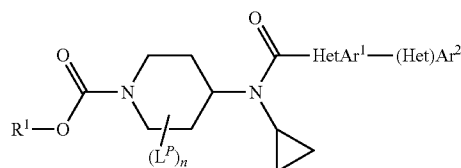




US 20140045823A1

(19) **United States**(12) **Patent Application Publication**  
**NOSSE et al.**(10) **Pub. No.: US 2014/0045823 A1**(43) **Pub. Date: Feb. 13, 2014**(54) **N-CYCLOPROPYL-N-PIPERIDINYL-AMIDES,  
PHARMACEUTICAL COMPOSITIONS  
CONTAINING THEM AND USES THEREOF**(71) Applicants: **Bernd NOSSE**, Biberach an der Riss  
(DE); **Matthias ECKHARDT**, Biberach  
an der Riss (DE); **Frank  
HIMMELSBACH**, Mittelbiberach (DE);  
**Elke LANGKOPF**, Biberach an der Riss  
(DE); **Neil J. ASHWEEK**, Escondido,  
CA (US); **Nicole HARRIOTT**, San  
Diego, CA (US)(72) Inventors: **Bernd NOSSE**, Biberach an der Riss  
(DE); **Matthias ECKHARDT**, Biberach  
an der Riss (DE); **Frank  
HIMMELSBACH**, Mittelbiberach (DE);  
**Elke LANGKOPF**, Biberach an der Riss  
(DE); **Neil J. ASHWEEK**, Escondido,  
CA (US); **Nicole HARRIOTT**, San  
Diego, CA (US)(73) Assignees: **Neurocrine Biosciences, Inc.**, San  
Diego, CA (US); **Boehringer Ingelheim  
International GmbH**, Ingelheim am  
Rhein (DE)(21) Appl. No.: **13/955,170**(22) Filed: **Jul. 31, 2013**(30) **Foreign Application Priority Data**

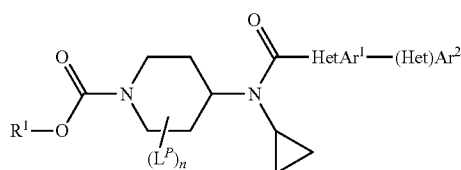
Aug. 2, 2012 (EP) ..... 12179028.1

**Publication Classification**(51) **Int. Cl.**  
**C07D 401/12** (2006.01)  
**C07D 413/14** (2006.01)**C07D 413/12** (2006.01)  
**A61K 45/06** (2006.01)  
**A61K 31/497** (2006.01)  
**A61K 31/454** (2006.01)  
**A61K 31/506** (2006.01)  
**A61K 31/553** (2006.01)  
**C07D 401/14** (2006.01)  
**A61K 31/4545** (2006.01)(52) **U.S. Cl.**  
CPC ..... **C07D 401/12** (2013.01); **C07D 401/14**  
(2013.01); **C07D 413/14** (2013.01); **C07D**  
**413/12** (2013.01); **A61K 31/4545** (2013.01);  
**A61K 31/497** (2013.01); **A61K 31/454**  
(2013.01); **A61K 31/506** (2013.01); **A61K**  
**31/553** (2013.01); **A61K 45/06** (2013.01)  
USPC ..... **514/211.15**; 546/194; 544/238; 544/333;  
544/405; 544/331; 544/296; 540/544; 514/318;  
514/252.03; 514/256; 514/255.05; 514/326;  
514/275(57) **ABSTRACT**The present invention relates to compounds of general for-  
mula I,wherein R<sup>1</sup>, L<sup>p</sup>, HetAr<sup>1</sup>, (Het)Ar<sup>2</sup> and n are as defined in the  
application, which have valuable pharmacological proper-  
ties, and in particular bind to the GPR119 receptor and modu-  
late its activity.

# N-CYCLOPROPYL-N-PIPERIDINYL-AMIDES, PHARMACEUTICAL COMPOSITIONS CONTAINING THEM AND USES THEREOF

## FIELD OF THE INVENTION

[0001] The present invention relates to new compounds, in particular compounds of formula I



wherein  $R^1$ ,  $L^p$ ,  $HetAr^1$ ,  $(Het)Ar^2$ , and  $n$  are defined as hereinafter, to processes for preparing such compounds, to their use as modulators of the G-protein-coupled receptor GPR119, to methods for their therapeutic use, in particular to methods of treating diseases and conditions mediated by the modulation of the G-protein-coupled receptor GPR119, and to pharmaceutical compositions comprising them.

## BACKGROUND OF THE INVENTION

[0002] 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.

[0003] 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 ~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, 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.

[0004] 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. 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 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. 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 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.

[0005] Dyslipidemia is a disorder of lipoprotein metabolism, including lipoprotein 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).

[0006] 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 glycaemic 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 knock-out 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

[0007] 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.

[0008] 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.

[0009] 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

[0010] The aim of the present invention is to provide new compounds, in particular new N-cyclopropyl-N-piperidinyl-amide derivatives, which are active with regard to the G-protein-coupled receptor GPR119.

[0011] Another aim of the present invention is to provide new compounds, in particular new N-cyclopropyl-N-piperidinyl-amide derivatives, which are agonists of the G-protein-coupled receptor GPR119.

[0012] A further aim of the present invention is to provide new compounds, in particular new N-cyclopropyl-N-piperidinyl-amide 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.

[0013] 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.

[0014] 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.

[0015] A further aim of the present invention is to provide a pharmaceutical composition comprising at least one compound according to the invention.

[0016] 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.

[0017] A further aim of the present invention is to provide methods for the synthesis of the new compounds, in particular N-cyclopropyl-N-piperidinyl-amide derivatives.

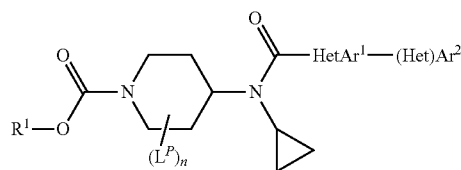
[0018] A further aim of the present invention is to provide starting and/or intermediate compounds suitable in methods for the synthesis of the new compounds.

[0019] 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.

#### OBJECT OF THE INVENTION

[0020] It has now been found that the compounds according to the invention described in more detail hereinafter have surprising and particularly advantageous properties, in particular as GPR119 agonists.

[0021] In a first aspect the invention relates to compounds of formula I



wherein

[0022]  $R^1$  is selected from the group  $R^1$ -G1 consisting of linear and branched  $C_{1-6}$ -alkyl and  $C_{3-7}$ -cycloalkyl, each of which is optionally substituted with one or more F and optionally substituted with 1 or 2 groups independently selected from  $H_3C-$ ,  $FH_2C-$ ,  $F_2HC-$  and  $F_3C-$ ; and

[0023]  $HetAr^1$  is selected from the group  $HetAr^1$ -G1 consisting of a 5- or 6-membered heteroaromatic ring which contains 1, 2, or 3 heteroatoms independently of each other selected from N,  $NR^N$ , O and S;

[0024] wherein each heteroaromatic ring is optionally substituted with 1 or more substituents selected from  $L^Q$ ; and

[0025]  $R^N$  is independently 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)<sub>2</sub>—; and

[0026]  $(Het)Ar^2$  is selected from the group  $(Het)Ar^2$ -G1 consisting of:

[0027] a) phenyl, tetrazolyl, pyridinonyl and a 5- or 6-membered heteroaromatic ring which contains 1, 2, or 3 heteroatoms independently of each other selected from N,  $NR^N$ , O and S;

[0028] wherein each of said phenyl, pyridinonyl and heteroaromatic ring is optionally substituted with 1 or more substituents independently of each other selected from  $L^{Ar}$ ; and

[0029] wherein said phenyl, tetrazolyl, pyridinonyl and heteroaromatic ring are optionally substituted with a group T; and

[0030] b) 1,2,3,6-tetrahydropyridin-4-yl which is substituted at the N atom with —S(=O)<sub>2</sub>— $C_{1-6}$ -alkyl or —S(=O)<sub>2</sub>— $C_{3-6}$ -cycloalkyl,

[0031] wherein the alkyl and cycloalkyl groups are optionally substituted with one or more substituents independently of each other selected from F, Cl, CN, OH and  $C_{1-3}$ -alkyl-O—;

[0032] T is selected from the group T-G1 consisting of F, Cl, Br, I, CN, OH,  $NO_2$ ,  $C_{1-6}$ -alkyl-,  $C_{2-6}$ -alkenyl-,  $C_{2-6}$ -alkynyl-,  $C_{3-6}$ -cycloalkyl,  $C_{1-6}$ -alkyl-O—,  $C_{3-6}$ -cy-

