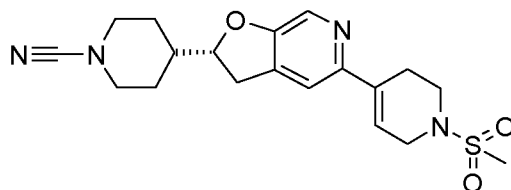
(S)-N-Hydroxy-4-[5-(1-methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-2-methyl-2,3-  
 10 dihydro-furo[2,3-c]pyridin-2-yl]-piperidine-1-carboxamide



The title compound is prepared from (S)-4-[5-(1-methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-2-methyl-2,3-dihydro-furo[2,3-c]pyridin-2-yl]-piperidine-1-carbonitrile (Intermediate 42; the configuration of the stereocenter is arbitrarily assigned) and  
 15 hydroxylamine hydrochloride following a procedure analogous to that described for Intermediate 11. LC (method 4):  $t_R = 0.46$  min; Mass spectrum (ESI<sup>+</sup>):  $m/z = 436$  [M+H]<sup>+</sup>.

### Intermediate 44

(R)-4-[5-(1-Methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-2,3-dihydro-furo[2,3-  
 20 c]pyridine-2-yl]-piperidine-1-carbonitrile



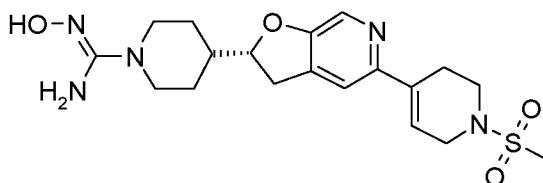
The title compound is prepared from (R)-5-(1-methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-2-piperidin-4-yl-2,3-dihydro-furo[2,3-c]pyridine (Intermediate 39, the

configuration of the stereocenter is arbitrarily assigned) and bromonitrile following a procedure analogous to that described for Intermediate 5. LC (method 6):  $t_R = 1.02$  min; Mass spectrum ( $ESI^+$ ):  $m/z = 389 [M+H]^+$ .

5

**Intermediate 45**

(R)-N-Hydroxy-4-[5-(1-methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-2,3-dihydro-furo[2,3-c]pyridin-2-yl]-piperidine-1-carboxamide



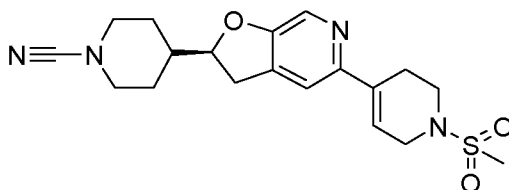
10

The title compound is prepared from (R)-4-[5-(1-methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-2,3-dihydro-furo[2,3-c]pyridine-2-yl]-piperidine-1-carbonitrile (Intermediate 44, the configuration of the stereocenter is arbitrarily assigned) and hydroxylamine hydrochloride following a procedure analogous to that described for Intermediate 11. LC (method 6):  $t_R = 0.75$  min; Mass spectrum ( $ESI^+$ ):  $m/z = 422 [M+H]^+$ .

15

**Intermediate 46**

(S)-4-[5-(1-Methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-2,3-dihydro-furo[2,3-c]pyridine-2-yl]-piperidine-1-carbonitrile



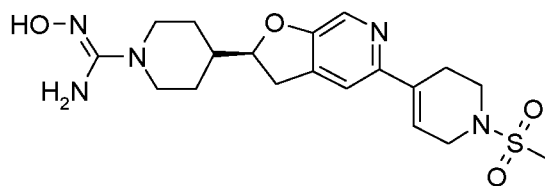
20

The title compound is prepared from (S)-5-(1-methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-2-piperidin-4-yl-2,3-dihydro-furo[2,3-c]pyridine (Intermediate 37, the configuration of the stereocenter is arbitrarily assigned) and bromonitrile following a procedure analogous to that described for Intermediate 5. LC (method 6):  $t_R = 1.02$  min; Mass spectrum ( $ESI^+$ ):  $m/z = 389 [M+H]^+$ .

25

**Intermediate 47**

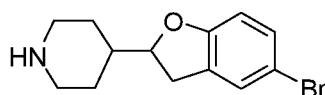
(S)-N-Hydroxy-4-[5-(1-methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-2,3-dihydro-furo[2,3-c]pyridin-2-yl]-piperidine-1-carboxamide



The title compound is prepared from (S)-4-[5-(1-methanesulfonyl-1,2,3,6-tetrahydropyridin-4-yl)-2,3-dihydro-furo[2,3-c]pyridine-2-yl]-piperidine-1-carbonitrile (Intermediate 46, the configuration of the stereocenter is arbitrarily assigned) and hydroxylamine hydrochloride following a procedure analogous to that described for Intermediate 11. LC (method 6):  $t_R$  = 0.75 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$  = 422 [M+H]<sup>+</sup>.

### Intermediate 48

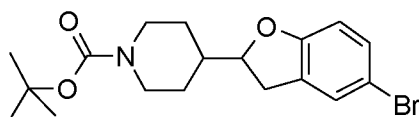
#### 4-(5-Bromo-2,3-dihydro-benzofuran-2-yl)-piperidine



Potassium carbonate (10.17 g) is added to an ice-cooled mixture of 1-[4-(5-bromo-2,3-dihydro-benzofuran-2-yl)-piperidin-1-yl]-2,2,2-trifluoro-ethanone (4.64 g), methanol (120 mL), and water (30 mL). The reaction mixture is stirred over night at room temperature. Brine (150 mL) is added and the mixture is extracted with dichloromethane. The combined organic phases are dried over MgSO<sub>4</sub> and concentrated *in vacuo*. The crude product is used for the next step without further purification. LC (method 2):  $t_R$  = 1.05 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$  = 282, 284 [M+H]<sup>+</sup>.

### Intermediate 49

#### 4-(5-Bromo-2,3-dihydro-benzofuran-2-yl)-piperidine-1-carboxylic acid tert-butyl ester

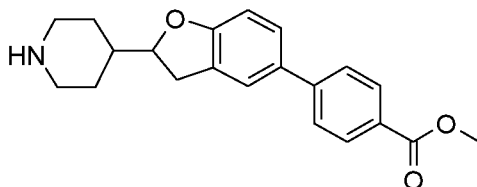


A mixture of 4-(5-bromo-2,3-dihydro-benzofuran-2-yl)-piperidine (2.37 g) and di-tert-butyl dicarbonate (1.83 g) in tetrahydrofuran (25 mL) is stirred for 4 h at room temperature. The solvent is evaporated *in vacuo* and the residue is chromatographed on silica gel (cyclohexane/ethyl acetate 90:10 → 40:60) to give the title compound.

TLC:  $r_f = 0.40$  (silica gel, cyclohexane/ethyl acetate 4:1); Mass spectrum ( $\text{ESI}^+$ ):  $m/z = 382, 384 [\text{M}+\text{H}]^+$

### Intermediate 50

#### 5 4-(2-Piperidin-4-yl-2,3-dihydro-benzofuran-5-yl)-benzoic acid methyl ester



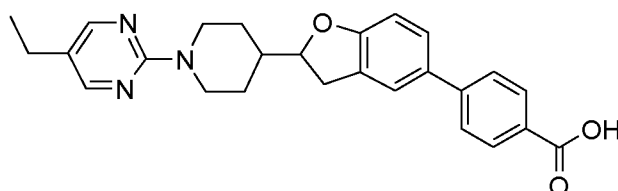
To a mixture of 4-(5-bromo-2,3-dihydro-benzofuran-2-yl)-piperidine-1-carboxylic acid tert-butyl ester (1.00 g) and 4-(methoxycarbonyl)phenyl boronic acid (565 mg) in N,N-dimethylformamide (50 mL) a 2 M aqueous  $\text{Na}_2\text{CO}_3$  solution (3.27 mL) is added. The mixture is sparged with argon for 10 min and  $\text{PdCl}_2[1,1'\text{-bis(diphenylphosphino)-ferrocene}]\cdot\text{CH}_2\text{Cl}_2$  complex (213 mg) is added. The resulting mixture is stirred for 5 h at 90 °C. After cooling to room temperature water (50 mL) and ethyl acetate (100 mL) are added and the aqueous phase is extracted with ethyl acetate. The organic phase is washed with water and brine, dried over  $\text{MgSO}_4$ , and the solvent is evaporated.

The residue is mixed with trifluoroacetic acid (1.4 mL), dichloromethane (1.4 mL), and water (0.15 mL) and stirred for 3 h. The solvents are evaporated and the residue is mixed with diethyl ether. The title compound is collected by filtration as the trifluoroacetic acid salt. LC (method 8):  $t_R = 1.19$  min; Mass spectrum ( $\text{ESI}^+$ ):  $m/z = 338 [\text{M}+\text{H}]^+$ .

20

### Intermediate 51

#### 4-{2-[1-(5-Ethyl-pyrimidin-2-yl)-piperidin-4-yl]-2,3-dihydro-benzofuran-5-yl}-benzoic acid



25 Ethyldiisopropylamine (1.38 mL) and 2-chloro-5-ethylpyrimidine (380  $\mu\text{L}$ ) are added to a solution of 4-(2-piperidin-4-yl-2,3-dihydro-benzofuran-5-yl)-benzoic acid methyl ester (0.90 g) in tetrahydrofuran (20 mL) and the reaction mixture is heated to reflux

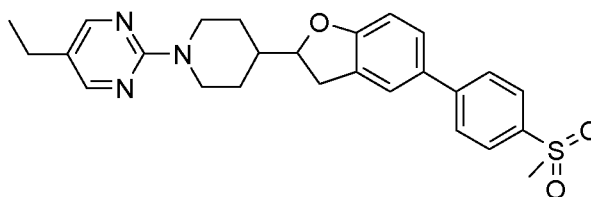
for 48 h. The solvent is evaporated after cooling to room temperature.

Dichloromethane and water are added; the aqueous phase is separated and extracted with dichloromethane. The combined organic phases are dried over  $\text{MgSO}_4$  and the solvent is evaporated. The residue is mixed with methanol (20 mL) and 1 M aqueous sodium hydroxide solution (6.67 mL). The reaction mixture is stirred at 55°C for 12 h. The solvent is evaporated after cooling to room temperature.

Dichloromethane and water are added; the organic phase is separated and extracted with water. The combined aqueous phases were adjusted to pH 2 with 1 M hydrochloric acid. The title compound is collected by filtration and dried at 50°C *in vacuo*. LC (method 8):  $t_R = 1.56$  min; Mass spectrum ( $\text{ESI}^+$ ):  $m/z = 430$   $[\text{M}+\text{H}]^+$ .

### Example 1

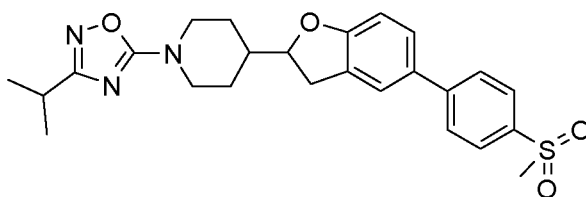
5-Ethyl-2-{4-[5-(4-methanesulfonyl-phenyl)-2,3-dihydro-benzofuran-2-yl]-piperidin-1-yl}-pyrimidine



Ethyl-diisopropylamine (50  $\mu\text{L}$ ) and 2-chloro-5-ethylpyrimidine (17  $\mu\text{L}$ ) are added to a solution of 4-[5-(4-methanesulfonyl-phenyl)-2,3-dihydro-benzofuran-2-yl]-piperidine (50 mg) in *N,N*-dimethylformamide (1 mL) and the reaction mixture is stirred at 120°C for 2 h. After cooling to room temperature over night, dichloromethane and water are added. The aqueous phase is separated and extracted with dichloromethane. The combined organic phases are washed with water, 10%  $\text{NH}_4\text{Cl}$  solution, and brine, and dried over  $\text{MgSO}_4$ . The solvent is evaporated and the residue is triturated with diethyl ether to give the title compound. LC (method 4):  $t_R = 1.26$  min; Mass spectrum ( $\text{ESI}^+$ ):  $m/z = 464$   $[\text{M}+\text{H}]^+$ .

### Example 2

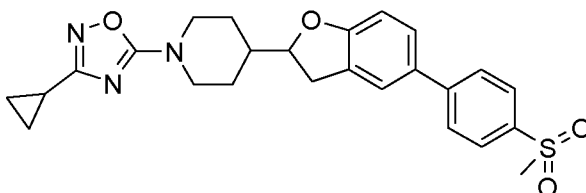
1-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-4-[5-(4-methanesulfonyl-phenyl)-2,3-dihydro-benzofuran-2-yl]-piperidine



A 0.5 M solution of zinc chloride in tetrahydrofuran (0.78 mL) is diluted with tetrahydrofuran (5 mL) and added dropwise at room temperature to a mixture of N-hydroxy-isobutyramidine (40 mg) and 4-[5-(4-methanesulfonyl-phenyl)-2,3-dihydro-benzofuran-2-yl]-piperidine-1-carbonitrile (100mg) in ethyl acetate (5 mL). The reaction mixture is stirred at 50 °C for 4 h and cooled to room temperature. The precipitate is filtered off and heated to 100 °C for 2 h in a mixture of ethanol (5 mL) and glacial acetic acid (2.5 mL). The solvents are evaporated and the residue is mixed with dichloromethane and 10% aqueous K<sub>2</sub>CO<sub>3</sub> solution. The organic phase is washed with brine, dried over MgSO<sub>4</sub> and concentrated *in vacuo*. The residue is triturated with diethyl ether to give the title compound. LC (method 2): t<sub>R</sub> = 1.12 min; Mass spectrum (ESI<sup>+</sup>): m/z = 468 [M+H]<sup>+</sup>.

### Example 3

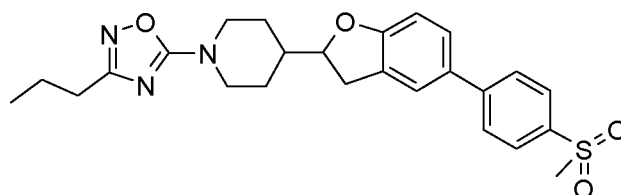
1-(3-Cyclopropyl-[1,2,4]oxadiazol-5-yl)-4-[5-(4-methanesulfonyl-phenyl)-2,3-dihydro-benzofuran-2-yl]-piperidine



The title compound is prepared from 4-[5-(4-methanesulfonyl-phenyl)-2,3-dihydro-benzofuran-2-yl]-piperidine-1-carbonitrile and N-hydroxy-cyclopropanecarboxamide following a procedure analogous to that described in Example 2. LC (method 2): t<sub>R</sub> = 1.08 min; Mass spectrum (ESI<sup>+</sup>): m/z = 466 [M+H]<sup>+</sup>.

### Example 4

4-[5-(4-Methanesulfonyl-phenyl)-2,3-dihydro-benzofuran-2-yl]-1-(3-propyl-[1,2,4]oxadiazol-5-yl)-piperidine

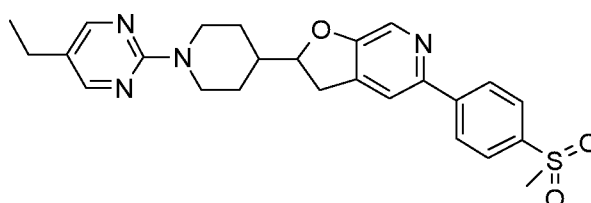


The title compound is prepared from 4-[5-(4-methanesulfonyl-phenyl)-2,3-dihydro-benzofuran-2-yl]-piperidine-1-carbonitrile and N-hydroxy-butynamidine following a procedure analogous to that described in Example 2. LC (method 2):  $t_R = 1.40$  min;

5 Mass spectrum (ESI<sup>+</sup>):  $m/z = 468$  [M+H]<sup>+</sup>.

### Example 5

2-[1-(5-Ethyl-pyrimidin-2-yl)-piperidin-4-yl]-5-(4-methanesulfonyl-phenyl)-2,3-dihydro-furo[2,3-c]pyridine



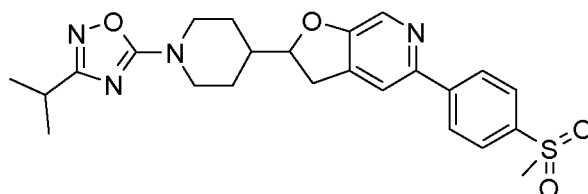
10

The title compound is prepared from 5-(4-methanesulfonyl-phenyl)-2-piperidin-4-yl-2,3-dihydro-furo[2,3-c]pyridine and 2-chloro-5-ethylpyrimidine following a procedure analogous to that described in Example 1. LC (method 5):  $t_R = 1.14$  min; Mass spectrum (ESI<sup>+</sup>):  $m/z = 465$  [M+H]<sup>+</sup>.