- cloalkyl-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—,
- [0033] wherein each alkyl, alkenyl, alkynyl and cycloalkyl group is 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
- [0034] wherein aryl denotes phenyl or naphthyl, and
- [0035] 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, NR<sup>N</sup>, O, and S; and
- [0036] wherein heterocyclyl is a 4- to 7-membered unsaturated or saturated carbocyclic ring in which 1, 2, or 3-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
- [0037] wherein each aryl, heteroaryl, and heterocyclyl group is optionally substituted with one or more substituents independently of each other selected from L<sup>Ar</sup>; and
- [0038] R<sup>NT1</sup> is selected from the group R<sup>NT1</sup>-G1 consisting of H, C<sub>1-6</sub>-alkyl, C<sub>3-6</sub>-cycloalkyl, C<sub>1-6</sub>-alkyl-C(=O)—, C<sub>1-6</sub>-alkyl-S(=O)<sub>2</sub>—, heterocyclyl, aryl and heteroaryl,
- [0039] wherein each alkyl and cycloalkyl group is optionally substituted with one or more substituents independently of each other selected from the group consisting of F, C<sub>1-4</sub>-alkyl, NC—, (H<sub>3</sub>C)<sub>2</sub>N—C(=O)—, HO—, C<sub>1-4</sub>-alkyl-O—, cyclopropyl-CH<sub>2</sub>—O—, F<sub>3</sub>C—O—, (R<sup>N</sup>)<sub>2</sub>N—, C<sub>1-4</sub>-alkyl-S(=O)<sub>2</sub>—, C<sub>3-6</sub>-cycloalkyl optionally substituted with 1 or 2 groups independently selected from F, H<sub>3</sub>C—, HO— and H<sub>3</sub>CO—, heterocyclyl, phenyl and heteroaryl; and
- [0040] wherein heterocyclyl is a C<sub>4-7</sub>-cycloalkyl 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
- [0041] wherein heterocyclyl is optionally substituted with 1 or more substituents independently of each other selected from F, C<sub>1-4</sub>-alkyl, (R<sup>N</sup>)<sub>2</sub>N, HO— and C<sub>1-4</sub>-alkyl-O—; and
- [0042] wherein aryl is phenyl or naphthyl; and
- [0043] wherein heteroaryl is a 5- or 6-membered aromatic ring which contains 1, 2, or 3 heteroatoms independently of each other selected from N, NR<sup>N</sup>, O and S; and
- [0044] wherein aryl, phenyl, and heteroaryl are optionally substituted with one or more substituents L<sup>Ar</sup>; and
- [0045] R<sup>NT2</sup> is selected from the group R<sup>NT2</sup>-G1 consisting of H and C<sub>1-6</sub>-alkyl; or
- [0046] R<sup>NT1</sup> and R<sup>NT2</sup> are linked to form one group selected from the group R<sup>NT1</sup>R<sup>NT2</sup>-G1 consisting of a C<sub>3-6</sub>-alkylene group,
- [0047] wherein 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
- [0048] which is optionally substituted with one or more substituents independently of each other selected from F, C<sub>1-4</sub>-alkyl, HO—C<sub>1-3</sub>-alkyl, H<sub>3</sub>C—O—(C<sub>1-3</sub>-alkyl)-, F<sub>3</sub>C—, NC—, (R<sup>N</sup>)<sub>2</sub>N—, HO—, C<sub>1-4</sub>-alkyl-O— and 3-methyl-[1,2,4]oxadiazol-5-yl;
- [0049] L<sup>Ar</sup> is selected from the group L<sup>Ar</sup>-G1 consisting of F, Cl, Br, I, CN, OH, NO<sub>2</sub>, C<sub>1-4</sub>-alkyl-, cyclopropyl, C<sub>1-4</sub>-alkyl-O—, (R<sup>N</sup>)<sub>2</sub>N—C(=O)—, (R<sup>N</sup>)<sub>2</sub>N— and C<sub>1-4</sub>-alkyl-S(=O)<sub>2</sub>—,
- [0050] wherein each alkyl group is optionally substituted with one or more substituents independently of each other selected from F, Cl, CN, OH and C<sub>1-3</sub>-alkyl-O—; and
- [0051] L<sup>P</sup> is selected from the group L<sup>P</sup>-G1 consisting of F and C<sub>1-3</sub>-alkyl, wherein the alkyl group may be substituted with one or more F atoms; and
- [0052] L<sup>Q</sup> is selected from the group L<sup>Q</sup>-G1 consisting of 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
- [0053] n is an integer selected from 0, 1, 2, 3, or 4; including any tautomers and stereoisomers thereof, or a salt thereof or a solvate or hydrate thereof.
- [0054] 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.
- [0055] 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.
- [0056] In a further aspect this invention relates to a pharmaceutical composition, comprising 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.
- [0057] In a further aspect this invention relates to 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 of general formula I or a pharmaceutically acceptable salt thereof is administered to the patient.
- [0058] According to another aspect of the invention, there is provided a method for treating 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.
- [0059] According to another aspect of the invention, there is provided the use of a 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.
- [0060] 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.
- [0061] 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 effective amount of one or more additional therapeutic agents.
- [0062] 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 addi-

tional therapeutic agents for the treatment of diseases or conditions which are mediated by the activation of the G-protein-coupled receptor GPR119.

**[0063]** 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 together with one or more inert carriers and/or diluents.

**[0064]** 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.

#### DETAILED DESCRIPTION

**[0065]** Unless otherwise stated, the groups, residues, and substituents, particularly  $R^1$ ,  $R^N$ , HetAr<sup>1</sup>, (Het)Ar<sup>2</sup>, T,  $R^{NT1}$ ,  $R^{NT2}$ ,  $L^{Ar}$ ,  $L^P$ ,  $L^Q$  and n are defined as above and hereinafter. If residues, substituents, or groups occur several times in a compound, as for example  $R^N$ ,  $L^{Ar}$ ,  $L^P$  or  $L^Q$ , they may have the same or different meanings. 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.

$R^1$ :

$R^1$ -G1:

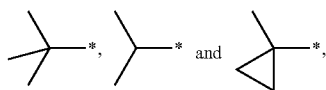
**[0066]** According to one embodiment, the group  $R^1$  is selected from the group  $R^1$ -G1 as defined hereinbefore and hereinafter.

$R^1$ -G2:

**[0067]** According to another embodiment, the group  $R^1$  is selected from the group  $R^1$ -G2 consisting of linear and branched  $C_{1-4}$ -alkyl and  $C_{3-6}$ -cycloalkyl, each of which is optionally substituted with 1 to 3 F atoms and optionally substituted with one group selected from  $H_3C$ — and  $F_3C$ —.

$R^1$ -G3:

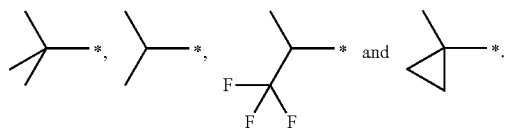
**[0068]** In another embodiment, the group  $R^1$  is selected from the group  $R^1$ -G3 consisting of



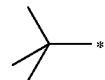
each of which is optionally substituted with 1 to 3 F atoms.

$R^1$ -G4:

**[0069]** In another embodiment, the group  $R^1$  is selected from the group  $R^1$ -G4 consisting of



**[0070]** Preferably,  $R^1$  is



HetAr<sup>1</sup>:

HetAr<sup>1</sup>-G1:

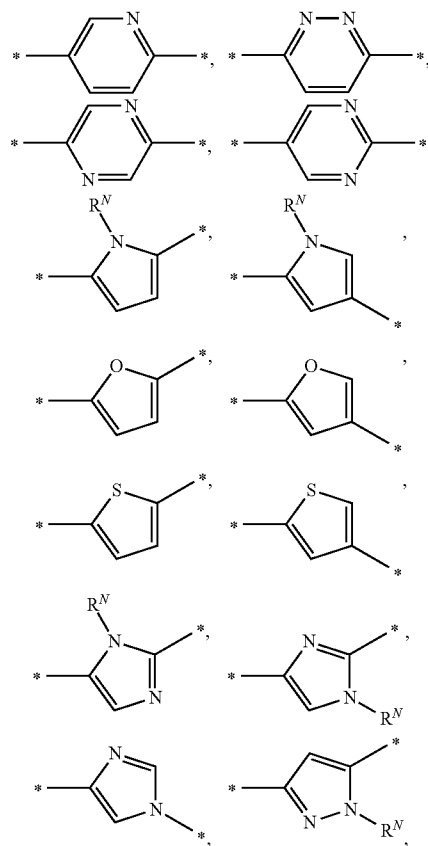
**[0071]** In one embodiment, the group HetAr<sup>1</sup> is selected from the group HetAr<sup>1</sup>-G1 as defined hereinbefore and hereinafter.

HetAr<sup>1</sup>-G2:

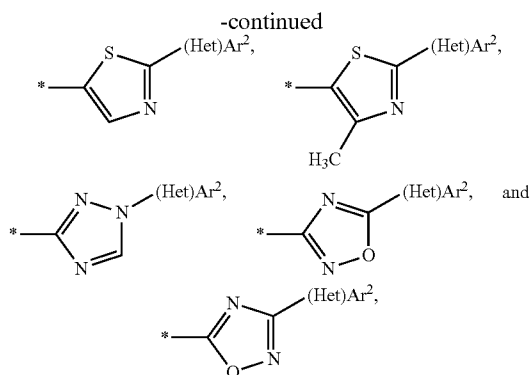
**[0072]** In another embodiment, the group HetAr<sup>1</sup> is selected from the group HetAr<sup>1</sup>-G2 consisting of pyridinylene, pyridazinylene, pyrimidinylene, pyrazinylene, pyrrolylene, furanylene, thiophenylene, imidazolylene, pyrazolylene, oxazolylene, isoxazolylene, thiazolylene, triazolylene, oxadiazolylene and thiadiazolylene, wherein each group is optionally additionally substituted with 1 or 2 substituents independently of each other selected from  $L^Q$ .

HetAr<sup>1</sup>-G3:

**[0073]** In another embodiment the group HetAr<sup>1</sup> is selected from the group HetAr<sup>1</sup>-G3 consisting of:



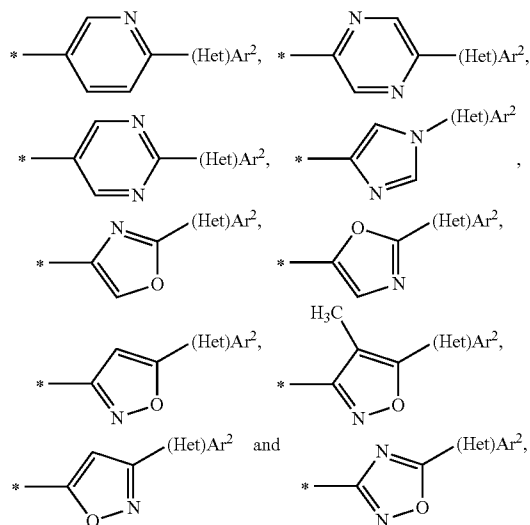




wherein the (Het)Ar<sup>2</sup>-group is depicted in order to show the position of the HetAr<sup>2</sup>-moiety within the compound of formula I.

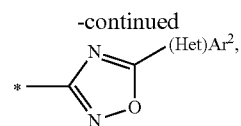
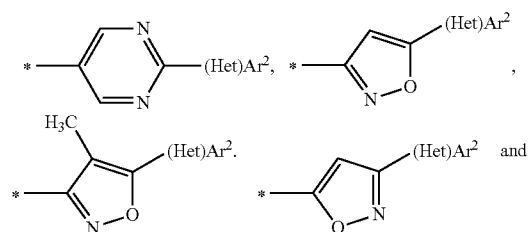
HetAr<sup>1</sup>-G6:

**[0076]** In another embodiment the group HetAr<sup>1</sup> is selected from the group HetAr<sup>1</sup>-G6 consisting of:



wherein the (Het)Ar<sup>2</sup>-group is depicted in order to show the position of the HetAr<sup>2</sup>-moiety within the compound of formula I.

**[0077]** Preferred examples for HetAr<sup>1</sup> are:



wherein the (Het)Ar<sup>2</sup>-group is depicted in order to show the position of the HetAr<sup>2</sup>-moiety within the compound of formula I.

R<sup>N</sup>

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

**[0078]** In one embodiment, the group R<sup>N</sup> is selected from the group R<sup>N</sup>-G1 as defined hereinbefore and hereinafter.

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

**[0079]** In another embodiment the group R<sup>N</sup> is selected from the group R<sup>N</sup>-G2 consisting of H, H<sub>3</sub>C—, H<sub>3</sub>CH<sub>2</sub>C—, (H<sub>3</sub>C)<sub>2</sub>HC—, H<sub>3</sub>C—C(=O)— and H<sub>3</sub>C—S(=O)<sub>2</sub>—.

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

**[0080]** In another embodiment the group R<sup>N</sup> is selected from the group R<sup>N</sup>-G3 consisting of H, H<sub>3</sub>C—, H<sub>3</sub>C—C(=O)— and H<sub>3</sub>C—S(=O)<sub>2</sub>—.

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

**[0081]** In another embodiment the group R<sup>N</sup> is selected from the group R<sup>N</sup>-G4 consisting of H and H<sub>3</sub>C—.

R<sup>N</sup>-G5:

**[0082]** In another embodiment the group R<sup>N</sup> is selected from the group R<sup>N</sup>-G5 consisting of H.

(Het)Ar<sup>2</sup>:

(Het)Ar<sup>2</sup>-G1:

**[0083]** In one embodiment, the group (Het)Ar<sup>2</sup> is selected from the group (Het)Ar<sup>2</sup>-G1 as defined hereinbefore and hereinafter.

(Het)Ar<sup>2</sup>-G2:

**[0084]** In another embodiment the group (Het)Ar<sup>2</sup> is selected from the group (Het)Ar<sup>2</sup>-G2 consisting of phenyl, tetrazolyl, pyridinonyl, 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, NR<sup>N</sup>, O and S;

**[0085]** wherein said phenyl, tetrazolyl, pyridinonyl, and heteroaromatic ring is optionally substituted with one group T, and

**[0086]** wherein said phenyl, pyridinonyl and heteroaromatic ring are optionally substituted with one or more substituents independently of each other selected from L<sup>Ar</sup>;

and additionally, the group (Het)Ar<sup>2</sup>-G2 comprises a 1,2,3,6-tetrahydropyridin-4-yl group substituted at the N atom with a —S(=O)<sub>2</sub>—C<sub>1-6</sub>-alkyl group, wherein the alkyl group is optionally substituted with 1 or 2 substituents independently of each other selected from F, Cl, CN, OH and H<sub>3</sub>C—O—.

(Het)Ar<sup>2</sup>-G3:

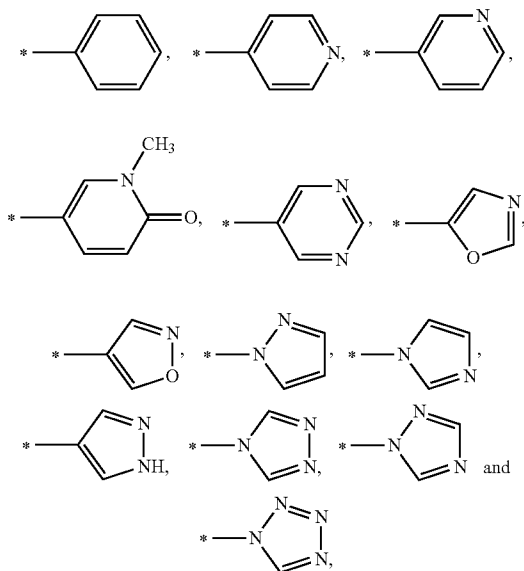
[0087] In another embodiment, the group (Het)Ar<sup>2</sup> is selected from the group (Het)Ar<sup>2</sup>-G3 consisting of phenyl, tetrazolyl, pyridinonyl and a heteroaromatic ring selected from pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, isoxazolyl, oxazolyl, oxadiazolyl, imidazolyl, pyrazolyl, triazolyl, thienyl and thiazolyl,

[0088] wherein said phenyl and heteroaromatic ring are optionally substituted with one or more substituents independently of each other selected from L<sup>Ar</sup>; and wherein said phenyl, tetrazolyl and heteroaromatic ring are optionally substituted with one group T, and

[0089] wherein in said heteroaromatic ring the H-atom in one NH group is optionally replaced by R<sup>N</sup>.

(Het)Ar<sup>2</sup>-G4:

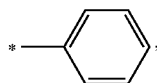
[0090] In another embodiment, the group (Het)Ar<sup>2</sup> is selected from the group (Het)Ar<sup>2</sup>-G4 consisting of:



wherein each group is optionally substituted with one group T and with 1 or 2 substituents independently of each other selected from L<sup>Ar</sup>.

(Het)Ar<sup>2</sup>-G4a:

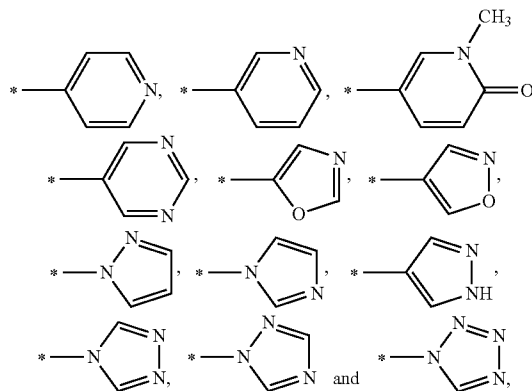
[0091] In another embodiment, the group (Het)Ar<sup>2</sup> is selected from the group (Het)Ar<sup>2</sup>-G4a consisting of:



which is substituted with one group T and optionally substituted with 1 or 2 F atoms.

(Het)Ar<sup>2</sup>-G4b:

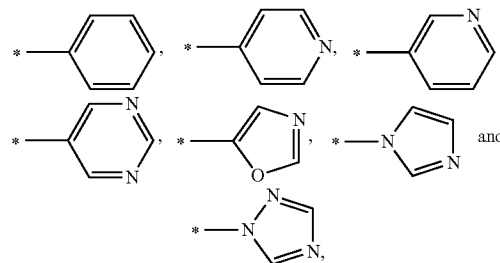
[0092] In another embodiment, the group (Het)Ar<sup>2</sup> is selected from the group (Het)Ar<sup>2</sup>-G4b consisting of:



wherein each group is optionally substituted with one group selected from C<sub>1-3</sub>-alkyl, HO—(CH<sub>2</sub>)<sub>1-3</sub>—, CN, (H<sub>3</sub>C)<sub>2</sub>N— and C<sub>1-3</sub>-alkyl-O— and may be additionally substituted with one H<sub>3</sub>C— group.

(Het)Ar<sup>2</sup>-G5:

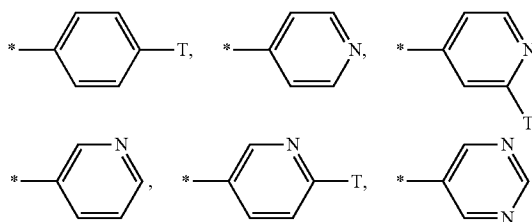
[0093] In another embodiment, the group (Het)Ar<sup>2</sup> is selected from the group (Het)Ar<sup>2</sup>-G5 consisting of:



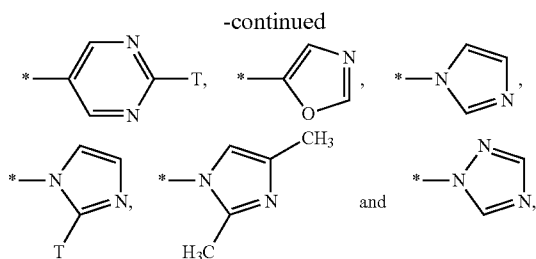
wherein each group is optionally substituted with one group T and with 1 or 2 substituents independently of each other selected from L<sup>Ar</sup>.

(Het)Ar<sup>2</sup>-G6:

[0094] In another embodiment, the group (Het)Ar<sup>2</sup> is selected from the group (Het)Ar<sup>2</sup>-G6 consisting of:







wherein the phenyl group may be additionally substituted with one F, and wherein T is CN, C<sub>1-3</sub>-alkyl, —CH<sub>2</sub>—CN, —CH<sub>2</sub>—OH, —O—(C<sub>1-3</sub>-alkyl), —OCF<sub>3</sub>, —SO<sub>2</sub>—(C<sub>1-3</sub>-alkyl), —C(=O)—NH—R<sup>NT1</sup> or —C(=O)—N(CH<sub>3</sub>)—R<sup>NT1</sup>,

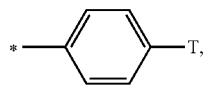
[0095] wherein R<sup>NT1</sup> is

[0096] C<sub>1-4</sub>-alkyl optionally substituted with CN, —O—(C<sub>1-3</sub>-alkyl), —OCF<sub>3</sub>, —O—CH<sub>2</sub>—cyclopropyl, tetrahydrofuryl, tetrahydropyranyl, pyridinyl or 5-methylthiazol-2-yl; or

[0097] phenyl or pyridinyl which are each optionally substituted with one or two —O—CH<sub>3</sub> or with one —CH<sub>2</sub>—OH.