15

### Example 6

2-[1-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yl]-5-(4-methanesulfonyl-phenyl)-2,3-dihydro-furo[2,3-c]pyridine

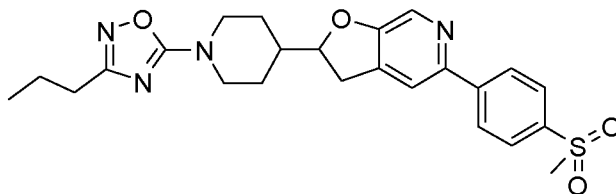


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The title compound is prepared from 4-[5-(4-methanesulfonyl-phenyl)-2,3-dihydro-furo[2,3-c]pyridin-2-yl]-piperidine-1-carbonitrile and N-hydroxy-isobutyramidine following a procedure analogous to that described in Example 2. LC (method 5):  $t_R = 1.15$  min; Mass spectrum (ESI<sup>+</sup>):  $m/z = 469$  [M+H]<sup>+</sup>.

**Example 7**

5-(4-Methanesulfonyl-phenyl)-2-[1-(3-propyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yl]-2,3-dihydro-furo[2,3-c]pyridine

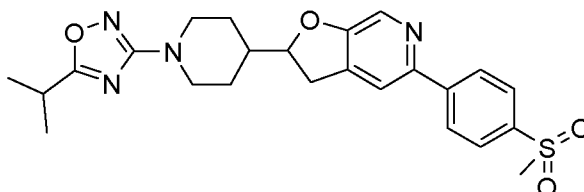


- 5 The title compound is prepared from 4-[5-(4-methanesulfonyl-phenyl)-2,3-dihydro-furo[2,3-c]pyridin-2-yl]-piperidine-1-carbonitrile and N-hydroxy-butynamidine following a procedure analogous to that described in Example 2. LC (method 5):  $t_R = 1.15$  min; Mass spectrum (ESI<sup>+</sup>):  $m/z = 469$  [M+H]<sup>+</sup>.

10

**Example 8**

2-[1-(5-Isopropyl-[1,2,4]oxadiazol-3-yl)-piperidin-4-yl]-5-(4-methanesulfonyl-phenyl)-2,3-dihydro-furo[2,3-c]pyridine

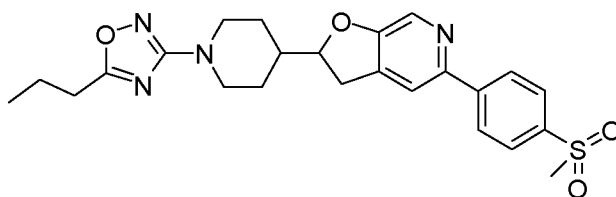


- A mixture of N-hydroxy-4-[5-(4-methanesulfonyl-phenyl)-2,3-dihydro-furo[2,3-c]pyridin-2-yl]-piperidine-1-carboxamide (45 mg), isobutyryl chloride (12  $\mu$ L), and triethylamine (50  $\mu$ L) in tetrahydrofuran (5 mL) is stirred for 30 min at room temperature prior to heating to 80°C for 5 h. The heating is continued over night at reflux. The reaction mixture is diluted with ethyl acetate after cooling to room temperature, washed with water and brine, dried over MgSO<sub>4</sub>, and concentrated *in vacuo*. The residue is triturated with a small amount of methanol and the precipitate is filtered off, washed with diethyl ether, and dried to give the title compound. LC (method 5):  $t_R = 1.30$  min; Mass spectrum (ESI<sup>+</sup>):  $m/z = 469$  [M+H]<sup>+</sup>.

25

**Example 9**

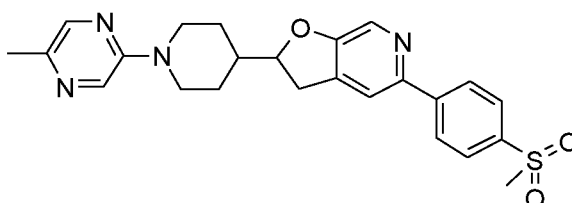
5-(4-Methanesulfonyl-phenyl)-2-[1-(5-propyl-[1,2,4]oxadiazol-3-yl)-piperidin-4-yl]-2,3-dihydro-furo[2,3-c]pyridine



The title compound is prepared from N-hydroxy-4-[5-(4-methanesulfonyl-phenyl)-2,3-dihydro-furo[2,3-c]pyridin-2-yl]-piperidine-1-carboxamide and butyryl chloride following a procedure analogous to that described in Example 8. LC (method 5):  $t_R$  = 1.30 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$  = 469 [M+H]<sup>+</sup>.

### Example 10

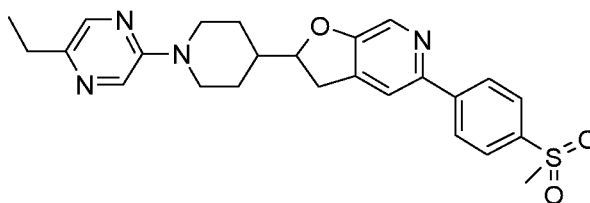
5-(4-Methanesulfonyl-phenyl)-2-[1-(5-methyl-pyrazin-2-yl)-piperidin-4-yl]-2,3-dihydro-furo[2,3-c]pyridine



A mixture of 5-(4-methanesulfonyl-phenyl)-2-piperidin-4-yl-2,3-dihydro-furo[2,3-c]pyridine (50 mg), 2-chloro-5-methylpyrazine (30 mg), and cesium carbonate (91 mg) in dimethylsulfoxide (1 mL) is heated to 150°C in a microwave oven. After cooling to room temperature the reaction mixture is diluted with water and extracted with ethyl acetate. The combined extracts are washed with brine, dried over MgSO<sub>4</sub>, and concentrated *in vacuo*. The residue is chromatographed on silica gel (ethyl acetate/methanol 98:2 → 97:3). The crude product is triturated with a small amount of methanol and the precipitate is filtered off, washed with diethyl ether, and dried to give the title compound. LC (method 5):  $t_R$  = 1.08 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$  = 451 [M+H]<sup>+</sup>.

### Example 11

2-[1-(5-Ethyl-pyrazin-2-yl)-piperidin-4-yl]-5-(4-methanesulfonyl-phenyl)-2,3-dihydro-furo[2,3-c]pyridine

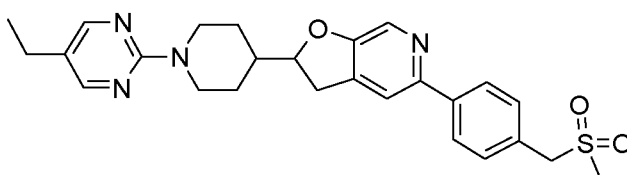


The title compound is prepared from 5-(4-methanesulfonylphenyl)-2-piperidin-4-yl-2,3-dihydro-furo[2,3-c]pyridine and 2-bromo-5-ethylpyrazine in N,N-dimethylformamide following a procedure analogous to that described in Example 10.

5 LC (method 5):  $t_R = 1.25$  min; Mass spectrum ( $ESI^+$ ):  $m/z = 465$   $[M+H]^+$ .

### Example 12

2-[1-(5-Ethyl-pyrimidin-2-yl)-piperidin-4-yl]-5-(4-methanesulfonylmethyl-phenyl)-2,3-dihydro-furo[2,3-c]pyridine



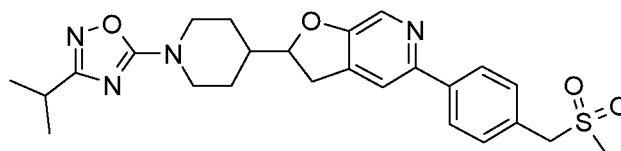
10

The title compound is prepared from 5-(4-methanesulfonylmethyl-phenyl)-2-piperidin-4-yl-2,3-dihydro-furo[2,3-c]pyridine and 2-chloro-5-ethylpyrimidine following a procedure analogous to that described in Example 1. LC (method 6):  $t_R = 1.55$  min; Mass spectrum ( $ESI^+$ ):  $m/z = 479$   $[M+H]^+$ .

15

### Example 13

2-[1-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yl]-5-(4-methanesulfonylmethyl-phenyl)-2,3-dihydro-furo[2,3-c]pyridine



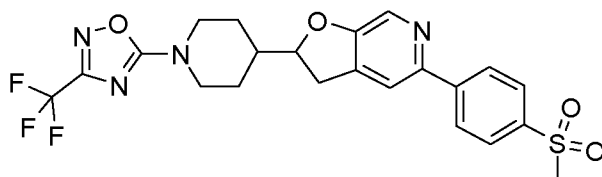
20

The title compound is prepared from 4-[5-(4-methanesulfonylmethyl-phenyl)-2,3-dihydro-furo[2,3-c]pyridin-2-yl]-piperidine-1-carbonitrile and N-hydroxy-isobutyramidine following a procedure analogous to that described in Example 2. LC (method 6):  $t_R = 1.46$  min; Mass spectrum ( $ESI^+$ ):  $m/z = 483$   $[M+H]^+$ .

25

### Example 14

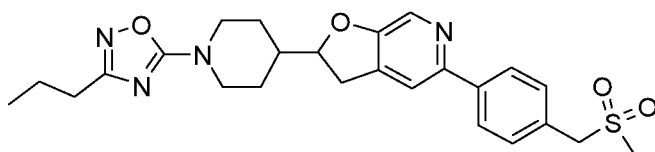
5-(4-Methanesulfonyl-phenyl)-2-[1-(3-trifluoromethyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yl]-2,3-dihydro-furo[2,3-c]pyridine



The title compound is prepared from 4-[5-(4-methanesulfonyl-phenyl)-2,3-dihydro-furo[2,3-c]pyridin-2-yl]-piperidine-1-carbonitrile and 2,2,2-trifluoro-N-hydroxy-acetamidine following a procedure analogous to that described in Example 2. LC (method 5):  $t_R = 1.32$  min; Mass spectrum ( $ESI^+$ ):  $m/z = 495$   $[M+H]^+$ .

### Example 15

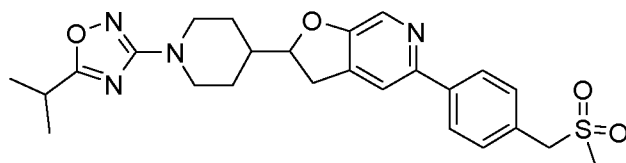
5-(4-Methanesulfonylmethyl-phenyl)-2-[1-(3-propyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yl]-2,3-dihydro-furo[2,3-c]pyridine



The title compound is prepared from 4-[5-(4-methanesulfonylmethyl-phenyl)-2,3-dihydro-furo[2,3-c]pyridin-2-yl]-piperidine-1-carbonitrile and N-hydroxy-butynamidine following a procedure analogous to that described in Example 2. LC (method 6):  $t_R = 1.46$  min; Mass spectrum ( $ESI^+$ ):  $m/z = 483$   $[M+H]^+$ .

### Example 16

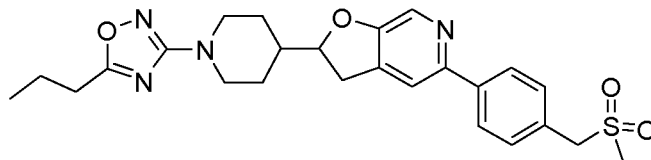
2-[1-(5-Isopropyl-[1,2,4]oxadiazol-3-yl)-piperidin-4-yl]-5-(4-methanesulfonylmethyl-phenyl)-2,3-dihydro-furo[2,3-c]pyridine



The title compound is prepared from N-hydroxy-4-[5-(4-methanesulfonylmethyl-phenyl)-2,3-dihydro-furo[2,3-c]pyridin-2-yl]-piperidine-1-carboxamide and isobutyl chloride following a procedure analogous to that described in Example 8. LC (method 6):  $t_R = 1.54$  min; Mass spectrum ( $ESI^+$ ):  $m/z = 483$   $[M+H]^+$ .

**Example 17**

5-(4-Methanesulfonylmethyl-phenyl)-2-[1-(5-propyl-[1,2,4]oxadiazol-3-yl)-piperidin-4-yl]-2,3-dihydro-furo[2,3-c]pyridine

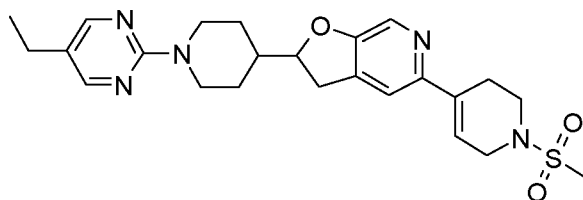


- 5 The title compound is prepared from N-hydroxy-4-[5-(4-methanesulfonylmethyl-phenyl)-2,3-dihydro-furo[2,3-c]pyridin-2-yl]-piperidine-1-carboxamide and butyryl chloride following a procedure analogous to that described in Example 8. LC (method 6):  $t_R = 1.52$  min; Mass spectrum (ESI<sup>+</sup>):  $m/z = 483$  [M+H]<sup>+</sup>.

10

**Example 18**

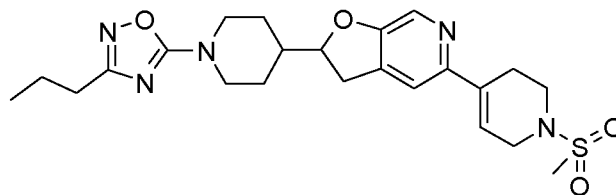
2-[1-(5-Ethyl-pyrimidin-2-yl)-piperidin-4-yl]-5-(1-methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-2,3-dihydro-furo[2,3-c]pyridine



- 15 The title compound is prepared from 5-(1-methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-2-piperidin-4-yl-2,3-dihydro-furo[2,3-c]pyridine and 2-chloro-5-ethylpyrimidine following a procedure analogous to that described in Example 1. LC (method 5):  $t_R = 0.91$  min; Mass spectrum (ESI<sup>+</sup>):  $m/z = 470$  [M+H]<sup>+</sup>.

**Example 19**

20 5-(1-Methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-2-[1-(3-propyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yl]-2,3-dihydro-furo[2,3-c]pyridine

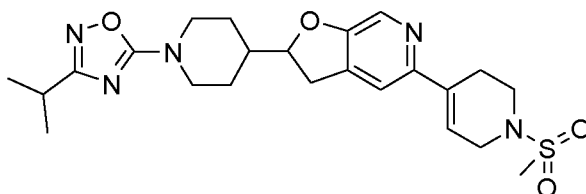


The title compound is prepared from 4-[5-(1-methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-2,3-dihydro-furo[2,3-c]pyridin-2-yl]-piperidine-1-carbonitrile and N-

hydroxy-butynamidine following a procedure analogous to that described in Example 2. LC (method 5):  $t_R = 1.02$  min; Mass spectrum (ESI<sup>+</sup>):  $m/z = 474$  [M+H]<sup>+</sup>.

### Example 20

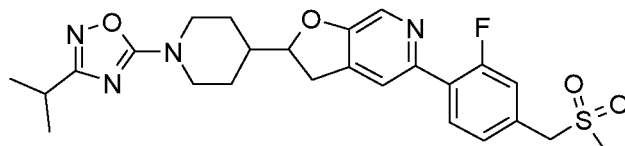
- 5 2-[1-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yl]-5-(1-methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-2,3-dihydro-furo[2,3-c]pyridine



- The title compound is prepared from 4-[5-(1-methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-2,3-dihydro-furo[2,3-c]pyridin-2-yl]-piperidine-1-carbonitrile and N-  
10 hydroxy-isobutyramidine following a procedure analogous to that described in Example 2. LC (method 5):  $t_R = 1.02$  min; Mass spectrum (ESI<sup>+</sup>):  $m/z = 474$  [M+H]<sup>+</sup>.

### Example 21

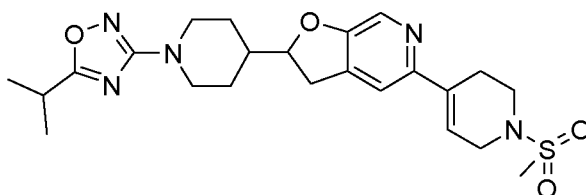
- 15 5-(2-Fluoro-4-methanesulfonylmethyl-phenyl)-2-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yl]-2,3-dihydro-furo[2,3-c]pyridine



- The title compound is prepared from 4-[5-(2-fluoro-4-methanesulfonylmethyl-phenyl)-2,3-dihydro-furo[2,3-c]pyridin-2-yl]-piperidine-1-carbonitrile and N-hydroxy-  
20 isobutyramidine following a procedure analogous to that described in Example 2. LC (method 6):  $t_R = 1.53$  min; Mass spectrum (ESI<sup>+</sup>):  $m/z = 501$  [M+H]<sup>+</sup>.

### Example 22

- 2-[1-(5-Isopropyl-[1,2,4]oxadiazol-3-yl)-piperidin-4-yl]-5-(1-methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-2,3-dihydro-furo[2,3-c]pyridine

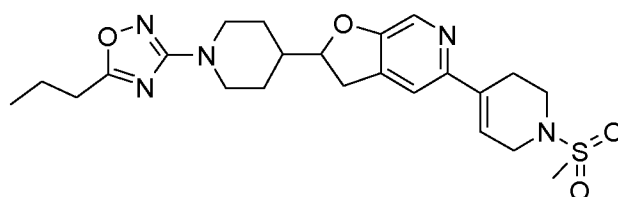


The title compound is prepared from N-hydroxy-4-[5-(1-methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-2,3-dihydro-furo[2,3-c]pyridin-2-yl]-piperidine-1-carboxamide and isobutyryl chloride following a procedure analogous to that described in Example 8. LC (method 5):  $t_R$  = 1.08 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$  = 474 [M+H]<sup>+</sup>.

5

### Example 23

5-(1-Methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-2-[1-(5-propyl-[1,2,4]oxadiazol-3-yl)-piperidin-4-yl]-2,3-dihydro-furo[2,3-c]pyridine

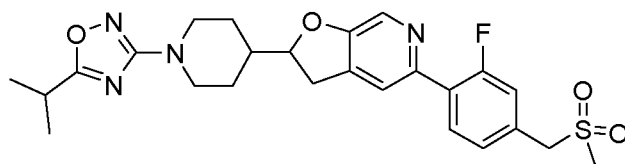


- 10 The title compound is prepared from N-hydroxy-4-[5-(1-methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-2,3-dihydro-furo[2,3-c]pyridin-2-yl]-piperidine-1-carboxamide and butyryl chloride following a procedure analogous to that described in Example 8. LC (method 5):  $t_R$  = 1.10 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$  = 474 [M+H]<sup>+</sup>.

15

### Example 24

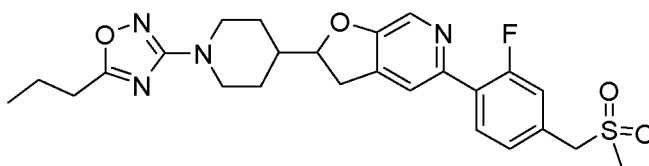
5-(2-Fluoro-4-methanesulfonylmethyl-phenyl)-2-[1-(5-isopropyl-[1,2,4]oxadiazol-3-yl)-piperidin-4-yl]-2,3-dihydro-furo[2,3-c]pyridine



- 20 The title compound is prepared from 4-[5-(2-fluoro-4-methanesulfonylmethyl-phenyl)-2,3-dihydro-furo[2,3-c]pyridin-2-yl]-N-hydroxy-piperidine-1-carboxamide and isobutyryl chloride following a procedure analogous to that described in Example 8. LC (method 6):  $t_R$  = 1.59 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$  = 501 [M+H]<sup>+</sup>.

### Example 25

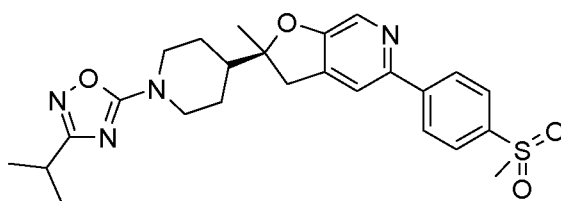
5-(2-Fluoro-4-methanesulfonylmethyl-phenyl)-2-[1-(5-propyl-[1,2,4]oxadiazol-3-yl)-piperidin-4-yl]-2,3-dihydro-furo[2,3-c]pyridine



The title compound is prepared from 4-[5-(2-fluoro-4-methanesulfonylmethyl-phenyl)-2,3-dihydro-furo[2,3-c]pyridin-2-yl]-N-hydroxy-piperidine-1-carboxamide and butyryl chloride following a procedure analogous to that described in Example 8. LC (method 6):  $t_R = 1.58$  min; Mass spectrum (ESI<sup>+</sup>):  $m/z = 501$  [M+H]<sup>+</sup>.

### Example 26

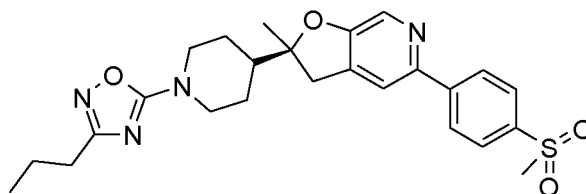
(S)-2-[1-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yl]-5-(4-methanesulfonyl-phenyl)-2-methyl-2,3-dihydro-furo[2,3-c]pyridine



The title compound is prepared from (S)-4-[5-(4-methanesulfonyl-phenyl)-2-methyl-2,3-dihydro-furo[2,3-c]pyridin-2-yl]-piperidine-1-carbonitrile (Intermediate 33; the configuration of the stereocenter is arbitrarily assigned) and N-hydroxy-isobutyramidine following a procedure analogous to that described in Example 2. LC (method 4):  $t_R = 1.13$  min; Mass spectrum (ESI<sup>+</sup>):  $m/z = 483$  [M+H]<sup>+</sup>.

### Example 27

(S)-5-(4-Methanesulfonyl-phenyl)-2-methyl-2-[1-(3-propyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yl]-2,3-dihydro-furo[2,3-c]pyridine



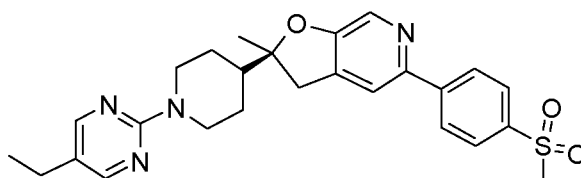
The title compound is prepared from (S)-4-[5-(4-methanesulfonyl-phenyl)-2-methyl-2,3-dihydro-furo[2,3-c]pyridin-2-yl]-piperidine-1-carbonitrile (Intermediate 33; the

configuration of the stereocenter is arbitrarily assigned) and N-hydroxy-butynamidine following a procedure analogous to that described in Example 2. LC (method 6):  $t_R$  = 1.25 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$  = 483 [M+H]<sup>+</sup>.

5

**Example 28**

(S)-2-[1-(5-Ethyl-pyrimidin-2-yl)-piperidin-4-yl]-5-(4-methanesulfonyl-phenyl)-2-methyl-2,3-dihydro-furo[2,3-c]pyridine



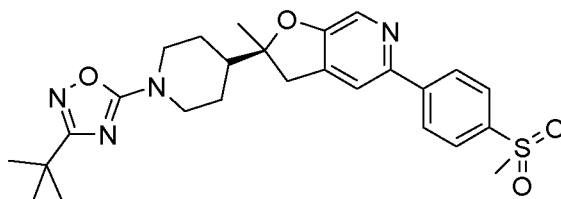
10

The title compound is prepared from (S)-5-(4-methanesulfonyl-phenyl)-2-methyl-2,3-dihydro-furo[2,3-c]pyridine (Intermediate 32; the configuration of the stereocenter is arbitrarily assigned) and 2-chloro-5-ethylpyrimidine in dimethylsulfoxide at 105°C in the presence of potassium carbonate. LC (method 4):  $t_R$  = 1.09 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$  = 479 [M+H]<sup>+</sup>.

15

**Example 29**

(S)-2-[1-(3-tert-Butyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yl]-5-(4-methanesulfonyl-phenyl)-2-methyl-2,3-dihydro-furo[2,3-c]pyridine



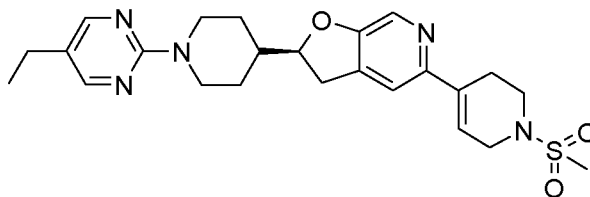
20

The title compound is prepared from (S)-4-[5-(4-methanesulfonyl-phenyl)-2-methyl-2,3-dihydro-furo[2,3-c]pyridin-2-yl]-piperidine-1-carbonitrile (Intermediate 33; the configuration of the stereocenter is arbitrarily assigned) and N-hydroxy-2,2-dimethyl-propionamidine following a procedure analogous to that described in Example 2. LC (method 4):  $t_R$  = 0.93 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$  = 497 [M+H]<sup>+</sup>.

25

**Example 30**

(S)-2-[1-(5-Ethyl-pyrimidin-2-yl)-piperidin-4-yl]-5-(1-methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-2,3-dihydro-furo[2,3-c]pyridine

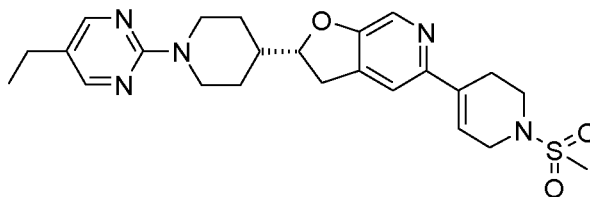


The title compound is prepared from (S)-5-(1-methanesulfonyl-1,2,3,6-tetrahydropyridin-4-yl)-2-piperidin-4-yl-2,3-dihydro-furo[2,3-c]pyridine (Intermediate 37, the configuration of the stereocenter is arbitrarily assigned) and 2-chloro-5-

5 ethylpyrimidine following a procedure analogous to that described in Example 1. LC (method 5):  $t_R = 0.87$  min; Mass spectrum (ESI<sup>+</sup>):  $m/z = 470$  [M+H]<sup>+</sup>.

### Example 31

(R)-2-[1-(5-Ethyl-pyrimidin-2-yl)-piperidin-4-yl]-5-(1-methanesulfonyl-1,2,3,6-  
tetrahydro-pyridin-4-yl)-2,3-dihydro-furo[2,3-c]pyridine

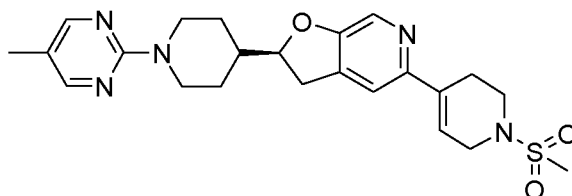


The title compound is prepared from (R)-5-(1-methanesulfonyl-1,2,3,6-tetrahydropyridin-4-yl)-2-piperidin-4-yl-2,3-dihydro-furo[2,3-c]pyridine (Intermediate 39, the configuration of the stereocenter is arbitrarily assigned) and 2-chloro-5-

15 ethylpyrimidine following a procedure analogous to that described in Example 1. LC (method 5):  $t_R = 0.87$  min; Mass spectrum (ESI<sup>+</sup>):  $m/z = 470$  [M+H]<sup>+</sup>.

### Example 32

(S)-5-(1-Methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-2-[1-(5-methyl-pyrimidin-2-  
yl)-piperidin-4-yl]-2,3-dihydro-furo[2,3-c]pyridine

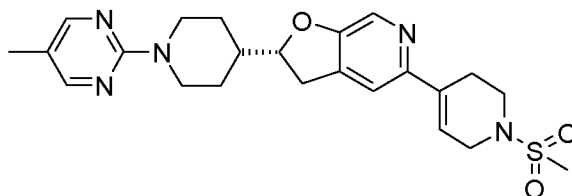


The title compound is prepared from (S)-5-(1-methanesulfonyl-1,2,3,6-tetrahydropyridin-4-yl)-2-piperidin-4-yl-2,3-dihydro-furo[2,3-c]pyridine (Intermediate 37, the configuration of the stereocenter is arbitrarily assigned) and 2-bromo-5-

methylpyrimidine following a procedure analogous to that described in Example 1. LC (method 5):  $t_R = 0.84$  min; Mass spectrum ( $ESI^+$ ):  $m/z = 456$   $[M+H]^+$ .

### Example 33

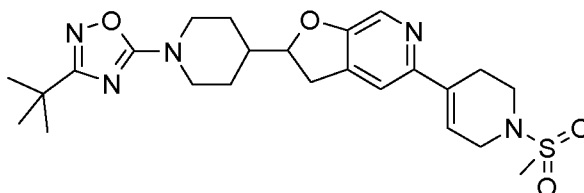
- 5 (R)-5-(1-Methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-2-[1-(5-methyl-pyrimidin-2-yl)-piperidin-4-yl]-2,3-dihydro-furo[2,3-c]pyridine



- The title compound is prepared from (R)-5-(1-methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-2-piperidin-4-yl-2,3-dihydro-furo[2,3-c]pyridine (Intermediate 39, the configuration of the stereocenter is arbitrarily assigned) and 2-bromo-5-methylpyrimidine following a procedure analogous to that described in Example 1. LC (method 5):  $t_R = 0.84$  min; Mass spectrum ( $ESI^+$ ):  $m/z = 456$   $[M+H]^+$ .

### Example 34

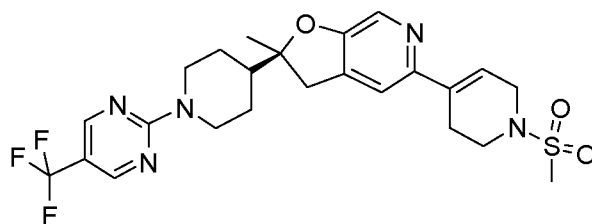
- 15 2-[1-(3-tert-Butyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yl]-5-(1-methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-2,3-dihydro-furo[2,3-c]pyridine



- The title compound is prepared from 4-[5-(1-methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-2,3-dihydro-furo[2,3-c]pyridin-2-yl]-piperidine-1-carbonitrile and N-hydroxy-2,2-dimethyl-propionamidine following a procedure analogous to that described in Example 2. LC (method 6):  $t_R = 1.51$  min; Mass spectrum ( $ESI^+$ ):  $m/z = 488$   $[M+H]^+$ .

### Example 35

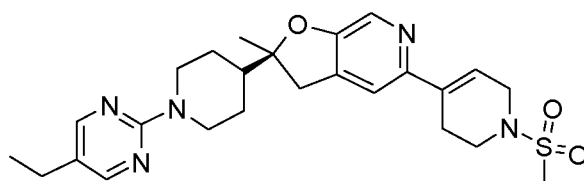
- 25 (S)-5-(1-Methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-2-methyl-2-[1-(5-trifluoromethyl-pyrimidin-2-yl)-piperidin-4-yl]-2,3-dihydro-furo[2,3-c]pyridine



The title compound is prepared from (S)-5-(1-methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-2-methyl-2-piperidin-4-yl-2,3-dihydro-furo[2,3-c]pyridine (Intermediate 41; the configuration of the stereocenter is arbitrarily assigned) and 2-chloro-5-(trifluoromethyl)pyrimidine in dimethylsulfoxide at 105°C in the presence of potassium carbonate. LC (method 4):  $t_R$  = 1.14 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$  = 524 [M+H]<sup>+</sup>.

### Example 36

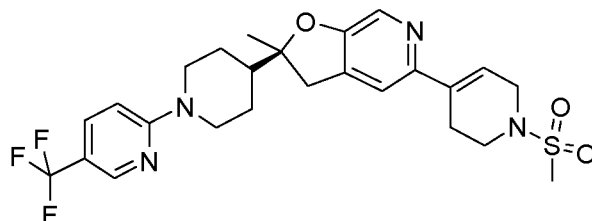
(S)-2-[1-(5-Ethyl-pyrimidin-2-yl)-piperidin-4-yl]-5-(1-methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-2-methyl-2,3-dihydrofuro[2,3-c]pyridine



The title compound is prepared from (S)-5-(1-methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-2-methyl-2-piperidin-4-yl-2,3-dihydro-furo[2,3-c]pyridine (Intermediate 41; the configuration of the stereocenter is arbitrarily assigned) and 2-chloro-5-ethyl-pyrimidine in dimethylsulfoxide at 105°C in the presence of potassium carbonate. LC (method 4):  $t_R$  = 0.91 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$  = 484 [M+H]<sup>+</sup>.

### Example 37

(S)-5-(1-Methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-2-methyl-2-[1-(5-trifluoromethyl-pyridin-2-yl)-piperidin-4-yl]-2,3-dihydro-furo[2,3-c]pyridine



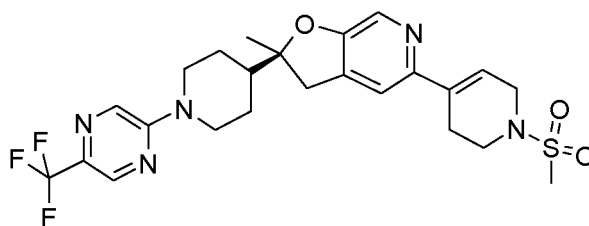
The title compound is prepared from (S)-5-(1-methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-2-methyl-2-piperidin-4-yl-2,3-dihydro-furo[2,3-c]pyridine (Intermediate

41; the configuration of the stereocenter is arbitrarily assigned) and 2-chloro-5-(trifluoromethyl)pyridine in dimethylsulfoxide at 100°C in the presence of potassium carbonate. LC (method 4):  $t_R = 1.04$  min; Mass spectrum (ESI<sup>+</sup>):  $m/z = 523$  [M+H]<sup>+</sup>.