(Het)Ar<sup>2</sup>-G6a:

[0098] In another embodiment, the group (Het)Ar<sup>2</sup> is selected from the group (Het)Ar<sup>2</sup>-G6a consisting of:



wherein the phenyl group may be additionally substituted with one F, and

wherein T is CN, —CH<sub>2</sub>—CN, —CH<sub>2</sub>—OH, —O—(C<sub>1-3</sub>-alkyl), —OCF<sub>3</sub>, —SO<sub>2</sub>—CH<sub>3</sub>, —C(=O)—NH—R<sup>NT1</sup> or —C(=O)—N(CH<sub>3</sub>)—R<sup>NT1</sup>,

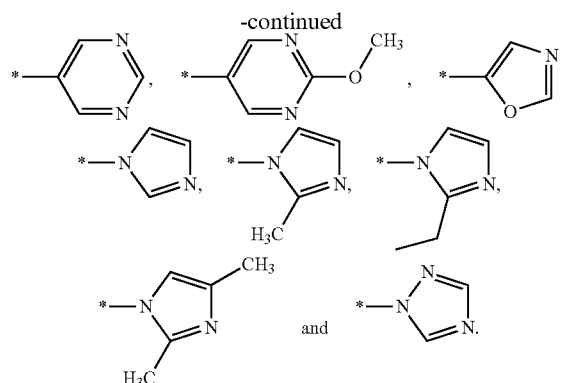
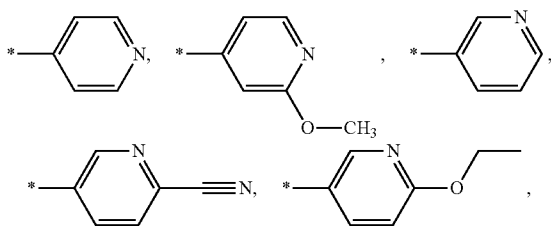
[0099] wherein R<sup>NT1</sup> is

[0100] C<sub>1-4</sub>-alkyl optionally substituted with CN, —O—(C<sub>1-3</sub>-alkyl), —OCF<sub>3</sub>, —O—CH<sub>2</sub>—cyclopropyl, tetrahydrofuryl, tetrahydropyranyl, pyridinyl or 5-methylthiazol-2-yl; or

[0101] phenyl or pyridinyl which are each optionally substituted with one or two —O—CH<sub>3</sub> or with one —CH<sub>2</sub>—OH.

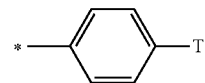
(Het)Ar<sup>2</sup>-G6b:

[0102] In another embodiment, the group (Het)Ar<sup>2</sup> is selected from the group (Het)Ar<sup>2</sup>-G6b consisting of:



(Het)Ar<sup>2</sup>-G7:

[0103] In another embodiment, the group (Het)Ar<sup>2</sup> is selected from the group (Het)Ar<sup>2</sup>-G7 consisting of:



wherein the phenyl group may be additionally substituted with one F, and

wherein T is CN or —CH<sub>2</sub>—CN.

T

T-G1:

[0104] According to one embodiment, the group T is selected from the group T-G1 as defined hereinbefore and hereinafter.

T-G2:

[0105] According to another embodiment, the group T is selected from the group T-G2 consisting of F, Cl, Br, C<sub>1-4</sub>-alkyl-, NC—, HO—, —NO<sub>2</sub>, 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>—, 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>— and R<sup>NT1</sup>R<sup>NT2</sup>N—,

[0106] wherein each alkyl group is optionally substituted with one or more substituents independently of each other selected from F, Cl, ON, OH, phenyl, heteroaryl and heterocyclyl,

[0107] wherein heteroaryl is selected from the group consisting of pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, pyrazolyl, imidazolyl, [1,2,4]triazolyl and tetrazolyl; and

[0108] wherein heterocyclyl is selected from the group consisting of azetidyl, pyrrolidinyl, piperidinyl, piperazinyl and morpholinyl, wherein in each of the before-mentioned heterocyclyl groups a —CH<sub>2</sub>— group may be replaced by a group selected from —C(=O)— and —S(=O)<sub>2</sub>—, and wherein each of the before-mentioned groups is optionally substituted with one or more substituents independently of each other selected from C<sub>1-3</sub>-alkyl; and

[0109] wherein phenyl and heteroaryl are optionally substituted independently of each other with one or more substituents  $L^{Ar}$ ;

and, in addition, the group T-G2 consists of  $R^{NT1}R^{NT2}N-C(=O)-C_{1-4}\text{-alkyl-}$ ,  $C_{1-3}\text{-alkyl-}C(=O)NH-C_{1-3}\text{-alkyl-}$  and  $C_{1-4}\text{-alkyl-}S(=O)_2-C_{1-4}\text{-alkyl-}$ .

T-G3:

[0110] According to another embodiment the group T is selected from the group T-G3 consisting of F, Br,  $C_{1-3}\text{-alkyl-}$ ,  $NC-C_{1-3}\text{-alkyl-}$ ,  $C_{1-3}\text{-alkyl-}C(=O)NH-C_{1-3}\text{-alkyl-}$ ,  $HO-C_{1-3}\text{-alkyl-}$ , CN,  $-CO_2OH_3$ ,  $C_{1-3}\text{-alkyl-O-}$ ,  $-O-CF_3$ ,  $-NO_2$ ,  $-N(OH_3)_2$ , morpholin-4-yl,  $C_{1-3}\text{-alkyl-S(=O)-}$ ,  $C_{1-3}\text{-alkyl-S(=O)}_2$ ,  $R^{NT1}R^{NT2}N-S(=O)_2$ ,  $R^{NT1}R^{NT2}N-C(=O)-$ ,  $R^{NT1}R^{NT2}N-$ ,  $C_{1-3}\text{-alkyl-S(=O)}_2-CH_2-$  and  $R^{NT1}R^{NT2}N-C(=O)-CH_2-$ .

T-G4:

[0111] According to another embodiment, the group T is selected from the group T-G4 consisting of F, Br,  $-CH_3$ ,  $-CH_2CH_3$ ,  $-CH_2-ON$ ,  $-CH_2-C(=O)-NR^{NT1}R^{NT2}$ ,  $-CH_2-NHC(=O)CH_3$ ,  $-CH_2-OH$ ,  $-CH_2CH_2-OH$ ,  $-ON$ ,  $-C(=O)-NR^{NT1}R^{NT2}$ ,  $-CO_2CH_3$ ,  $-NO_2$ ,  $-N(CH_3)_2$ , morpholin-4-yl,  $-NH-S(=O)_2-CH_3$ ,  $-O-CH_3$ ,  $-O-CH_2CH_3$ ,  $-O-CF_3$ ,  $-S(=O)_2-CH_3$ ,  $-S(=O)_2-NH_2$  and  $-S(=O)_2-NHCH_3$ .

T-G4a:

[0112] According to another embodiment, the group T is selected from the group T-G4a consisting of  $-CH_3$ ,  $-CH_2CH_3$ ,  $-CH_2-CN$ ,  $-CH_2-NHC(=O)CH_3$ ,  $-CH_2-OH$ ,  $-CH_2CH_2-OH$ ,  $-ON$ ,  $-N(CH_3)_2$ , morpholin-1-yl,  $-NH-S(=O)_2-CH_3$ ,  $-O-CH_3$ ,  $-O-CH_2CH_3$ ,  $-O-CF_3$ ,  $-S(=O)_2-CH_3$ ,  $-S(=O)_2-NH_2$  and  $-S(=O)_2-NHCH_3$ .

T-G4b:

[0113] According to another embodiment, the group T is selected from the group T-G4b consisting of  $-CH_2-C(=O)-NR^{NT1}R^{NT2}$  and  $-C(=O)-NR^{NT1}R^{NT2}$ .

$R^{NT1}$

$R^{NT1}$ -G1:

[0114] In one embodiment,  $R^{NT1}$  is selected from the group  $R^{NT1}$ -G1 as defined hereinbefore and hereinafter.

$R^{NT1}$ -G2:

[0115] In another embodiment,  $R^{NT1}$  is selected from the group  $R^{NT1}$ -G2 consisting of H,  $C_{1-6}\text{-alkyl-}$ ,  $C_{3-6}\text{-cycloalkyl-}$ , heterocyclyl, phenyl and heteroaryl,

[0116] wherein each alkyl and cycloalkyl is optionally substituted with 1 or 2 substituents independently of each other selected from the group consisting of F, NC-,  $(H_3C)_2N-C(=O)-$ , HO-,  $C_{1-3}\text{-alkyl-O-}$ , cyclopropyl- $CH_2-O-$ ,  $F_3C-O-$ ,  $(R^N)_2N-$ ,  $H_3C-S(=O)_2-$ , cyclohexyl optionally substituted with one HO- group, heterocyclyl and heteroaryl;

[0117] wherein phenyl is optionally substituted with 1 or 2 groups independently selected from F,  $H_3C-$ , HO-  $(CH_2)_{1-2}-$ ,  $H_3C-O-CH_2-$ , HO- and  $H_3C-O-$ ;

[0118] wherein each heteroaryl is selected from the group consisting of pyrazolyl, oxazolyl, thiazolyl, pyridyl and pyridazinyl, each of which is optionally substituted with 1 or 2 substituents independently selected from  $H_3C-$ ,  $H_3C-O-CH_2-$ , cyclopropyl, HO- and  $H_3C-O-$ ; and

[0119] wherein each heterocyclyl is selected from the group consisting of oxetanyl, tetrahydrofuranyl and tetrahydropyranyl, each of which is optionally substituted with one  $H_3C-$  group.

$R^{NT1}$ -G3:

[0120] In another embodiment,  $R^{NT1}$  is selected from the group  $R^{NT1}$ -G3 consisting of H,  $C_{1-5}\text{-alkyl-}$ ,  $C_{3-6}\text{-cycloalkyl-}$ , phenyl and heteroaryl,

[0121] wherein each alkyl and cycloalkyl is optionally substituted with 1 or 2 substituents independently of each other selected from the group consisting of F, NC-, HO-,  $C_{1-3}\text{-alkyl-O-}$ ,  $F_3C-O-$ ,  $H_3C-S(=O)_2-$ , heterocyclyl and heteroaryl;

[0122] wherein phenyl is optionally substituted with 1 or 2 groups independently selected from F,  $H_3C-$ , HO-  $(CH_2)_{1-2}-$ ,  $H_3C-O-CH_2-$ , HO- and  $H_3C-O-$ ;

[0123] wherein each heteroaryl is selected from the group consisting of pyrazolyl, oxazolyl, thiazolyl, pyridyl and pyridazinyl, each of which is optionally substituted with 1 or 2 substituents independently selected from  $H_3C-$ ,  $H_3C-O-CH_2-$ , cyclopropyl, HO- and  $H_3C-O-$ ; and

[0124] wherein each heterocyclyl is selected from the group consisting of oxetanyl, tetrahydrofuranyl and tetrahydropyranyl, each of which is optionally substituted with one  $H_3C-$  group; and

additionally, the group  $R^{NT1}$ -G3 comprises the residues  $(H_3C)_2N-C(=O)-CH_2-$ , cyclopropyl- $CH_2-O-CH_2CH_2-$ , 2-hydroxycyclohexyl- $CH_2-$  and tetrahydropyranyl.

$R^{NT1}$ -G4:

[0125] In another embodiment,  $R^{NT1}$  is selected from the group  $R^{NT1}$ -G4 consisting of:

[0126] a) a methyl group substituted with CN,  $(H_3C)_2N-C(=O)-$ , 2-hydroxycyclohexyl, 3-methyloxetan-3-yl, tetrahydrofuran-3-yl, tetrahydrofuran-2-yl, 2-methyltetrahydrofuran-2-yl, tetrahydropyran-2-yl, tetrahydropyran-4-yl, 1-methylpyrazol-4-yl, oxazol-4-yl, 2-methylthiazol-4-yl, 5-methylthiazol-2-yl, pyrid-2-yl, pyrid-3-yl, pyrid-4-yl or pyridazin-3-yl,

[0127] b) an ethyl group optionally substituted with CN, OH,  $-OCH_3$ ,  $-OCH_2CH_3$ ,  $-OCF_3$ ,  $-O-CH_2$ -cyclopropyl,  $-S(=O)_2-CH_3$  or 3-cyclopropylpyrazol-1-yl, and

[0128] c) a group selected from among:

[0129]  $-CH_2-C(CH_3)_2-OH$ ,  $-CH_2-C(CH_3)_2-CH_2-OH$ ,  $-CH(CH_3)-O-CH_3$ ,  $-CH_2-CH(CH_3)-O-CH_3$ , 4-hydroxycyclohexyl, tetrahydropyran-3-yl, tetrahydropyran-4-yl, phenyl, 3-(hydroxymethyl)-phenyl, 4-(hydroxymethyl)-phenyl, 3-(1-hydroxyethyl)-phenyl, 3-(methoxymethyl)-phenyl, 4-hydroxy-phenyl, 2,4-dimethoxy-phenyl, pyrazol-3-yl, 4-methyl-5-(methoxymethyl)-thiazol-2-yl, pyrid-3-yl and pyridazin-4-yl.

$R^{NT2}$

$R^{NT2}$ -G1:

[0130] In one embodiment,  $R^{NT2}$  is selected from the group  $R^{NT2}$ -G1 as defined hereinbefore and hereinafter.

$R^{NT2}$ -G2:

[0131] In another embodiment,  $R^{NT2}$  is selected from the group  $R^{NT2}$ -G2 consisting of H and  $H_3C$ —.

$R^{NT2}$ -G2a:

[0132] In another embodiment,  $R^{NT2}$  is selected from the group  $R^{NT2}$ -G2a consisting of H.

$R^{NT2}$ -G2b:

[0133] In another embodiment,  $R^{NT2}$  is selected from the group  $R^{NT2}$ -G2b consisting of  $H_3C$ —.

$R^{NT1}R^{NT2}$

$R^{NT1}R^{NT2}$ -G1:

[0134] According to one embodiment, the groups  $R^{NT1}$  and  $R^{NT2}$  are linked and form a group which is selected from the group  $R^{NT1}R^{NT2}$ -G1 as defined hereinbefore and hereinafter.

$R^{NT1}R^{NT2}$ -G2:

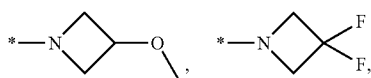
[0135] According to another embodiment the groups  $R^{NT1}$  and  $R^{NT2}$  are linked and together with the N atom to which they are attached form a group which is selected from the group  $R^{NT1}R^{NT2}$ -G2 consisting of azetidiny, pyrrolidiny, piperidiny, morpholinyl, piperazinyl, N—( $C_{1-3}$ -alkyl)-piperazinyl, N—( $C_{1-3}$ -alkyl-C(=O))—piperazinyl and 1,4-oxazepanyl, each of which is optionally substituted with 1 or 2 substituents independently of each other selected from F,  $C_{1-3}$ -alkyl,  $F_3C$ —,  $HO-C_{1-3}$ -alkyl-,  $H_3CO-C_{1-3}$ -alkyl-,  $NC$ —,  $HO$ —,  $C_{1-3}$ -alkyl-O— and 3-methyl-[1,2,4]oxadiazol-5-yl.

$R^{NT1}R^{NT2}$ -G3:

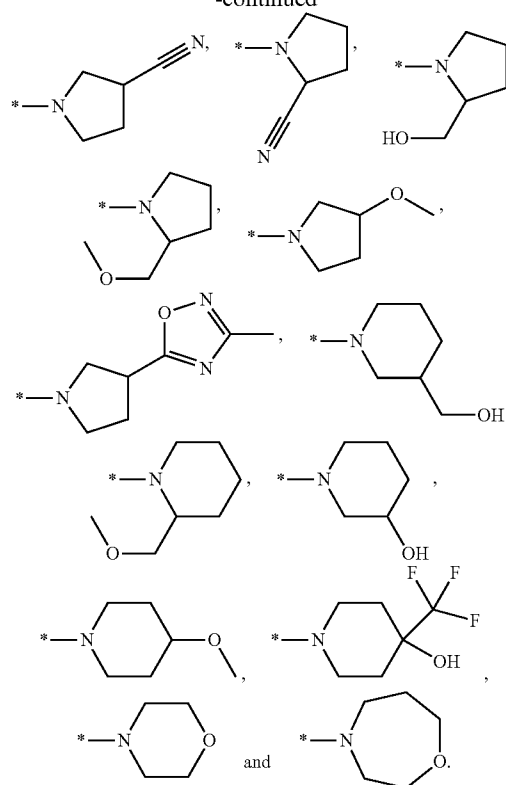
[0136] According to another embodiment, the groups  $R^{NT1}$  and  $R^{NT2}$  are linked and together with the N atom to which they are attached form a group which is selected from the group  $R^{NT1}R^{NT2}$ -G3 consisting of azetidiny, pyrrolidiny, piperidiny, morpholinyl and 1,4-oxazepanyl, each of which is optionally substituted with 1 or 2 substituents independently of each other selected from F,  $F_3C$ —,  $HO-CH_2$ —,  $H_3CO-CH_2$ —,  $NC$ —,  $HO$ —,  $CH_3-O$ — and 3-methyl-[1,2,4]oxadiazol-5-yl.

$R^{NT1}R^{NT2}$ -G4:

[0137] According to another embodiment the groups  $R^{NT1}$  and  $R^{NT2}$  are linked and together with the N atom to which they are attached form a group which is selected from the group  $R^{NT1}R^{NT2}$ -G3 consisting of:



-continued



$L^{Ar}$ :

$L^{Ar}$ -G1:

[0138] In one embodiment, the group  $L^{Ar}$  is selected from the group  $L^{Ar}$ -G1 as defined hereinbefore and hereinafter.

$L^{Ar}$ -G2:

[0139] In another embodiment, the group  $L^{Ar}$  is selected from the group  $L^{Ar}$ -G2 consisting of F, Cl, Br, I,  $C_{1-3}$ -alkyl-,  $CN$ ,  $HO$ —,  $C_{1-3}$ -alkyl-O—,  $H_2N$ —,  $(C_{1-3}$ -alkyl)NH— and  $(C_{1-3}$ -alkyl) $_2N$ —, wherein the  $C_{1-3}$ -alkyl- and  $C_{1-3}$ -alkyl-O— groups are optionally substituted with one or more F atoms.

$L^{Ar}$ -G3:

[0140] In another embodiment, the group  $L^{Ar}$  is selected from the group  $L^{Ar}$ -G3 consisting of F,  $H_3C$ —,  $F_3C$ —,  $HF_2C$ —,  $CN$ ,  $OH$ ,  $H_3C-O$ —,  $HF_2C-O$ — and  $F_3C-O$ —.

$L^{Ar}$ -G4:

[0141] In another embodiment, the group  $L^{Ar}$  is selected from the group  $L^{Ar}$ -G4 consisting of F and  $H_3C$ —.

$L^P$ :

$L^P$ -G1:

[0142] In one embodiment, the group  $L^P$  is selected from the group  $L^P$ -G1 as defined hereinbefore and hereinafter.

$L^P$ -G2:

[0143] In another embodiment, the group  $L^P$  is selected from the group  $L^P$ -G2 consisting of F and  $H_3C-$ .

$L^P$ -G3:

[0144] According to the embodiment  $L^P$ -G3, the group  $L^P$  is F.

$L^Q$ :

$L^Q$ -G1:

[0145] In one embodiment, the group  $L^Q$  is selected from the group  $L^Q$ -G1 as defined hereinbefore and hereinafter.