5

**Example 38**

(S)-5-(1-Methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-2-methyl-2-[1-(5-trifluoromethyl-pyrazin-2-yl)-piperidin-4-yl]-2,3-dihydro-furo[2,3-c]pyridine



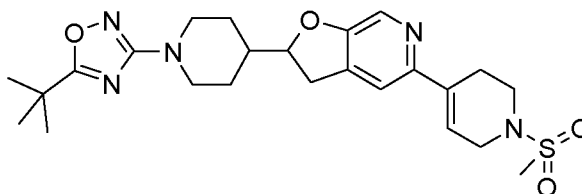
10

The title compound is prepared from (S)-5-(1-methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-2-methyl-2-piperidin-4-yl-2,3-dihydro-furo[2,3-c]pyridine (Intermediate 41; the configuration of the stereocenter is arbitrarily assigned) and 2-chloro-5-(trifluoromethyl)pyrazine in dimethylsulfoxide at 100°C in the presence of potassium carbonate. LC (method 4):  $t_R = 1.06$  min; Mass spectrum (ESI<sup>+</sup>):  $m/z = 524$  [M+H]<sup>+</sup>.

15

**Example 39**

2-[1-(5-tert-Butyl-[1,2,4]oxadiazol-3-yl)-piperidin-4-yl]-5-(1-methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-2,3-dihydro-furo[2,3-c]pyridine



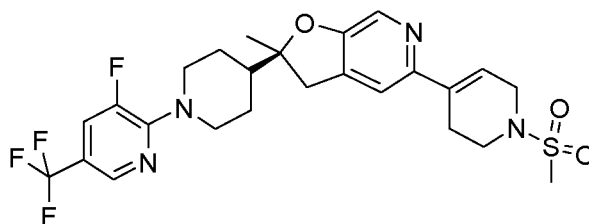
20

A mixture of N-hydroxy-4-[5-(1-methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-2,3-dihydro-furo[2,3-c]pyridin-2-yl]-piperidine-1-carboxamide (30 mg) and trimethylacetic anhydride (30  $\mu$ l) in toluene (2 mL) is heated under reflux for 2 h. The reaction mixture is concentrated *in vacuo* and chromatographed on silica gel (cyclohexane/ethyl acetate = 50:50). The crude product is triturated with diethyl ether, filtered off, and dried to give the title compound. LC (method 6):  $t_R = 1.58$  min; Mass spectrum (ESI<sup>+</sup>):  $m/z = 488$  [M+H]<sup>+</sup>.

25

**Example 40**

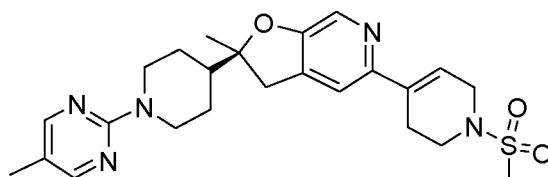
(S)-5-(1-Methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-2-methyl-2-[1-(3-fluor-5-trifluoromethyl-pyridin-2-yl)-piperidin-4-yl]-2,3-dihydro-furo[2,3-c]pyridine



The title compound is prepared from (S)-5-(1-methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-2-methyl-2-piperidin-4-yl-2,3-dihydro-furo[2,3-c]pyridine (Intermediate 41; the configuration of the stereocenter is arbitrarily assigned) and 2-bromo-3-fluoro-5-(trifluoromethyl)pyridine in dimethylsulfoxide at 100°C in the presence of potassium carbonate. LC (method 4):  $t_R = 1.21$  min; Mass spectrum (ESI<sup>+</sup>):  $m/z = 541$  [M+H]<sup>+</sup>.

#### Example 41

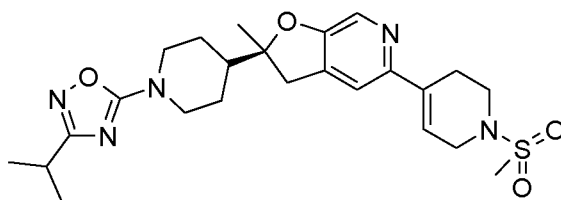
(S)-5-(1-Methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-2-methyl-2-[1-(5-methyl-pyrimidin-2-yl)-piperidin-4-yl]-2,3-dihydro-furo[2,3-c]pyridine



The title compound is prepared from (S)-5-(1-methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-2-methyl-2-piperidin-4-yl-2,3-dihydro-furo[2,3-c]pyridine (Intermediate 41; the configuration of the stereocenter is arbitrarily assigned) and 2-bromo-5-methyl-pyrimidine in dimethylsulfoxide at 100°C in the presence of potassium carbonate. LC (method 4):  $t_R = 0.81$  min; Mass spectrum (ESI<sup>+</sup>):  $m/z = 470$  [M+H]<sup>+</sup>.

#### Example 42

(S)-2-[1-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yl]-5-(1-methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-2-methyl-2,3-dihydro-furo[2,3-c]pyridine

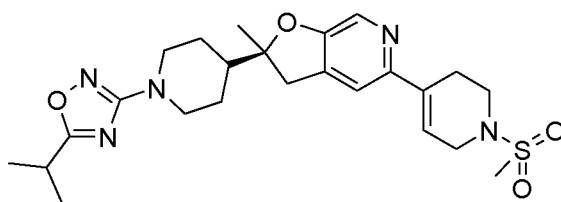


The title compound is prepared from (S)-4-[5-(1-methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-2-methyl-2,3-dihydro-furo[2,3-c]pyridin-2-yl]-piperidine-1-carbonitrile (Intermediate 42; the configuration of the stereocenter is arbitrarily assigned) and N-hydroxy-isobutyramidine following a procedure analogous to that described in

5 Example 2. LC (method 4):  $t_R = 0.97$  min; Mass spectrum (ESI<sup>+</sup>):  $m/z = 488$  [M+H]<sup>+</sup>.

### Example 43

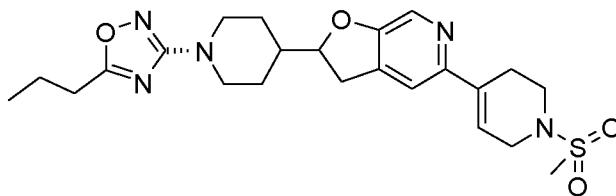
(S)-2-[1-(5-Isopropyl-[1,2,4]oxadiazol-3-yl)-piperidin-4-yl]-5-(1-methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-2-methyl-2,3-dihydro-furo[2,3-c]pyridine



The title compound is prepared from (S)-N-hydroxy-4-[5-(1-methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-2-methyl-2,3-dihydro-furo[2,3-c]pyridin-2-yl]-piperidine-1-carboxamide (Intermediate 43; the configuration of the stereocenter is arbitrarily assigned) and isobutyryl chloride following a procedure analogous to that described in Example 8. LC (method 4):  $t_R = 1.01$  min; Mass spectrum (ESI<sup>+</sup>):  $m/z = 488$  [M+H]<sup>+</sup>.

### Example 44

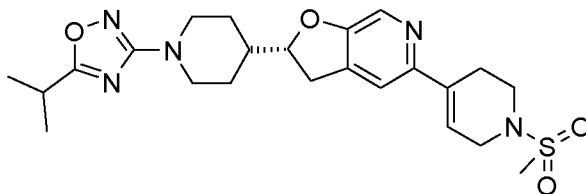
(R)-5-(1-Methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-2-[1-(5-propyl-[1,2,4]oxadiazol-3-yl)-piperidin-4-yl]-2,3-dihydro-furo[2,3-c]pyridine



The title compound is prepared from (R)-N-hydroxy-4-[5-(1-methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-2,3-dihydro-furo[2,3-c]pyridin-2-yl]-piperidine-1-carboxamide (Intermediate 45; the configuration of the stereocenter is arbitrarily assigned) and n-butyric anhydride following a procedure analogous to that described in Example 39. LC (method 6):  $t_R = 1.47$  min; Mass spectrum (ESI<sup>+</sup>):  $m/z = 474$  [M+H]<sup>+</sup>.

**Example 45**

(R)-2-[1-(5-Isopropyl-[1,2,4]oxadiazol-3-yl)-piperidin-4-yl]-5-(1-methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-2,3-dihydro-furo[2,3-c]pyridine

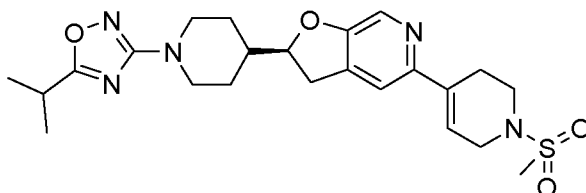


- 5 The title compound is prepared from (R)-N-hydroxy-4-[5-(1-methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-2,3-dihydro-furo[2,3-c]pyridin-2-yl]-piperidine-1-carboxamide (Intermediate 45; the configuration of the stereocenter is arbitrarily assigned) and isobutyric anhydride following a procedure analogous to that described in Example 39. LC (method 6):  $t_R = 1.47$  min; Mass spectrum (ESI<sup>+</sup>):  $m/z = 474$  [M+H]<sup>+</sup>.

10

**Example 46**

(S)-2-[1-(5-Isopropyl-[1,2,4]oxadiazol-3-yl)-piperidin-4-yl]-5-(1-methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-2,3-dihydro-furo[2,3-c]pyridine

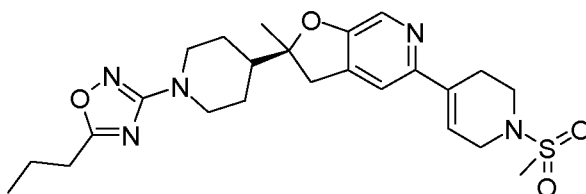


- 15 The title compound is prepared from (S)-N-hydroxy-4-[5-(1-methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-2,3-dihydro-furo[2,3-c]pyridin-2-yl]-piperidine-1-carboxamide (Intermediate 47; the configuration of the stereocenter is arbitrarily assigned) and isobutyric anhydride following a procedure analogous to that described in Example 39. LC (method 6):  $t_R = 1.47$  min; Mass spectrum (ESI<sup>+</sup>):  $m/z = 474$  [M+H]<sup>+</sup>.

20

**Example 47**

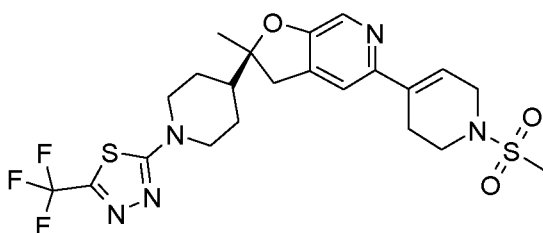
(S)-5-(1-Methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-2-methyl-2-[1-(5-propyl-[1,2,4]oxadiazol-3-yl)-piperidin-4-yl]-2,3-dihydro-furo[2,3-c]pyridine



The title compound is prepared from (S)-N-hydroxy-4-[5-(1-methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-2-methyl-2,3-dihydro-furo[2,3-c]pyridin-2-yl]-piperidine-1-carboxamide (Intermediate 43; the configuration of the stereocenter is arbitrarily assigned) and butyryl chloride following a procedure analogous to that described in  
 5 Example 8. LC (method 4):  $t_R$  = 1.00 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$  = 488 [M+H]<sup>+</sup>.

### Example 48

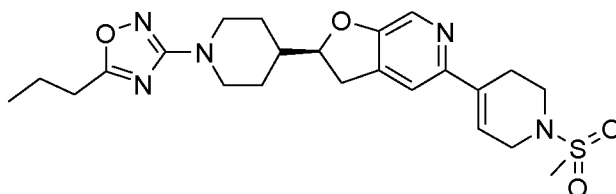
5-(1-Methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-2-methyl-2-[1-(5-trifluoromethyl-  
 [1,3,4]thiadiazol-2-yl)-piperidin-4-yl]-2,3-dihydro-furo[2,3-c]pyridine



The title compound is prepared from (S)-5-(1-methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-2-methyl-2-piperidin-4-yl-2,3-dihydro-furo[2,3-c]pyridine (Intermediate 41; the configuration of the stereocenter is arbitrarily assigned) and 2-chloro-5-trifluoromethyl-[1,3,4]thiadiazole in dimethylsulfoxide at 85°C in the presence of  
 15 potassium carbonate. LC (method 4):  $t_R$  = 0.98 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$  = 530 [M+H]<sup>+</sup>.

### Example 49

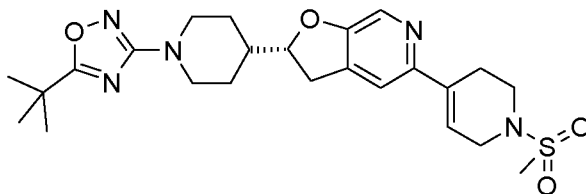
(S)-5-(1-Methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-2-[1-(5-propyl-  
 [1,2,4]oxadiazol-3-yl)-piperidin-4-yl]-2,3-dihydro-furo[2,3-c]pyridine



The title compound is prepared from (S)-N-hydroxy-4-[5-(1-methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-2,3-dihydro-furo[2,3-c]pyridin-2-yl]-piperidine-1-carboxamide (Intermediate 47; the configuration of the stereocenter is arbitrarily assigned) and n-butyr-  
 25 ic anhydride following a procedure analogous to that described in Example 39. LC (method 6):  $t_R$  = 1.47 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$  = 474 [M+H]<sup>+</sup>.

**Example 50**

(R)-2-[1-(5-tert-Butyl-[1,2,4]oxadiazol-3-yl)-piperidin-4-yl]-5-(1-methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-2,3-dihydro-furo[2,3-c]pyridine

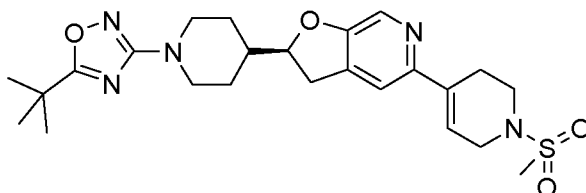


- 5 The title compound is prepared from (R)-N-hydroxy-4-[5-(1-methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-2,3-dihydro-furo[2,3-c]pyridin-2-yl]-piperidine-1-carboxamide (Intermediate 45; the configuration of the stereocenter is arbitrarily assigned) and trimethylacetic anhydride following a procedure analogous to that described in Example 39. LC (method 6):  $t_R = 1.58$  min; Mass spectrum ( $ESI^+$ ):  $m/z = 488$   $[M+H]^+$ .

10

**Example 51**

(S)-2-[1-(5-tert-Butyl-[1,2,4]oxadiazol-3-yl)-piperidin-4-yl]-5-(1-methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-2,3-dihydro-furo[2,3-c]pyridine

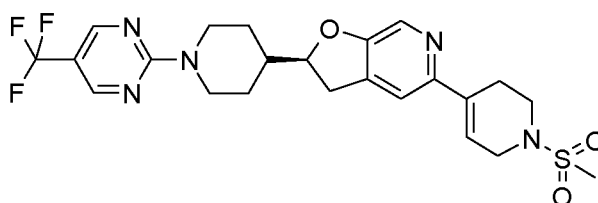


- 15 The title compound is prepared from (S)-N-hydroxy-4-[5-(1-methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-2,3-dihydro-furo[2,3-c]pyridin-2-yl]-piperidine-1-carboxamide (Intermediate 47; the configuration of the stereocenter is arbitrarily assigned) and trimethylacetic anhydride following a procedure analogous to that described in Example 39. LC (method 6):  $t_R = 1.58$  min; Mass spectrum ( $ESI^+$ ):  $m/z = 488$   $[M+H]^+$ .

20

**Example 52**

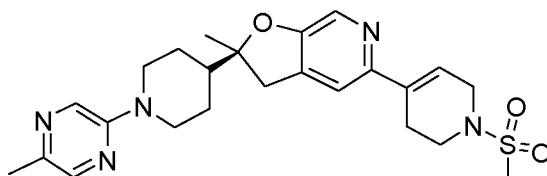
(S)-5-(1-Methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-2-[1-(5-trifluoromethyl-pyrimidin-2-yl)-piperidin-4-yl]-2,3-dihydro-furo[2,3-c]pyridine



The title compound is prepared from (S)-5-(1-methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-2-piperidin-4-yl-2,3-dihydro-furo[2,3-c]pyridine (Intermediate 37, the configuration of the stereocenter is arbitrarily assigned) and 2-chloro-5-(trifluoromethyl)pyrimidine in dimethylsulfoxide at 110°C in the presence of potassium carbonate. LC (method 5):  $t_R$  = 1.28 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$  = 510 [M+H]<sup>+</sup>.

### Example 53

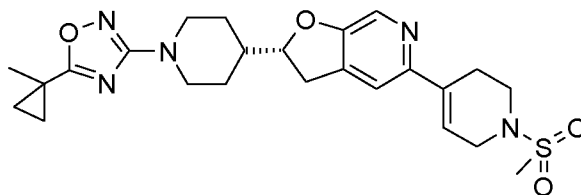
(S)-5-(1-Methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-2-methyl-2-[1-(5-methyl-pyrazin-2-yl)-piperidin-4-yl]-2,3-dihydro-furo[2,3-c]pyridine



The title compound is prepared from (S)-5-(1-methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-2-methyl-2-piperidin-4-yl-2,3-dihydro-furo[2,3-c]pyridine (Intermediate 41; the configuration of the stereocenter is arbitrarily assigned) and 2-bromo-5-methyl-pyrazine in dimethylsulfoxide at 125°C in the presence of potassium carbonate. LC (method 4):  $t_R$  = 0.84 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$  = 470 [M+H]<sup>+</sup>.

### Example 54

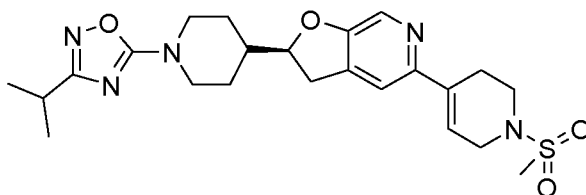
(R)-5-(1-Methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-2-{1-[5-(1-methyl-cyclopropyl)-[1,2,4]oxadiazol-3-yl]-piperidin-4-yl}-2,3-dihydro-furo[2,3-c]pyridine



The title compound is prepared from (R)-N-hydroxy-4-[5-(1-methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-2,3-dihydro-furo[2,3-c]pyridin-2-yl]-piperidine-1-carboxamide (Intermediate 45; the configuration of the stereocenter is arbitrarily assigned) and 1-methyl-cyclopropanecarbonyl chloride following a procedure analogous to that described in Example 8. LC (method 6):  $t_R$  = 1.53 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$  = 486 [M+H]<sup>+</sup>.

### Example 55

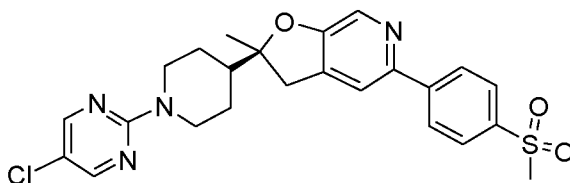
(S)-2-[1-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yl]-5-(1-methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-2,3-dihydro-furo[2,3-c]pyridine



The title compound is prepared from (S)-4-[5-(1-methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-2,3-dihydro-furo[2,3-c]pyridine-2-yl]-piperidine-1-carbonitrile (Intermediate 46; the configuration of the stereocenter is arbitrarily assigned) and N-hydroxy-isobutyramidine following a procedure analogous to that described in Example 2. LC (method 6):  $t_R = 1.40$  min; Mass spectrum ( $ESI^+$ ):  $m/z = 474$   $[M+H]^+$ .

### Example 56

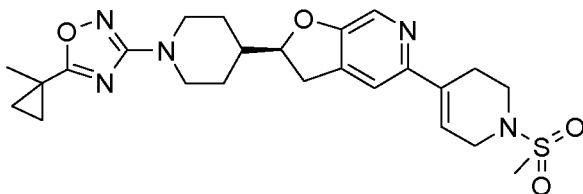
(S)-2-[1-(5-Chloro-pyrimidin-2-yl)-piperidin-4-yl]-5-(4-methanesulfonyl-phenyl)-2-methyl-2,3-dihydro-furo[2,3-c]pyridine



The title compound is prepared from (S)-5-(4-methanesulfonyl-phenyl)-2-methyl-2-piperidin-4-yl-2,3-dihydro-furo[2,3-c]pyridine (Intermediate 32; the configuration of the stereocenter is arbitrarily assigned) and 2,5-dichloro-pyrimidine in dimethylsulfoxide at 105°C in the presence of potassium carbonate. LC (method 6):  $t_R = 1.78$  min; Mass spectrum ( $ESI^+$ ):  $m/z = 485$   $[M+H]^+$ .

### Example 57

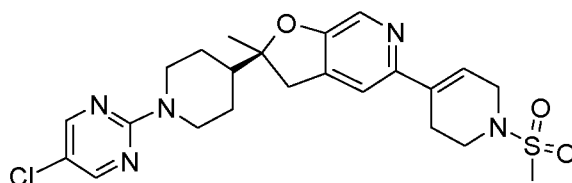
(S)-5-(1-Methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-2-{1-[5-(1-methyl-cyclopropyl)-[1,2,4]oxadiazol-3-yl]-piperidin-4-yl}-2,3-dihydro-furo[2,3-c]pyridine



The title compound is prepared from (S)-N-hydroxy-4-[5-(1-methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-2,3-dihydro-furo[2,3-c]pyridin-2-yl]-piperidine-1-carboxamide (Intermediate 47; the configuration of the stereocenter is arbitrarily assigned) and 1-methyl-cyclopropanecarbonyl chloride following a procedure analogous to that described in Example 8. LC (method 6):  $t_R$  = 1.53 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$  = 486 [M+H]<sup>+</sup>.

### Example 58

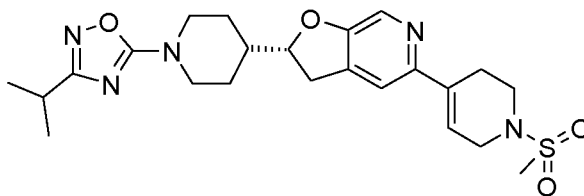
(S)-2-[1-(5-Chloro-pyrimidin-2-yl)-piperidin-4-yl]-5-(1-methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-2-methyl-2,3-dihydro-furo[2,3-c]pyridine



The title compound is prepared from (S)-5-(1-methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-2-methyl-2-piperidin-4-yl-2,3-dihydro-furo[2,3-c]pyridine (Intermediate 41; the configuration of the stereocenter is arbitrarily assigned) and 2,5-dichloro-pyrimidine in dimethylsulfoxide at 105°C in the presence of potassium carbonate. LC (method 6):  $t_R$  = 1.78 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$  = 490 [M+H]<sup>+</sup>.

### Example 59

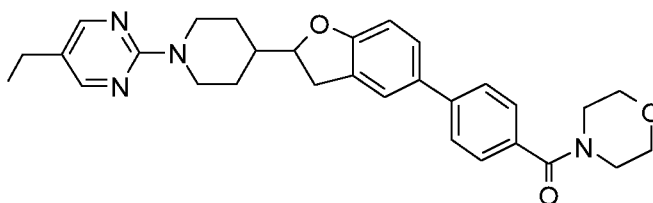
(R)-2-[1-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-yl]-5-(1-methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-2,3-dihydro-furo[2,3-c]pyridine



The title compound is prepared from (R)-4-[5-(1-methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-2,3-dihydro-furo[2,3-c]pyridine-2-yl]-piperidine-1-carbonitrile (Intermediate 44; the configuration of the stereocenter is arbitrarily assigned) and N-hydroxy-isobutyramidine following a procedure analogous to that described in Example 2. LC (method 6):  $t_R$  = 1.40 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$  = 474 [M+H]<sup>+</sup>.

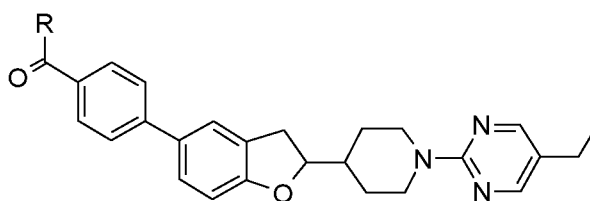
### Example 60

(4-{2-[1-(5-Ethyl-pyrimidin-2-yl)-piperidin-4-yl]-2,3-dihydro-benzofuran-5-yl}-phenyl)-  
morpholin-4-yl-methanone



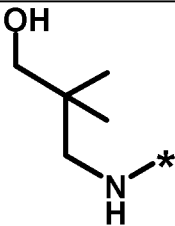
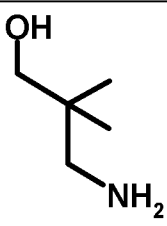
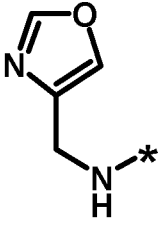
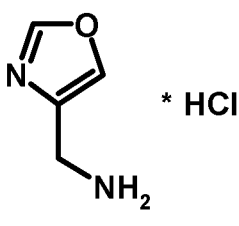
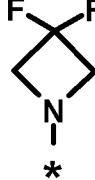
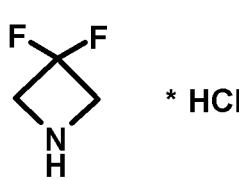
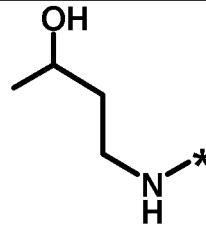
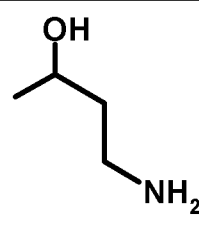
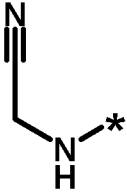
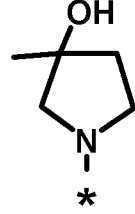
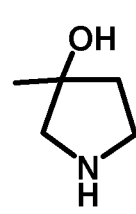
- To a mixture of 4-{2-[1-(5-ethyl-pyrimidin-2-yl)-piperidin-4-yl]-2,3-dihydro-benzofuran-  
5-yl}-benzoic acid (43 mg) in *N,N*-dimethylformamide (1.5 mL) diethyl-isopropylamine  
(52  $\mu$ L) and 2-(1 H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate  
(TBTU, 32 mg) are added. After 10 min morpholine (11 mg) in *N,N*-dimethyl-  
formamide (0.5 mL) is added. The mixture is stirred for 12 h and purified by  
preparative HPLC (eluent water (+0.1% TFA)/methanol) to yield the desired product.  
HPLC (method 9):  $t_R$  = 1.95 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$  = 499 [M+H]<sup>+</sup>.

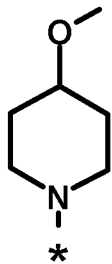
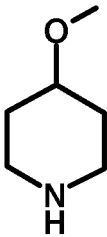
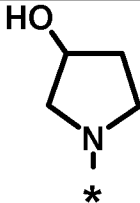
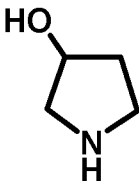
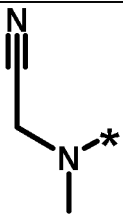
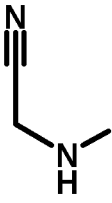
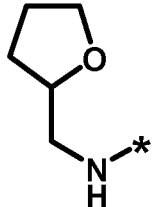
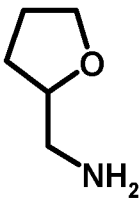
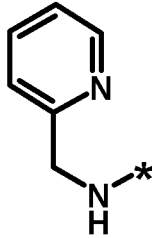
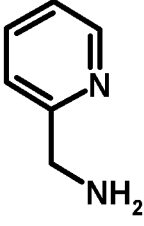
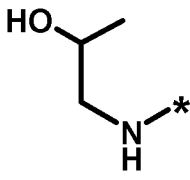
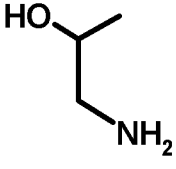
The following compounds of general formula (1-1) are prepared analogously to Example 60, the starting materials used being shown in the column headed "SM 1":

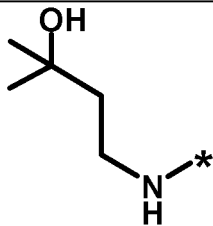
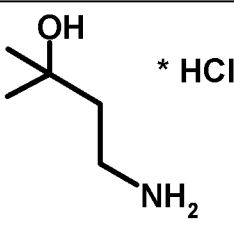
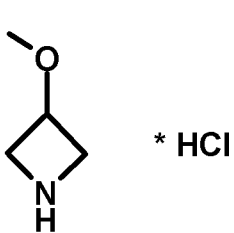
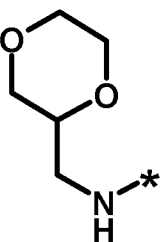
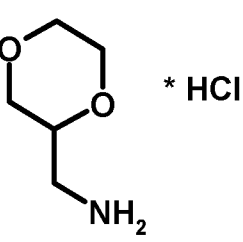
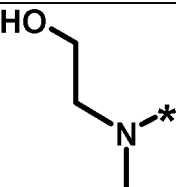
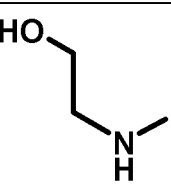


(1-1)

| Ex. | R | SM 1 | ESI-MS [ $m/z$ ]<br>[M+H] <sup>+</sup> | $R_t$ (HPLC) [min]<br>(method 6) |
|-----|---|------|----------------------------------------|----------------------------------|
| 61  |   |      | 527                                    | 2.01                             |
| 62  |   |      | 501                                    | 1.98                             |

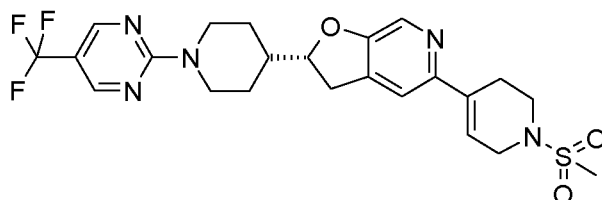
| Ex. | R                                                                                   | SM 1                                                                                | ESI-MS [m/z]<br>[M+H] <sup>+</sup> | R <sub>t</sub> (HPLC) [min]<br>(method 6) |
|-----|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|------------------------------------|-------------------------------------------|
| 63  |    |    | 515                                | 2.02                                      |
| 64  |    |    | 510                                | 1.92                                      |
| 65  |   |   | 505                                | 2.05                                      |
| 66  |  |  | 501                                | 1.95                                      |
| 67  |  |  | 468                                | 1.91                                      |
| 68  |  |  | 513                                | 1.93                                      |

| Ex. | R                                                                                   | SM 1                                                                                | ESI-MS [m/z]<br>[M+H] <sup>+</sup> | R <sub>t</sub> (HPLC) [min]<br>(method 6) |
|-----|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|------------------------------------|-------------------------------------------|
| 69  |    |    | 527                                | 2.02                                      |
| 70  |    |    | 499                                | 1.86                                      |
| 71  |   |   | 482                                | 1.92                                      |
| 72  |  |  | 513                                | 1.99                                      |
| 73  |  |  | 520                                | 1.67                                      |
| 74  |  |  | 487                                | 1.92                                      |

| Ex. | R                                                                                   | SM 1                                                                                | ESI-MS [m/z]<br>[M+H] <sup>+</sup> | R <sub>t</sub> (HPLC) [min]<br>(method 6) |
|-----|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|------------------------------------|-------------------------------------------|
| 75  |    |    | 515                                | 1.98                                      |
| 76  |    |    | 499                                | 1.99                                      |
| 77  |   |   | 529                                | 1.94                                      |
| 78  |  |  | 487                                | 1.87                                      |

### Example 79

(R)-5-(1-Methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-2-[1-(5-trifluoromethyl-pyrimidin-2-yl)-piperidin-4-yl]-2,3-dihydro-furo[2,3-c]pyridine

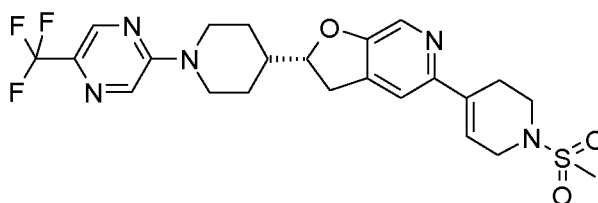


A mixture of (R)-5-(1-methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-2-piperidin-4-yl-2,3-dihydro-furo[2,3-c]pyridine (Intermediate 39, the configuration of the stereocenter is arbitrarily assigned; 110 mg), 2-chloro-5-trifluoromethyl-pyrimidine (76 mg), K<sub>2</sub>CO<sub>3</sub> (100 mg), and dimethyl sulfoxide (1.5 mL) is stirred at 110 °C for 3 h. After cooling to

room temperature, water is added and the resulting mixture is extracted with ethyl acetate. The combined extracts are washed with brine, dried ( $\text{Na}_2\text{SO}_4$ ), and concentrated. The residue is chromatographed on silica gel (cyclohexane/ethyl acetate 30:70→10:90) to give the title compound. LC (method 5):  $t_R = 1.32$  min; Mass spectrum ( $\text{ESI}^+$ ):  $m/z = 510$   $[\text{M}+\text{H}]^+$ .

### Example 80

(R)-5-(1-Methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-2-[1-(5-trifluoromethyl-pyrazin-2-yl)-piperidin-4-yl]-2,3-dihydro-furo[2,3-c]pyridine

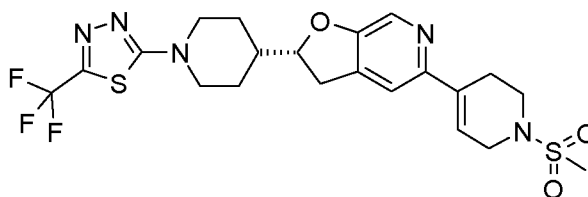


The title compound is prepared from (R)-5-(1-methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-2-piperidin-4-yl-2,3-dihydro-furo[2,3-c]pyridine (Intermediate 39, the configuration of the stereocenter is arbitrarily assigned) and 2-chloro-5-trifluoromethyl-pyrazine following a procedure analogous to that described for

Example 79. LC (method 7):  $t_R = 1.56$  min; Mass spectrum ( $\text{ESI}^+$ ):  $m/z = 510$   $[\text{M}+\text{H}]^+$ .