$L^Q$ -G2:

[0146] In another embodiment the group  $L^Q$  is selected from the group  $L^Q$ -G2 consisting of F,  $H_3C-$ ,  $F_2HC-$ ,  $F_3C-$ , CN, OH,  $H_3C-O-$ ,  $F_2HC-O-$ , and  $F_3C-O-$ .

$L^Q$ -G3:

[0147] In another embodiment, the group  $L^Q$  is selected from the group  $L^Q$ -G3 consisting of F and  $H_3C-$ .

$L^Q$ -G4:

[0148] According to the embodiment  $L^Q$ -G4, the group  $L^Q$  is  $H_3C-$ .

n:

[0149] The index n is an integer selected from 0, 1, 2, 3 or 4.

[0150] According to another embodiment, the index n is 0, 1 or 2.

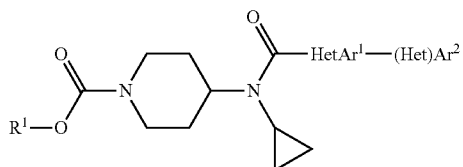
[0151] According to one embodiment, the index n is 1 or 2, in particular 1.

[0152] According to another embodiment, the index n is 0 or 1.

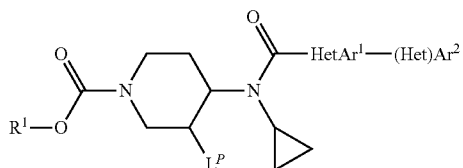
[0153] According to another embodiment, the index n is 1.

[0154] According to another embodiment, the index n is 0.

[0155] The following preferred embodiments of compounds of the formula I are described using generic formulae I.1 to I.5, wherein any tautomers and stereoisomers, solvates, hydrates and salts thereof, in particular the pharmaceutically acceptable salts thereof, are encompassed.

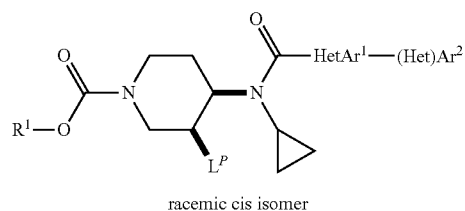


I.1

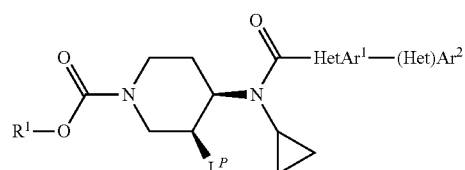


I.2

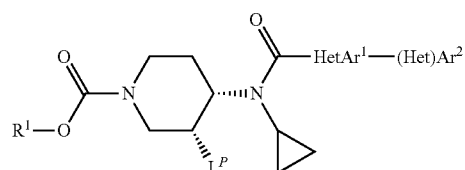
-continued



I.3



I.4



I.5

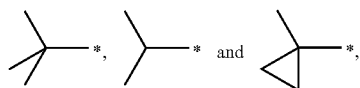
wherein the groups  $R^1$ ,  $L^P$ ,  $HetAr^1$ , and  $(Het)Ar^2$  are defined as hereinbefore and hereinafter.

[0156] 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:

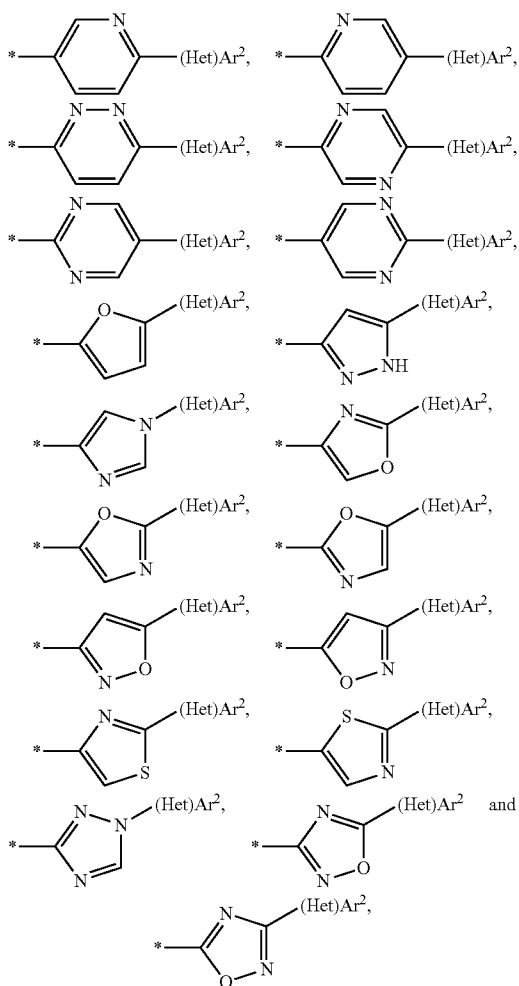
| Embodiment | $R^1$     | $HetAr^1$     | $(Het)Ar^2$      | $L^P$     | n      |
|------------|-----------|---------------|------------------|-----------|--------|
| E-1        | $R^1$ -G1 | $HetAr^1$ -G1 | $(Het)Ar^2$ -G1  | $L^P$ -G1 | 1 or 0 |
| E-2        | $R^1$ -G2 | $HetAr^1$ -G2 | $(Het)Ar^2$ -G2  | $L^P$ -G2 | 1 or 0 |
| E-3        | $R^1$ -G2 | $HetAr^1$ -G3 | $(Het)Ar^2$ -G2  | $L^P$ -G2 | 1 or 0 |
| E-4        | $R^1$ -G3 | $HetAr^1$ -G3 | $(Het)Ar^2$ -G2  | $L^P$ -G2 | 1 or 0 |
| E-5        | $R^1$ -G3 | $HetAr^1$ -G3 | $(Het)Ar^2$ -G3  | $L^P$ -G2 | 1 or 0 |
| E-6        | $R^1$ -G2 | $HetAr^1$ -G4 | $(Het)Ar^2$ -G2  | $L^P$ -G2 | 1 or 0 |
| E-7        | $R^1$ -G2 | $HetAr^1$ -G3 | $(Het)Ar^2$ -G3  | $L^P$ -G2 | 1 or 0 |
| E-8        | $R^1$ -G3 | $HetAr^1$ -G4 | $(Het)Ar^2$ -G3  | $L^P$ -G2 | 1 or 0 |
| E-9        | $R^1$ -G4 | $HetAr^1$ -G3 | $(Het)Ar^2$ -G3  | $L^P$ -G2 | 1 or 0 |
| E-10       | $R^1$ -G2 | $HetAr^1$ -G4 | $(Het)Ar^2$ -G3  | $L^P$ -G2 | 1 or 0 |
| E-11       | $R^1$ -G2 | $HetAr^1$ -G3 | $(Het)Ar^2$ -G4  | $L^P$ -G2 | 1 or 0 |
| E-12       | $R^1$ -G2 | $HetAr^1$ -G4 | $(Het)Ar^2$ -G4  | $L^P$ -G2 | 1 or 0 |
| E-13       | $R^1$ -G3 | $HetAr^1$ -G4 | $(Het)Ar^2$ -G4  | $L^P$ -G2 | 1 or 0 |
| E-14       | $R^1$ -G3 | $HetAr^1$ -G4 | $(Het)Ar^2$ -G4a | $L^P$ -G2 | 1 or 0 |
| E-15       | $R^1$ -G3 | $HetAr^1$ -G4 | $(Het)Ar^2$ -G4b | $L^P$ -G2 | 1 or 0 |
| E-16       | $R^1$ -G4 | $HetAr^1$ -G4 | $(Het)Ar^2$ -G3  | $L^P$ -G2 | 1 or 0 |
| E-17       | $R^1$ -G4 | $HetAr^1$ -G4 | $(Het)Ar^2$ -G4  | $L^P$ -G2 | 1 or 0 |
| E-18       | $R^1$ -G4 | $HetAr^1$ -G5 | $(Het)Ar^2$ -G4a | $L^P$ -G2 | 1 or 0 |
| E-19       | $R^1$ -G4 | $HetAr^1$ -G5 | $(Het)Ar^2$ -G4b | $L^P$ -G2 | 1 or 0 |
| E-20       | $R^1$ -G4 | $HetAr^1$ -G5 | $(Het)Ar^2$ -G4  | $L^P$ -G3 | 1 or 0 |

[0157] Another embodiment concerns those compounds of formula I, wherein

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



each of which is optionally substituted with 1 to 3 F atoms;  
HetAr<sup>1</sup> is selected from the group consisting of:



[0158] wherein each group is optionally additionally substituted with one H<sub>3</sub>C— group, and

[0159] wherein the (Het)Ar<sup>2</sup>-group is depicted in order to show the position of the HetAr<sup>2</sup>-moiety within the compound of formula I;

(Het)Ar<sup>2</sup> is selected from the group consisting of phenyl, tetrazolyl, pyridinonyl, and a heteroaromatic ring selected from pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, isoxazolyl, oxazolyl, oxadiazolyl, imidazolyl, pyrazolyl, triazolyl, thienyl and thiazolyl,

[0160] wherein said phenyl and heteroaromatic ring are optionally substituted with one or more substituents independently of each other selected from L<sup>Ar</sup>; and

[0161] wherein said phenyl, tetrazolyl and heteroaromatic ring are optionally substituted with one group T, and

[0162] wherein in said heteroaromatic ring the H-atom in one NH group is optionally replaced by R<sup>N</sup>;

R<sup>N</sup> is selected from the group consisting of H, H<sub>3</sub>C—, H<sub>3</sub>C—C(=O)— and H<sub>3</sub>C—S(=O)<sub>2</sub>—;