### Example 81

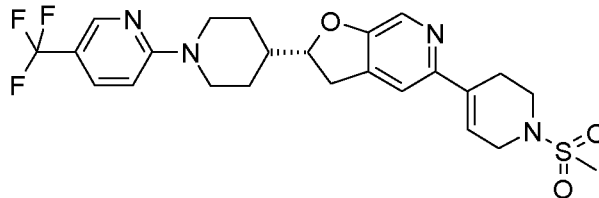
(R)-5-(1-Methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-2-[1-(5-trifluoromethyl-[1,3,4]thiadiazol-2-yl)-piperidin-4-yl]-2,3-dihydro-furo[2,3-c]pyridine



The title compound is prepared from (R)-5-(1-methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-2-piperidin-4-yl-2,3-dihydro-furo[2,3-c]pyridine (Intermediate 39, the configuration of the stereocenter is arbitrarily assigned) and 2-chloro-5-trifluoromethyl-[1,3,4]thiadiazole following a procedure analogous to that described for Example 79. LC (method 7):  $t_R = 1.46$  min; Mass spectrum ( $\text{ESI}^+$ ):  $m/z = 516$   $[\text{M}+\text{H}]^+$ .

**Example 82**

(R)-4-[5-(1-Methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-2,3-dihydro-furo[2,3-c]pyridin-2-yl]-5'-trifluoromethyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl

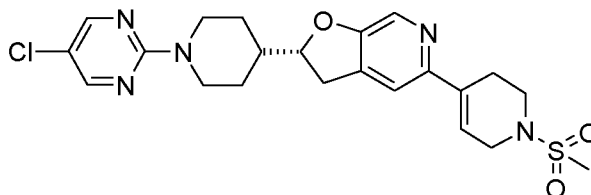


- 5 The title compound is prepared from (R)-5-(1-methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-2-piperidin-4-yl-2,3-dihydro-furo[2,3-c]pyridine (Intermediate 39, the configuration of the stereocenter is arbitrarily assigned) and 2-chloro-5-trifluoromethyl-pyridine following a procedure analogous to that described for Example 79. LC (method 7):  $t_R = 1.63$  min; Mass spectrum ( $ESI^+$ ):  $m/z = 509$   $[M+H]^+$ .

10

**Example 83**

(R)-2-[1-(5-Chloro-pyrimidin-2-yl)-piperidin-4-yl]-5-(1-methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-2,3-dihydro-furo[2,3-c]pyridine

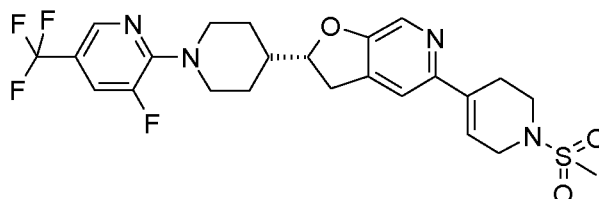


- 15 The title compound is prepared from (R)-5-(1-methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-2-piperidin-4-yl-2,3-dihydro-furo[2,3-c]pyridine (Intermediate 39, the configuration of the stereocenter is arbitrarily assigned) and 2,5-dichloro-pyrimidine following a procedure analogous to that described for Example 79. LC (method 7):  $t_R = 1.63$  min; Mass spectrum ( $ESI^+$ ):  $m/z = 476/478$  (Cl)  $[M+H]^+$ .

20

**Example 84**

(R)-3'-Fluoro-4-[5-(1-methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-2,3-dihydro-furo[2,3-c]pyridin-2-yl]-5'-trifluoromethyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl

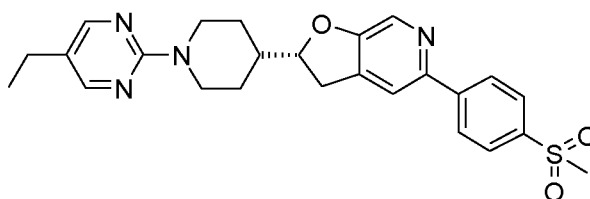


The title compound is prepared from (*R*)-5-(1-methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-2-piperidin-4-yl-2,3-dihydro-furo[2,3-*c*]pyridine (Intermediate 39, the configuration of the stereocenter is arbitrarily assigned) and 2-bromo-3-fluoro-5-trifluoromethyl-pyridine following a procedure analogous to that described for

5 Example 79. LC (method 7):  $t_R$  = 1.75 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$  = 527 [M+H]<sup>+</sup>.

### Example 85

(*R*)-2-[1-(5-Ethyl-pyrimidin-2-yl)-piperidin-4-yl]-5-(4-methanesulfonyl-phenyl)-2,3-  
dihydro-furo[2,3-*c*]pyridine



10 A mixture of (*R*)-5-(4-methanesulfonyl-phenyl)-2-piperidin-4-yl-2,3-dihydro-furo[2,3-*c*]pyridine {obtained from (*R*)-4-[5-(4-methanesulfonyl-phenyl)-2,3-dihydro-furo[2,3-*c*]pyridin-2-yl]-piperidine-1-carboxylic acid tert-butyl ester by cleavage of the carbamate group (following a procedure analogous to that described for Intermediate

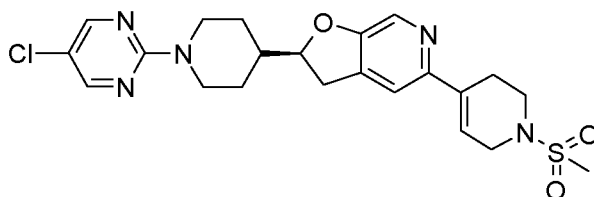
15 9), which in turn is synthesized from Intermediate 34 and 4-methanesulfonyl-phenylboronic acid following a procedure analogous to that described for Intermediate 7, the configuration of the stereocenter is arbitrarily assigned; 110 mg}, 2-chloro-5-ethyl-pyrimidine (52  $\mu$ L), *N,N*-diisopropyl-ethylamine (0.18 mL), and *N,N*-dimethylformamide (2 mL) is stirred at 120 °C for 5 h. After cooling to room

20 temperature, water is added and the resulting mixture is extracted with ethyl acetate. The combined extracts are washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated. The residue is chromatographed on silica gel (cyclohexane/ethyl acetate 40:60→30:70) to give the title compound. LC (method 6):  $t_R$  = 1.65 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$  = 465 [M+H]<sup>+</sup>.

### Example 86

(*S*)-2-[1-(5-Chloro-pyrimidin-2-yl)-piperidin-4-yl]-5-(1-methanesulfonyl-1,2,3,6-  
tetrahydro-pyridin-4-yl)-2,3-dihydro-furo[2,3-*c*]pyridine

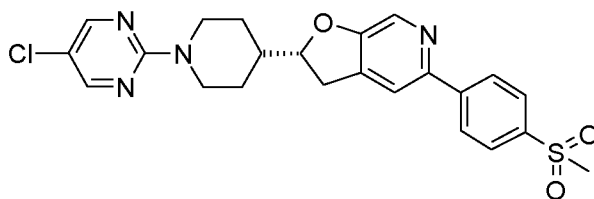
128



The title compound is prepared from (S)-5-(1-methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-2-piperidin-4-yl-2,3-dihydro-furo[2,3-c]pyridine (Intermediate 37, the configuration of the stereocenter is arbitrarily assigned) and 2,5-dichloro-pyrimidine following a procedure analogous to that described for Example 79. LC (method 7):  $t_R$  = 1.62 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$  = 476/478 (CI) [M+H]<sup>+</sup>.

### Example 87

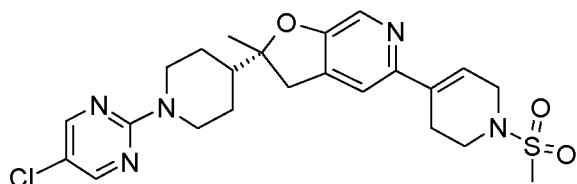
(R)-2-[1-(5-Chloro-pyrimidin-2-yl)-piperidin-4-yl]-5-(4-methanesulfonyl-phenyl)-2,3-dihydro-furo[2,3-c]pyridine



The title compound is prepared from (R)-5-(4-methanesulfonyl-phenyl)-2-piperidin-4-yl-2,3-dihydro-furo[2,3-c]pyridine {obtained from (R)-4-[5-(4-methanesulfonyl-phenyl)-2,3-dihydro-furo[2,3-c]pyridin-2-yl]-piperidine-1-carboxylic acid tert-butyl ester by cleavage of the carbamate group (following a procedure analogous to that described for Intermediate 9), which in turn is obtained from Intermediate 34 and 4-methanesulfonyl-phenylboronic acid following a procedure analogous to that described for Intermediate 7, the configuration of the stereocenter is arbitrarily assigned} and 2,5-dichloro-pyrimidine following a procedure analogous to that described for Example 79. LC (method 6):  $t_R$  = 1.63 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$  = 471/473 (CI) [M+H]<sup>+</sup>.

### Example 88

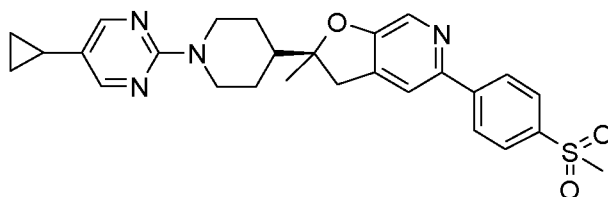
(R)-2-[1-(5-Chloro-pyrimidin-2-yl)-piperidin-4-yl]-5-(1-methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-2-methyl-2,3-dihydro-furo[2,3-c]pyridine



- 5 The title compound is prepared from (R)-5-(1-methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-2-piperidin-4-yl-2,3-dihydro-furo[2,3-c]pyridine {obtained from 4-[5-(1-methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-2-methyl-2,3-dihydro-furo[2,3-c]pyridin-2-yl]-piperidine-1-carboxylic acid tert-butyl ester by cleavage of the carbamate group (following a procedure analogous to that described for Intermediate
- 10 9), which in turn is obtained from Intermediate 30 and 1-(methanesulfonyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,6-tetrahydropyridine following a procedure analogous to that described for Intermediate 7, the configuration of the stereocenter is arbitrarily assigned} and 2,5-dichloro-pyrimidine following a procedure analogous to that described for Example 79. LC (method 4):  $t_R = 1.08$  min; Mass spectrum
- 15 (ESI<sup>+</sup>):  $m/z = 490/492$  (Cl) [M+H]<sup>+</sup>.

### Example 89

(S)-2-[1-(5-Cyclopropyl-pyrimidin-2-yl)-piperidin-4-yl]-5-(4-methanesulfonyl-phenyl)-2-methyl-2,3-dihydro-furo[2,3-c]pyridine



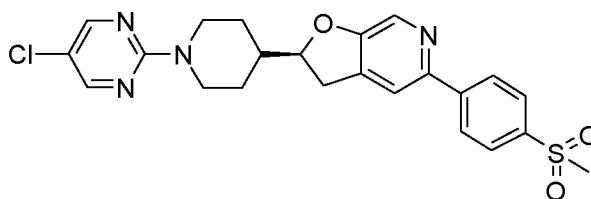
20

The title compound is prepared from (S)-5-(4-methanesulfonyl-phenyl)-2-piperidin-4-yl-2,3-dihydro-furo[2,3-c]pyridine (Intermediate 32, the configuration of the stereocenter is arbitrarily assigned) and 2-chloro-5-cyclopropyl-pyrimidine following a procedure analogous to that described for Example 79. LC (method 4):  $t_R = 0.95$  min;

25 Mass spectrum (ESI<sup>+</sup>):  $m/z = 496$  [M+H]<sup>+</sup>.

### Example 90

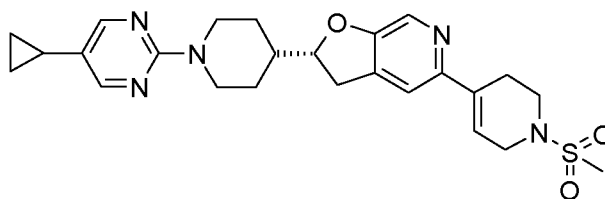
(S)-2-[1-(5-Chloro-pyrimidin-2-yl)-piperidin-4-yl]-5-(4-methanesulfonyl-phenyl)-2,3-dihydro-furo[2,3-c]pyridine



The title compound is prepared from (S)-5-(4-methanesulfonyl-phenyl)-2-piperidin-4-yl-2,3-dihydro-furo[2,3-c]pyridine {obtained from (S)-4-[5-(4-methanesulfonyl-phenyl)-2,3-dihydro-furo[2,3-c]pyridin-2-yl]-piperidine-1-carboxylic acid tert-butyl ester by cleavage of the carbamate group (following a procedure analogous to that described for Intermediate 9), which in turn is obtained from Intermediate 35 and 4-methanesulfonyl-phenylboronic acid following a procedure analogous to that described for Intermediate 7, the configuration of the stereocenter is arbitrarily assigned} and 2,5-dichloro-pyrimidine following a procedure analogous to that described for Example 79. LC (method 6):  $t_R$  = 1.75 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$  = 471/473 (Cl) [M+H]<sup>+</sup>.

### Example 91

(R)-2-[1-(5-Cyclopropyl-pyrimidin-2-yl)-piperidin-4-yl]-5-(1-methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-2,3-dihydro-furo[2,3-c]pyridine

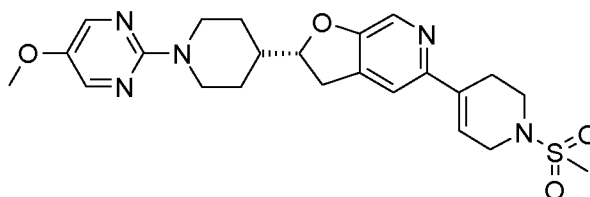


The title compound is prepared from (R)-5-(1-methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-2-piperidin-4-yl-2,3-dihydro-furo[2,3-c]pyridine (Intermediate 39, the configuration of the stereocenter is arbitrarily assigned) and 2-chloro-5-cyclopropyl-pyrimidine following a procedure analogous to that described for Example 79. LC (method 10):  $t_R$  = 1.61 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$  = 482 [M+H]<sup>+</sup>.

### Example 92

(R)-5-(1-Methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-2-[1-(5-methoxy-pyrimidin-2-yl)-piperidin-4-yl]-2,3-dihydro-furo[2,3-c]pyridine

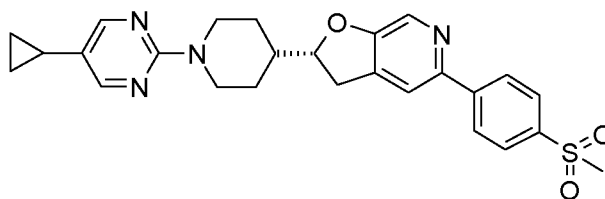
131



The title compound is prepared from (*R*)-5-(1-methanesulfonyl-1,2,3,6-tetrahydropyridin-4-yl)-2-piperidin-4-yl-2,3-dihydro-furo[2,3-c]pyridine (Intermediate 39, the configuration of the stereocenter is arbitrarily assigned) and 2-chloro-5-methoxy-pyrimidine following a procedure analogous to that described for Example 79. LC (method 10):  $t_R = 1.48$  min; Mass spectrum (ESI<sup>+</sup>):  $m/z = 472$  [M+H]<sup>+</sup>.

### Example 93

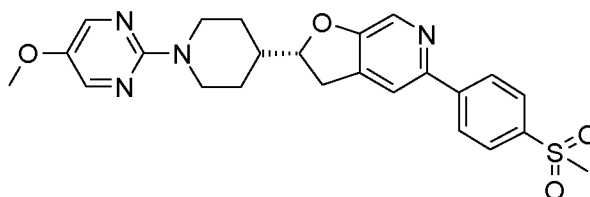
(*R*)-2-[1-(5-Cyclopropyl-pyrimidin-2-yl)-piperidin-4-yl]-5-(4-methanesulfonyl-phenyl)-2,3-dihydro-furo[2,3-c]pyridine



The title compound is prepared from (*R*)-5-(4-methanesulfonyl-phenyl)-2-piperidin-4-yl-2,3-dihydro-furo[2,3-c]pyridine {obtained from (*R*)-4-[5-(4-methanesulfonyl-phenyl)-2,3-dihydro-furo[2,3-c]pyridin-2-yl]-piperidine-1-carboxylic acid tert-butyl ester by cleavage of the carbamate group (following a procedure analogous to that described for Intermediate 9), which in turn is obtained from Intermediate 34 and 4-methanesulfonyl-phenylboronic acid following a procedure analogous to that described for Intermediate 7, the configuration of the stereocenter is arbitrarily assigned} and 2-chloro-5-cyclopropyl-pyrimidine following a procedure analogous to that described for Example 79. LC (method 10):  $t_R = 1.76$  min; Mass spectrum (ESI<sup>+</sup>):  $m/z = 477$  [M+H]<sup>+</sup>.

### Example 94

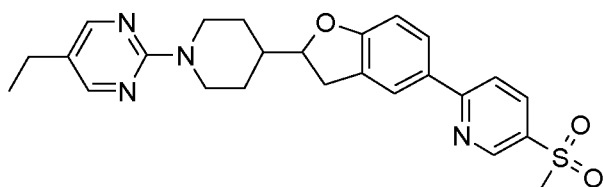
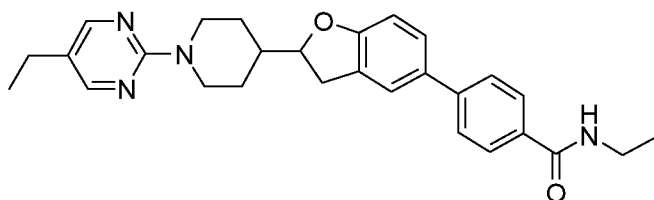
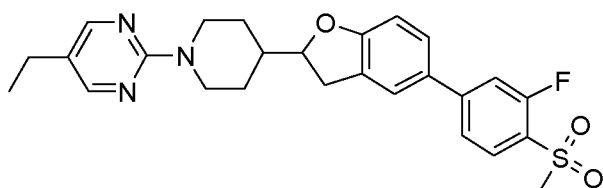
(*R*)-5-(4-Methanesulfonyl-phenyl)-2-[1-(5-methoxy-pyrimidin-2-yl)-piperidin-4-yl]-2,3-dihydro-furo[2,3-c]pyridine

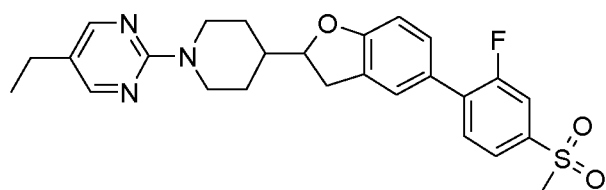
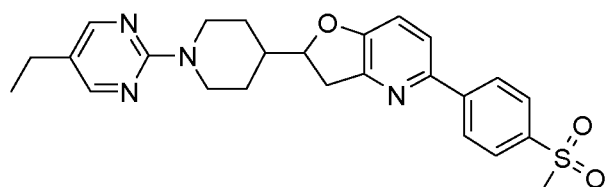
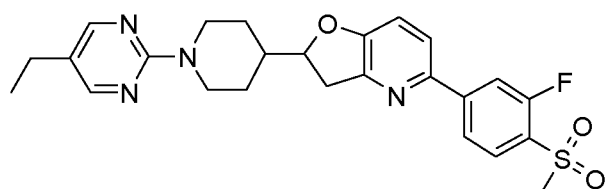
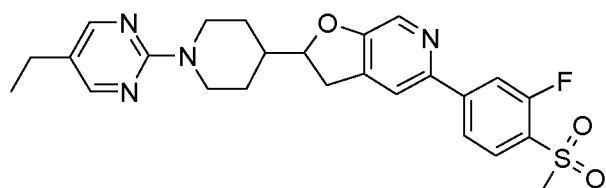
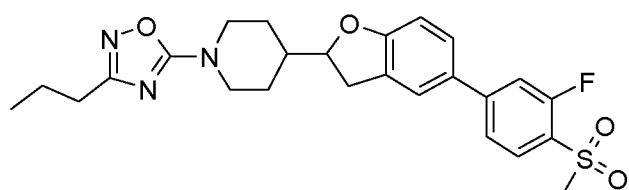
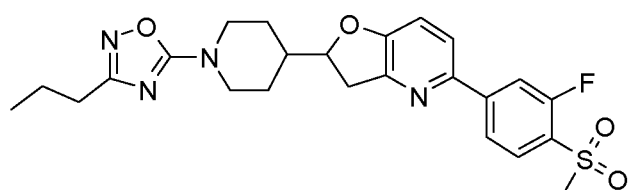


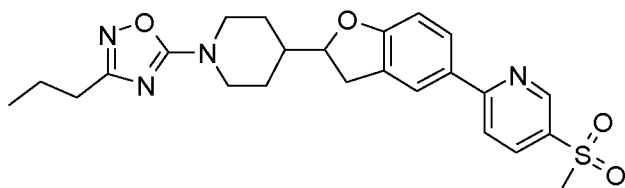
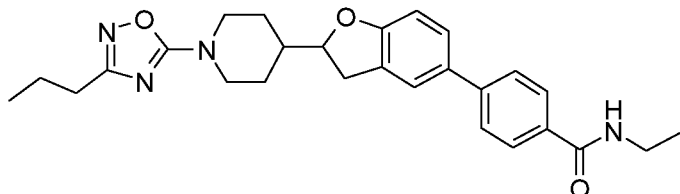
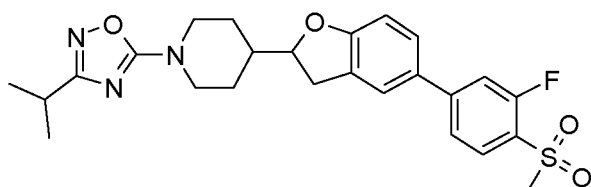
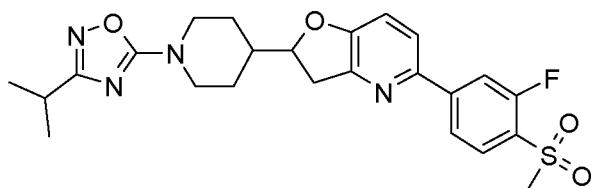
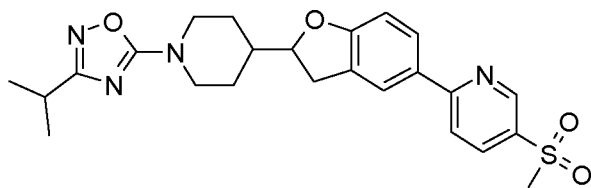
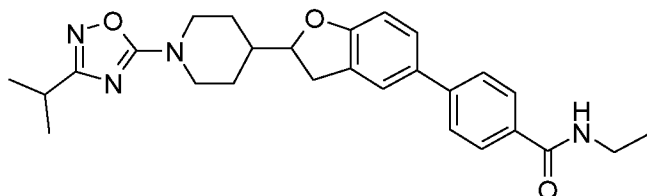
The title compound is prepared from (*R*)-5-(4-methanesulfonyl-phenyl)-2-piperidin-4-yl-2,3-dihydro-furo[2,3-c]pyridine {obtained from (*R*)-4-[5-(4-methanesulfonyl-phenyl)-2,3-dihydro-furo[2,3-c]pyridin-2-yl]-piperidine-1-carboxylic acid tert-butyl ester by  
5 cleavage of the carbamate group (following a procedure analogous to that described for Intermediate 9), which in turn is obtained from Intermediate 34 and 4-methanesulfonyl-phenylboronic acid following a procedure analogous to that described for Intermediate 7, the configuration of the stereocenter is arbitrarily assigned} and 2-chloro-5-methoxy-pyrimidine following a procedure analogous to  
10 that described for Example 79. LC (method 10):  $t_R = 1.69$  min; Mass spectrum (ESI<sup>+</sup>):  $m/z = 467$  [M+H]<sup>+</sup>.

The following compounds are prepared in analogy to the above described examples and other methods known from the literature.

15

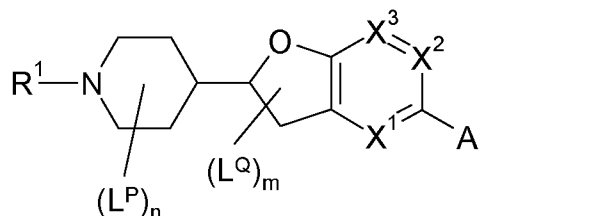
**Example 95****Example 96****Example 97**

**Example 98****Example 99****Example 100****Example 101****Example 102****Example 103****Example 104**

**Example 105****Example 106****Example 107****Example 108****Example 109**

## Claims

1. A compound of formula I



5 wherein

$R^1$  is selected from the group  $R^1$ -G1 consisting of a 5- or 6-membered heteroaromatic ring which contains 1, 2 or 3 heteroatoms independently of each other selected from N, O and S; and wherein optionally a second ring may be condensed to said heteroaromatic ring, wherein said second ring is unsaturated or aromatic and 5- or 6-membered and may contain 1, 2 or 3 heteroatoms independently of each other selected from N, O and S, and wherein in said second ring 1 or 2  $-CH_2$ -groups may be optionally replaced by  $-N(R^N)-$ ,  $-C(=O)-$ ,  $-S(=O)-$  or  $-S(=O)_2-$ , and

wherein in said heteroaromatic ring and/or said second ring the H-atom in one or more NH groups may be optionally replaced by  $R^N$ , and

wherein each of said heteroaromatic ring and/or second ring independently of each other may be optionally substituted with one or more substituents selected from  $L^A$ ; and

wherein said heteroaromatic ring or said second ring may be optionally substituted with a group  $R^C$ ; and

$R^N$  independently of each other is selected from the group  $R^N$ -G1 consisting of H,  $C_{1-4}$ -alkyl,  $C_{1-4}$ -alkyl- $C(=O)-$ , and  $C_{1-4}$ -alkyl- $S(=O)_2-$ ; and

A is selected from the group A-G1 consisting of a 1,2,3,6-tetrahydropyridin-4-yl ring substituted at the N with  $C_{1-4}$ -alkyl- $S(=O)_2-$ , a phenyl ring, and a 5- or 6-

membered heteroaromatic ring which contains 1, 2 or 3 heteroatoms independently of each other selected from N, O and S; and wherein optionally a second ring may be condensed to said phenyl ring or heteroaromatic ring, wherein said second ring is unsaturated or aromatic and

5 5- or 6-membered and may contain 1, 2 or 3 heteroatoms independently of each other selected from N, O and S, and wherein in said second ring 1 or 2 -CH<sub>2</sub>-groups may be optionally replaced by -N(R<sup>N</sup>)-, -C(=O)-, -S(=O)- or -S(=O)<sub>2</sub>-, and

10 wherein in said heteroaromatic ring and/or said second ring the H-atom in one or more NH groups may be optionally replaced by R<sup>N</sup>, and

wherein each of said phenyl ring, heteroaromatic ring and/or second ring independently of each other may be optionally substituted with one or more

15 substituents selected from L<sup>A</sup>; and

wherein said phenyl ring, heteroaromatic ring or second ring may be optionally substituted with a group T; and

20 T is selected from the group T-G1 consisting of F, Cl, Br, I, CN, OH, NO<sub>2</sub>, C<sub>1-6</sub>-alkyl-, C<sub>1-6</sub>-alkenyl-, C<sub>1-6</sub>-alkynyl-, C<sub>3-6</sub>-cycloalkyl, C<sub>1-6</sub>-alkyl-O-, C<sub>3-6</sub>-cycloalkyl-O-, C<sub>1-6</sub>-alkyl-S-, HO-C(=O)-, C<sub>1-6</sub>-alkyl-O-C(=O)-, C<sub>1-4</sub>-alkyl-C(=O)-, C<sub>3-6</sub>-cycloalkyl-C(=O)-, C<sub>1-4</sub>-alkyl-S(=O)-, C<sub>1-4</sub>-alkyl-S(=O)<sub>2</sub>-, R<sup>NT1</sup>R<sup>NT2</sup>N-, R<sup>NT1</sup>R<sup>NT2</sup>N-C(=O)-, R<sup>NT1</sup>R<sup>NT2</sup>N-S(=O)<sub>2</sub>-, R<sup>NT1</sup>R<sup>NT2</sup>N-C(=O)-(R<sup>N</sup>)N-,

25 heterocyclyl, heterocyclyl-O-, aryl, aryl-O-, heteroaryl and heteroaryl-O-, wherein each alkyl, alkenyl, alkynyl, and cycloalkyl group may be optionally substituted with one or more substituents independently of each other selected from F, Cl, CN, OH, C<sub>1-3</sub>-alkyl, C<sub>3-6</sub>-cycloalkyl, C<sub>1-3</sub>-alkyl-O-, R<sup>NT1</sup>R<sup>NT2</sup>N-, R<sup>NT1</sup>R<sup>NT2</sup>N-C(=O)-, C<sub>1-4</sub>-alkyl-S(=O)-, C<sub>1-4</sub>-alkyl-S(=O)<sub>2</sub>-,

30 R<sup>NT1</sup>R<sup>NT2</sup>N-S(=O)<sub>2</sub>-, aryl, heteroaryl, and heterocyclyl, and

wherein aryl denotes phenyl or naphthyl, and

wherein heteroaryl is a 5- or 6-membered aromatic ring which contains 1, 2, 3 or 4 heteroatoms independently of each other selected from N, O and S, wherein the H-atom in one or more NH groups may be optionally replaced by  $R^N$ ; and

5

wherein heterocyclyl is a 4- to 7-membered unsaturated or saturated carbocyclic ring in which 1 or 2  $-CH_2$ -groups independently of each other are replaced by  $NR^N$ , O,  $-C(=O)-$ , S,  $-S(=O)-$  or  $-S(=O)_2-$ , and/or in which a  $-CH-$  group is replaced by N; and

10

wherein each aryl, heteroaryl or heterocyclyl group may be optionally substituted with one or more substituents independently of each other selected from  $L^A$ ; and

15  $R^{NT1}$  is selected from the group  $R^{NT1}$ -G1 consisting of H,  $C_{1-6}$ -alkyl,  $C_{3-6}$ -cycloalkyl,  $C_{1-6}$ -alkyl- $C(=O)-$ ,  $C_{1-6}$ -alkyl- $S(=O)_2$ , heterocyclyl, aryl and heteroaryl,

wherein each alkyl and cycloalkyl group may be optionally substituted with one or more substituents independently of each other selected from the group consisting of F, OH, CN,  $C_{1-4}$ -alkyl,  $C_{1-4}$ -alkyl-O-,  $R^N_2N$ ,  $C_{1-4}$ -alkyl- $S(=O)_2$ ,  $C_{3-6}$ -cycloalkyl, heterocyclyl, phenyl and heteroaryl; and

20

wherein heterocyclyl may be optionally substituted with one or more substituents independently of each other selected from F,  $C_{1-4}$ -alkyl,  $R^N_2N$ , OH and  $C_{1-4}$ -alkyl-O-; and

25

wherein heterocyclyl is a  $C_{4-7}$ -cycloalkyl ring in which 1 or 2  $-CH_2$ -groups independently of each other are replaced by  $NR^N$ , O,  $C(=O)$ , S,  $S(=O)$  or  $S(=O)_2$ ; and

30

wherein aryl is phenyl or naphthyl; and

wherein heteroaryl is a 5- or 6-membered aromatic ring which contains 1, 2 or 3 heteroatoms independently of each other selected from N, O and S,

wherein the H-atom in one or more NH groups may be optionally replaced by  $R^N$ ; and

wherein aryl and heteroaryl may be optionally substituted with one or more substituents  $L^A$ ; and

$R^{NT2}$  is selected from the group  $R^{NT2}$ -G1 consisting of H and  $C_{1-6}$ -alkyl; or

$R^{NT1}$  and  $R^{NT2}$  are linked to form one group selected from the group  $R^{NT1}R^{NT2}$ -G1 consisting of a  $C_{3-5}$ -alkylene group,

wherein 1 or 2  $-CH_2$ -groups independently of each other are replaced by  $NR^N$ , O,  $C(=O)$ , S,  $S(=O)$  or  $S(=O)_2$ ; and

which may be optionally substituted with one or more substituents

independently of each other selected from F,  $C_{1-4}$ -alkyl,  $(R^N)_2N$ , OH and  $C_{1-4}$ -alkyl-O-;

$L^A$  is selected from the group  $L^A$ -G1 consisting of F, Cl, Br, CN, OH,  $NO_2$ ,  $C_{1-4}$ -alkyl-,  $C_{1-4}$ -alkyl-O-,  $(R^N)_2N-C(=O)$ ,  $(R^N)_2N$ -, and  $C_{1-4}$ -alkyl- $S(=O)_2$ -, wherein each alkyl group may be optionally substituted with one or more substituents independently of each other selected from F, Cl, CN, OH and  $C_{1-3}$ -alkyl-O-; and

$L^P$  is selected from the group  $L^P$ -G1 consisting of F and  $C_{1-3}$ -alkyl, wherein the alkyl group may be substituted with one or more F-atoms; and

$L^Q$  is selected from the group  $L^Q$ -G1 consisting of F and  $C_{1-3}$ -alkyl, wherein the alkyl group may be substituted with one or more F-atoms; and