T is selected from the group consisting of F, Br, —CH<sub>3</sub>, —CH<sub>2</sub>CH<sub>3</sub>, —CH<sub>2</sub>—CN, —CH<sub>2</sub>—C(=O)—NR<sup>NT1</sup>R<sup>NT2</sup>, —CH<sub>2</sub>—NHC(=O)CH<sub>3</sub>, —CH<sub>2</sub>—OH, —CH<sub>2</sub>CH<sub>2</sub>—OH, —CN, —C(=O)—NR<sup>NT1</sup>R<sup>NT2</sup>, —CO<sub>2</sub>CH<sub>3</sub>, —NO<sub>2</sub>, —N(CH<sub>3</sub>)<sub>2</sub>, morpholin-4-yl, —NH—S(=O)<sub>2</sub>—CH<sub>3</sub>, —O—CH<sub>3</sub>, —O—CH<sub>2</sub>CH<sub>3</sub>, —O—CF<sub>3</sub>, —S(=O)<sub>2</sub>—CH<sub>3</sub>, —S(=O)<sub>2</sub>—NH<sub>2</sub> and —S(=O)<sub>2</sub>—NHCH<sub>3</sub>;

R<sup>NT1</sup> is selected from the group consisting of H, C<sub>1-5</sub>-alkyl, C<sub>3-6</sub>-cycloalkyl, phenyl and heteroaryl,

[0163] wherein each alkyl and cycloalkyl group is optionally substituted with 1 or 2 substituents independently of each other selected from the group consisting of F, NC—, HO—, C<sub>1-3</sub>-alkyl-O—, F<sub>3</sub>C—O—, H<sub>3</sub>C—S(=O)<sub>2</sub>—, heterocyclyl and heteroaryl;

[0164] wherein phenyl is optionally substituted with 1 or 2 groups independently selected from F, H<sub>3</sub>C—, HO— (C<sub>1-2</sub>-alkyl)-, H<sub>3</sub>C—O—CH<sub>2</sub>—, HO— and H<sub>3</sub>C—O—;

[0165] wherein each heteroaryl is selected from the group consisting of pyrazolyl, oxazolyl, thiazolyl, pyridyl and pyridazinyl, each of which is optionally substituted with 1 or 2 substituents independently selected from H<sub>3</sub>C—, H<sub>3</sub>C—O—CH<sub>2</sub>—, cyclopropyl, HO— and H<sub>3</sub>C—O—; and

[0166] wherein each heterocyclyl is selected from the group consisting of oxetanyl, tetrahydrofuranyl and tetrahydropyranyl, each of which is optionally substituted with one H<sub>3</sub>C— group; and

[0167] additionally, the group R<sup>NT1</sup>-G3 comprises the residues (H<sub>3</sub>C)<sub>2</sub>N—C(=O)—CH<sub>2</sub>—, cyclopropyl-CH<sub>2</sub>—O—CH<sub>2</sub>CH<sub>2</sub>—, 2-hydroxycyclohexyl-CH<sub>2</sub>— and tetrahydropyranyl;

R<sup>NT2</sup> is selected from the group consisting of H and —CH<sub>3</sub>; or

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 consisting of:

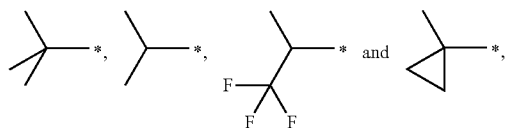
[0168] azetidiny, pyrrolidinyl, piperidinyl, morpholinyl and 1,4-oxazepanyl, each of which is optionally substituted with 1 or 2 substituents independently of each other selected from F, F<sub>3</sub>C—, HO—CH<sub>2</sub>—, H<sub>3</sub>CO—CH<sub>2</sub>—, NC—, HO—, CH<sub>3</sub>—O— and 3-methyl-[1,2,4]oxadiazol-5-yl;

L<sup>Ar</sup> is selected from the group consisting of F and H<sub>3</sub>C—; and

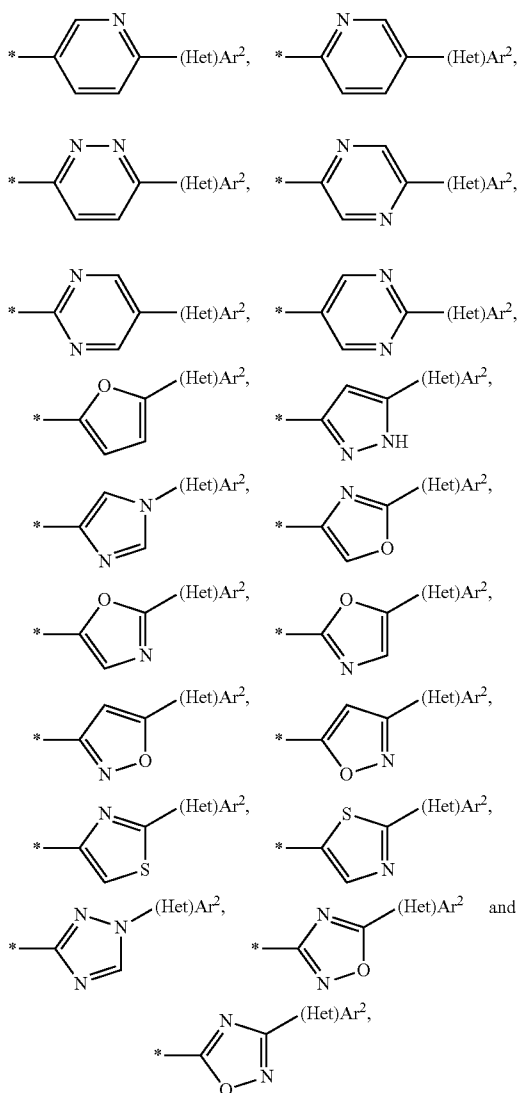
L<sup>P</sup> is H<sub>3</sub>C— or F and n is 0 or 1.

[0169] Another embodiment concerns those compounds of formula I, wherein

$R^1$  is selected from a group consisting of



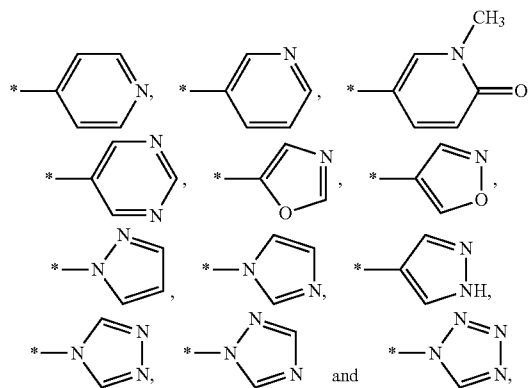
HetAr<sup>1</sup> is selected from the group consisting of:



[0170] wherein each group is optionally additionally substituted with one  $H_3C$ — group, and

[0171] wherein the (Het)Ar<sup>2</sup>-group is depicted in order to show the position of the HetAr<sup>2</sup>-moiety within the compound of formula I;

(Het)Ar<sup>2</sup> is selected from the group consisting of:



[0172] wherein each group is optionally substituted with one group selected from  $C_{1-3}$ -alkyl,  $HO-(C_{1-3}$ -alkyl)-,  $CN$ ,  $(H_3C)_2N$ — and  $C_{1-3}$ -alkyl-O— and may additionally be substituted with one  $H_3C$ — group; and

$L^P$  is F, and n is 0 or 1.

[0173] Particularly preferred compounds, including their tautomers and stereoisomers, the salts thereof, or any solvates or hydrates thereof, are described in the experimental section hereinafter.

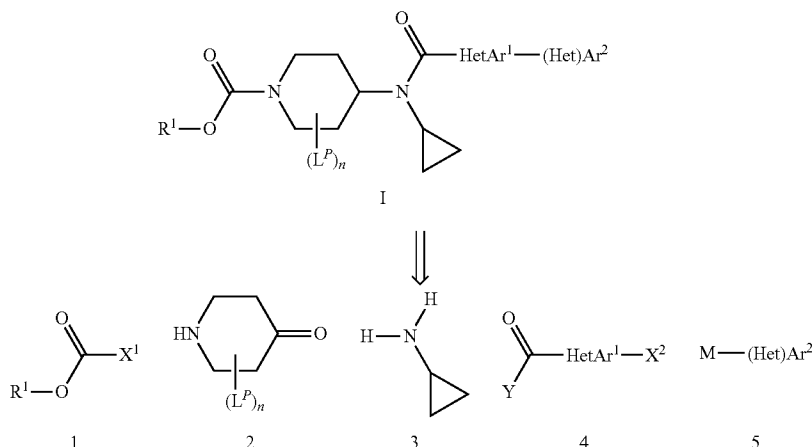
[0174] The compounds according to the invention and their intermediates may be obtained using methods of synthesis which are known to one skilled in the art and described in the literature of organic synthesis. Preferably the compounds are obtained analogously to the methods of preparation explained 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 one skilled in the art, 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 one skilled in the art 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 one skilled in the art.