$R^C$  is selected from the group  $R^C$ -G1 consisting of F, Cl, Br, I, CN, OH,  $NO_2$ ,  $C_{1-6}$ -alkyl-,  $C_{1-6}$ -alkenyl-,  $C_{1-6}$ -alkynyl-,  $C_{3-6}$ -cycloalkyl,  $C_{1-6}$ -alkyl-O-,  $C_{3-6}$ -cycloalkyl-O-,  $C_{1-6}$ -alkyl-S-,  $HO-C(=O)$ -,  $C_{1-6}$ -alkyl-O- $C(=O)$ -,  $C_{1-4}$ -alkyl- $C(=O)$ -,  $C_{3-6}$ -cycloalkyl- $C(=O)$ -,  $C_{1-4}$ -alkyl- $S(=O)$ -,  $C_{1-4}$ -alkyl- $S(=O)_2$ -,  $R^{NT1}R^{NT2}N$ -,  $R^{NT1}R^{NT2}N-C(=O)$ -,  $R^{NT1}R^{NT2}N-S(=O)_2$ -,  $R^{NT1}R^{NT2}N-C(=O)-(R^N)N$ -,

heterocyclyl, heterocyclyl-O-, aryl, aryl-O-, heteroaryl and heteroaryl-O-,  
 wherein each alkyl, alkenyl, alkynyl, and cycloalkyl group may be optionally  
 substituted with one or more substituents independently of each other  
 selected from F, Cl, CN, OH, C<sub>1-3</sub>-alkyl, C<sub>3-6</sub>-cycloalkyl, C<sub>1-3</sub>-alkyl-O-,  
 5 R<sup>NT1</sup>R<sup>NT2</sup>N-, R<sup>NT1</sup>R<sup>NT2</sup>N-C(=O)-, C<sub>1-4</sub>-alkyl-S(=O)-, C<sub>1-4</sub>-alkyl-S(=O)<sub>2</sub>-,  
 R<sup>NT1</sup>R<sup>NT2</sup>N-S(=O)<sub>2</sub>-, aryl, heteroaryl, and heterocyclyl, and

wherein aryl denotes phenyl or naphthyl, and

10 wherein heteroaryl is a 5- or 6-membered aromatic ring which contains 1, 2,  
 3 or 4 heteroatoms independently of each other selected from N, O and S,  
 wherein the H-atom in one or more NH groups may be optionally replaced by  
 R<sup>N</sup>; and

15 wherein heterocyclyl is a 4- to 7-membered unsaturated or saturated  
 carbocyclic ring in which 1 or 2 -CH<sub>2</sub>-groups independently of each other are  
 replaced by NR<sup>N</sup>, O, -C(=O)-, S, -S(=O)- or -S(=O)<sub>2</sub>-, and/or in which a -CH-  
 group is replaced by N; and

20 wherein each aryl, heteroaryl or heterocyclyl group may be optionally  
 substituted with one or more substituents independently of each other  
 selected from L<sup>A</sup>; and

25 X<sup>1</sup>, X<sup>2</sup>, X<sup>3</sup> are independently selected from the group X-G1 consisting of C(R<sup>2</sup>)  
 and N, such that 0, 1 or 2 members of the group consisting of X<sup>1</sup>, X<sup>2</sup>, and X<sup>3</sup>  
 have the meaning N; and

30 R<sup>2</sup> is selected from the group R<sup>2</sup>-G1 consisting of H, F, Cl, CN, OH, C<sub>1-4</sub>-alkyl,  
 C<sub>3-7</sub>-cycloalkyl-, F<sub>2</sub>HC, F<sub>3</sub>C, C<sub>1-4</sub>-alkyl-O-, F<sub>2</sub>HC-O-, F<sub>3</sub>C-O- and C<sub>3-7</sub>-  
 cycloalkyl-O-; and

n is an integer selected from 0, 1, 2, 3 or 4; and

m is an integer selected from 0, 1, or 2;

or a salt thereof.

5 2. A compound according to claim 1 wherein  $R^1$  is selected from a group consisting of a 5-membered heteroaromatic ring which contains 2 or 3 heteroatoms independently of each other selected from N, O and S and a 6-membered heteroaromatic ring which contains 1 or 2 N atoms; and wherein optionally a second  
10 said second ring is unsaturated or aromatic and 5- or 6-membered and may contain 1 or 2 heteroatoms independently of each other selected from N, O and S, and wherein in said second ring 1 or 2  $-CH_2$ -groups may be optionally replaced by  $-N(R^N)-$ ,  $-C(=O)-$  or  $-S(=O)_2-$ , and

15 wherein in said heteroaromatic ring and/or said second ring the H-atom in one or more NH groups may be optionally replaced by  $R^N$ , and

wherein each of said heteroaromatic ring and/or second ring independently of each other may be optionally substituted with one or two substituents selected from  $L^A$ ;  
20 and

wherein said heteroaromatic ring or said second ring may be optionally substituted with a group  $R^C$ ; wherein  $R^N$ ,  $L^A$  and  $R^C$  are defined as in claim 1.

25 3. A compound according to claim 1 or 2 wherein A is selected from a group consisting of a phenyl ring, a 6-membered heteroaromatic ring which contains 1 or 2 N-atoms and a 5-membered heteroaromatic ring which contains 1, 2 or 3 heteroatoms independently of each other selected from N, O and S; wherein said phenyl ring or heteroaromatic ring is substituted with a group T, and wherein said  
30 phenyl ring and heteroaromatic ring may be optionally substituted with one or more substituents independently of each other selected from  $L^A$ ,

wherein in said heteroaromatic rings the H-atom in one or more NH groups may be optionally replaced by  $R^N$ ,

wherein T, R<sup>N</sup> and L<sup>A</sup> are defined as in claim 1.

4. A compound according to claim 1 or 2 wherein A is selected from a  
 5 group consisting of a phenyl ring and a 5- or 6-membered heteroaromatic ring which  
 contains 1 or 2 heteroatoms independently of each other selected from N, O or S; and  
 wherein a second ring is condensed to said phenyl ring or said heteroaromatic ring,  
 wherein said second ring is unsaturated or aromatic and is 5- or 6-membered and  
 may optionally contain 1 or 2 heteroatoms independently of each other selected from  
 10 N, O and S, and wherein in said second ring 1 or 2 -CH<sub>2</sub>-groups may be optionally  
 replaced by -N(R<sup>N</sup>)-, -C(=O)-, -S(=O)- or -S(=O)<sub>2</sub>-, and

wherein in said heteroaromatic ring and/or said second ring the H-atom in one or  
 more NH groups may be optionally replaced by R<sup>N</sup>, and

15

wherein each of said phenyl ring, heteroaromatic ring and second ring may be  
 optionally substituted with one or more substituents independently of each other  
 selected from L<sup>A</sup>; and

- 20 wherein said phenyl ring, heteroaromatic ring or second ring may be optionally  
 substituted with a group T; and

wherein R<sup>N</sup>, T and L<sup>A</sup> are defined as in claim 1.

- 25 5. A compound according to claim 1 or 2 wherein A is selected from a  
 group consisting of 1,2,3,6-tetrahydropyridin-4-yl wherein the H of the NH group is  
 replaced by C<sub>1-4</sub>-alkyl-S(=O)<sub>2</sub>-.

6. A compound according to claim 1, 2, 3, 4 or 5 wherein T is selected  
 30 from a group consisting of CN, C<sub>1-4</sub>-alkyl-S(=O)<sub>2</sub>-CH<sub>2</sub>-, C<sub>1-4</sub>-alkyl-S(=O)<sub>2</sub>-, R<sup>NT1</sup>R<sup>NT2</sup>N-  
 S(=O)<sub>2</sub>-, R<sup>NT1</sup>R<sup>NT2</sup>N-C(=O)-, C<sub>1-4</sub>-alkyl-S(=O)<sub>2</sub>-(R<sup>N</sup>)N-, and R<sup>NT1</sup>R<sup>NT2</sup>N-, wherein R<sup>NT1</sup>,  
 R<sup>NT2</sup>, and R<sup>N</sup> are defined as in claim 1.

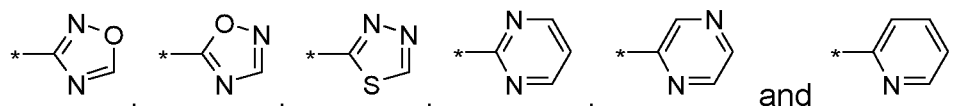
7. A compound according to claim 1, wherein

$X^1$  is CH;

$X^2$  is CH or N;

$X^3$  is CH;

- 5  $R^1$  is selected from the group  $R^1$ -G4a consisting of:

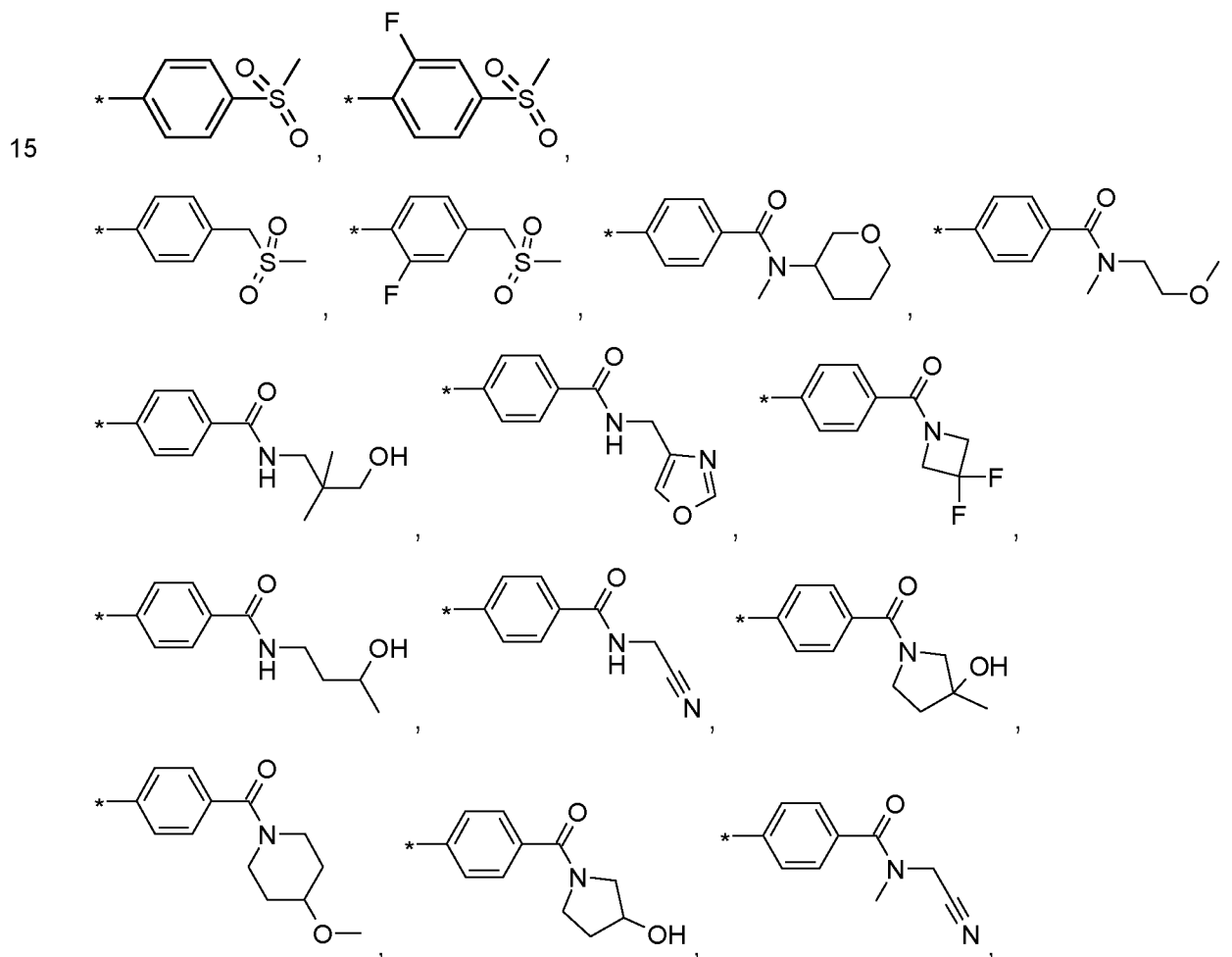


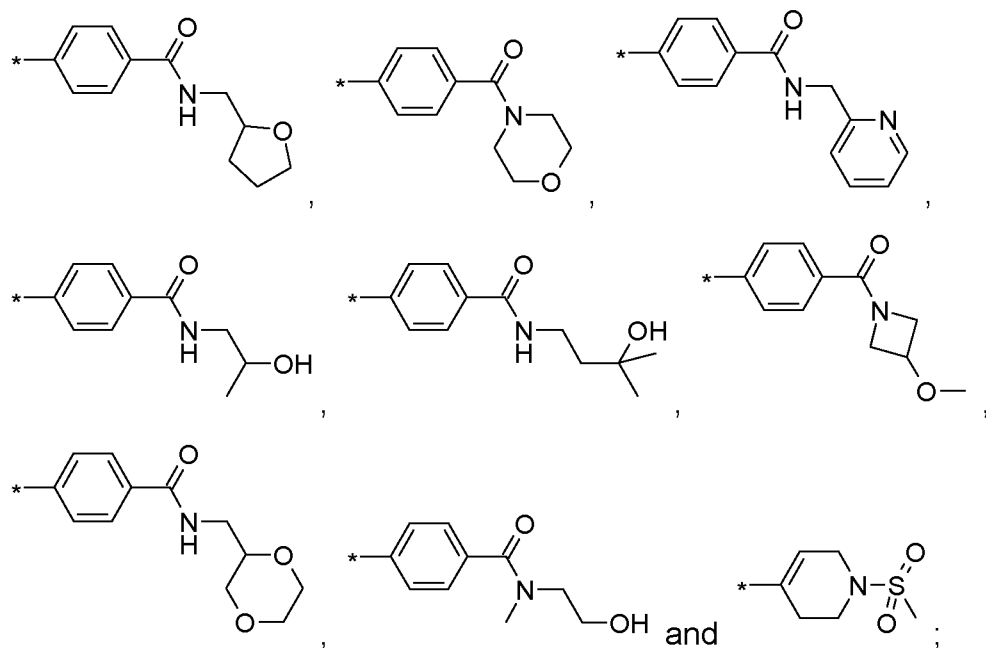
wherein each ring may be optionally substituted with one substituent  $R^C$ ;

- 10  $R^C$  is selected from the group  $R^C$ -G4b consisting of F, Cl,  $C_{1-4}$ -alkyl,  $F_3C$ - and cyclopropyl,

wherein the cyclopropyl group may be monosubstituted with  $CH_3$ ;

A is selected from the group A-G6a consisting of:





- 5 L<sup>Q</sup> is CH<sub>3</sub>;  
n is 0;  
m is 0 or 1;  
and the pharmaceutically acceptable salts thereof.

- 10 8. A compound according to claim 7, wherein

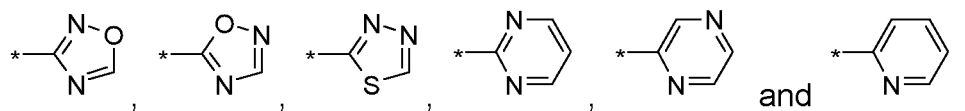
$X^1$  is CH;

$X^2$  is  $N$ ;

$X^3$  is CH;

15

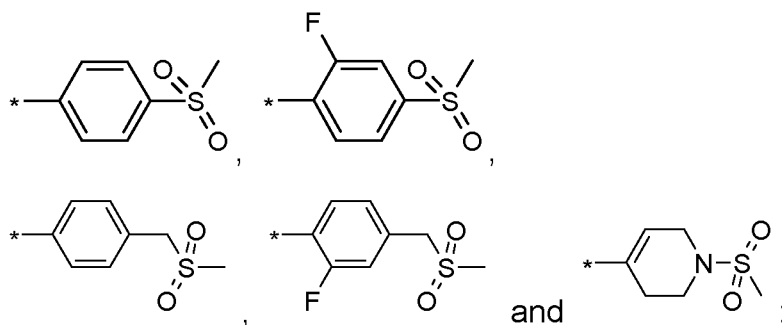
$R^1$  is selected from the group consisting of:



wherein each ring may be optionally substituted with one F and/or with one substituent R<sup>C</sup>;

R<sup>C</sup> is selected from the group consisting of F, Cl, C<sub>1-4</sub>-alkyl, F<sub>3</sub>C- and cyclopropyl, wherein the cyclopropyl group may be monosubstituted with CH<sub>3</sub>;

A is selected from the group consisting of:



5

$L^Q$  is  $\text{CH}_3$ ;

n is 0;

m is 0 or 1;

and the pharmaceutically acceptable salts thereof.

10

9. A pharmaceutically acceptable salt of a compound according to one or more of the claims 1 to 8.

10. A pharmaceutical composition comprising one or more compounds according to one or more of the claims 1 to 8 or one or more pharmaceutically acceptable salts thereof, optionally together with one or more inert carriers and/or diluents.

11. A method for treating diseases or conditions which are mediated by activating the G-protein-coupled receptor GPR119 in a patient in need thereof characterized in that a compound according to one or more of the claims 1 to 8 or a pharmaceutically acceptable salt thereof is administered to the patient.

12. A compound according to any one of claims 1 to 8 or a pharmaceutically acceptable salt thereof for use in a method of treating diabetes, obesity or dyslipidemia.

13. A pharmaceutical composition comprising one or more compounds according to one or more of the claims 1 to 8 or one or more pharmaceutically acceptable salts thereof and one or more additional therapeutic agents, optionally together with one or more inert carriers and/or diluents.