[0175] The compounds of the invention I can principally be assembled from the building blocks 1 to 5 as depicted in Scheme 1;  $R^1$ ,  $L^P$ , HetAr<sup>1</sup>, (Het)Ar<sup>2</sup> and n have the meanings as defined hereinbefore and hereinafter. Building blocks 1 to 5 are either known compounds that are commercially available or of which a synthesis is reported or which can be synthesized in analogy to proceedings described herein or in the literature for related compounds. The order of linking the building blocks is variable and the most effective way depends on the precise decoration of the building blocks and the reactivity of the groups to be linked and may vary for each of them. In principle, almost any order of linking is conceivable, however, combining building block 1 with building block 2 followed by attachment of building block 3 and

finally compound 4, optionally already bearing building block 5, may be preferred in most of the cases. For varying one individual residue or for the synthesis of particular target compounds a deviating proceeding may be more appropriate.

amination from a piperidinone, such as 6', and cyclopropylamine (3) (Scheme 3);  $R^1$ ,  $L^P$  and  $n$  have the meanings as defined hereinbefore and hereinafter. Suitable reducing agents may be complex metal hydrides, such as sodium boro-

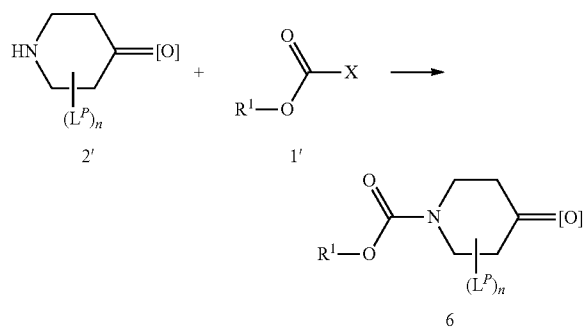
Scheme 1



$X^1, X^2, Y$  = leaving group  
 $M$  = H, metal or pseudo-metal group

**[0176]** A general way of attaching the residue  $R^1OC(=O)-$  to the N atom of the piperidine of the compounds of the invention (I) or an intermediate towards them is sketched in Scheme 2;  $R^1$ ,  $L^P$  and  $n$  have the meanings as defined hereinbefore and hereinafter.  $R^1OC(=O)-$  is preferably introduced from an electrophilic precursor 1', e.g., as chloride ( $X=Cl$ ) or anhydride ( $X=O-C(=O)-OR^1$ ), that is reacted with the piperidine derivative 2', preferably in the presence of a base, e.g.  $K_2CO_3$ , pyridine, 4-dimethylamino-pyridine, triethylamine or ethyldiisopropylamine, in a solvent such as toluene, dichloromethane, ether, tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane, acetonitrile, or mixtures thereof, at  $-10$  to  $120^\circ C$ .

Scheme 2

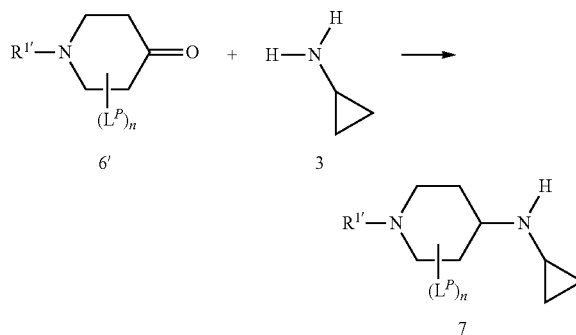


$[O]$  = O or protective group for  $=O$ , e.g.,  $OCH_2CH_2O$   
 $X$  = leaving group, e.g., F, Cl,  $O-C(=O)-OR^1$ ,  $O-C_6H_4-NO_2$ ,  
 $O-C_6F_5$ ,  
imidazole, 1-oxybenzotriazole

**[0177]** The linkage between the piperidine and the cyclopropylamine fragment is preferably established via reductive

hydride, lithium borohydride, sodium triacetoxyborohydride or sodium cyano-borohydride, which are optionally used in combination with an acid, e.g. acetic acid, or hydrogen that is employed in the presence of a transition metal catalyst, e.g. palladium on charcoal or Raney-Ni.

Scheme 3

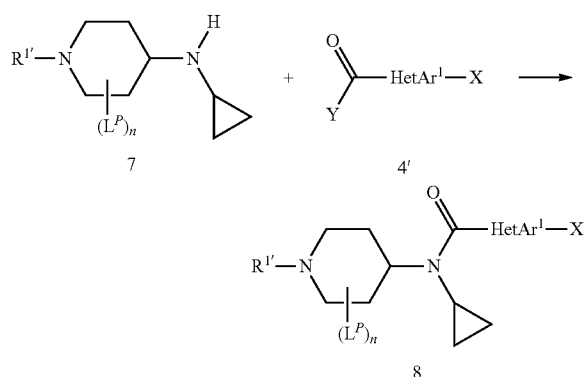


$R^1 = R^1OC(=O)$  or protective group, e.g.,  $PhCH_2$ ,  $PhCH_2OC(=O)$ ,  
 $F_3CC(=O)$

**[0178]** The amide linkage in compounds I or any intermediate towards I of the carboxylic carbon atom and the N bearing the cyclopropyl group is a routine transformation in organic synthesis with a plethora of methods and strategies known (Scheme 4);  $R^1$ ,  $L^P$ ,  $n$ ,  $HetAr^1$  and  $(Het)Ar^2$  have the meanings as defined hereinbefore and hereinafter. The carboxylic acid may be transformed into a sufficiently reactive derivative to be coupled with the amine in a separate reaction step or in situ. Suitable derivatives of the carboxylic acid for the former proceeding may be, for example, carboxylic chlorides, fluorides, cyanides, anhydrides, mixed anhydrides, imi-

dazolides, oxy-benzotriazolides, pentafluorophenyl esters or 4-nitrophenyl esters. In situ activation of the carboxylic acid may be achieved with, e.g., 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate or 2-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate. The couplings are preferably conducted in the presence of a base, e.g. ethyl-diisopropyl-amine, triethylamine, imidazole, pyridine, potassium carbonate or calcium oxide, and/or another additive, such as 4-dimethylaminopyridine or 1-hydroxybenzotriazol, in solvents, preferably selected from tetrahydrofuran, 1,2-dimethoxyethane, ether, 1,4-dioxane, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidinone, acetonitrile, ethyl acetate, dichloromethane, 1,2-dichloroethane, toluene, benzene, hexanes, and mixtures thereof, preferably at -10 to 140° C.

Scheme 4



$R' = R^1OC(=O)$  or protective group, e.g.,  $PhCH_2$ ,  $PhCH_2OC(=O)$ ,  $F_3CC(=O)$

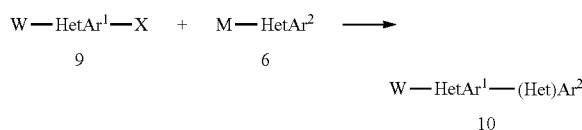
$X = (Het)Ar^2$  or leaving group, e.g., Cl, Br, I,  $OSO_2CF_3$ ,  $OSO_2Me$

$Y =$  leaving group, e.g., F, Cl, imidazolide,  $tBuC(=O)O$ ,  $iPrC(=O)O$ , benzotriazol-1-yl-O, pentafluorophenoxy, 4-nitrophenoxy

[0179] Attaching  $(Het)Ar^2$  to the heteroaromatic ring  $HetAr^1$  in I or an intermediate towards I, e.g. compound 9, may be accomplished as depicted in Scheme 5;  $HetAr^1$  and  $(Het)Ar^2$  have the meanings as defined hereinbefore and hereinafter. Compound 9 is preferably employed as the electrophilic component bearing a leaving group, such as Cl, Br, I,  $F_3CSO_3$ ,  $H_3CSO_3$  and  $PhSO_3$ , and  $(Het)Ar^2$  as the nucleophilic partner bearing an acidic H or a metal or pseudo metal group, e.g.  $B(OH)_2$ ,  $BF_3K$ ,  $B(OCMe_2CMe_2O)$ ,  $ZnCl$ ,  $ZnBr$  and  $ZnI$ . Coupling of the two components is preferably mediated by a transition metal species derived from Fe, Cu, Ni or Pd. The active catalyst may be a complex of the transition metal with ligands, such as phosphines, e.g. tri-tert-butylphosphine, tricyclohexyl-phosphine, optionally substituted biphenyl-dicyclohexylphosphines or biphenyl-di-tert-butylphosphines, 1,1'-bis(diphenyl-phosphino)-ferrocene, triphenylphosphine, tritolylphosphine or trifurylphosphine, pyridines, such as 2,2'-bipyridine or 1,10-phenanthroline, ethylenediamines, phosphites, 1,3-disubstituted imidazole or imidazolidine carbenes, dibenzylidene-acetone, allyl or nitriles, an elemental form of the transition metal, such as Pd on carbon or nanoparticles of Fe or Pd, a salt, such as fluoride, chloride, bromide, acetate, triflate or trifluoroacetate, or a combination of the different species mentioned. Depending on the nature of the electrophile and nucleophile, additives,

such as halide salts, e.g. LiCl, KF and  $nBu_4NF$ , hydroxide sources, e.g. KOH,  $K_2CO_3$ , silver salts, such as  $Ag_2O$  and  $Ag(O_3SCF_3)_2$ , and/or Cu salts, such as CuI and copper thiophene-2-carboxylate, may be advantageous or even essential for the coupling to proceed. The coupling is 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 180° C. The reactivity of the two building blocks may be reversed, i.e. compound 9 is the nucleophile bearing the metal or pseudo metal residue M and  $(Het)Ar^2$  is the electrophile bearing the leaving group X, to access the same products under analogous reaction conditions. Depending on the nature of the coupling partners either way may be employable or one of them only.

Scheme 5



$W =$  e.g., CN,  $C(=O)OC_{1-4}alkyl$ ,  $C(=O)OH$ ,  $C(=O)OCH_2aryl$ ,  $C(=O)Oallyl$

$X =$  leaving group, e.g., Cl, Br, I,  $OSO_2CF_3$ ,  $OSO_2Me$

$M =$  H or (pseudo)metal group, e.g.,  $B(OH)_2$ ,  $BF_3K$ ,  $B(OCMe_2CMe_2O)$ ,  $ZnCl/Br/I$ ,  $MgCl/Br/I$

[0180] The synthetic routes presented may rely on the use of protecting groups. For example, 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.

[0181] 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.

[0182] 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 physicochemical properties 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.

[0183] The racemates are preferably resolved by column chromatography on chiral phases 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 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 commonly used for such a purpose as well as optically active alcohols applicable as auxiliary residues are known to those skilled in the art.

[0184] 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.

#### TERMS AND DEFINITIONS

[0185] 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.

[0186] 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.

[0187] 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.

[0188] When this invention refers to patients requiring treatment, it relates primarily to treatment in mammals, in particular humans.

[0189] 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.

[0190] 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.

[0191] 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.

[0192] 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.

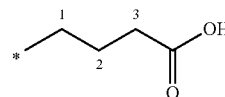
[0193] In the groups, radicals, or moieties defined below, the number of carbon atoms is often specified preceding the group, for example, C<sub>1-6</sub>-alkyl means an alkyl group or radical having 1 to 6 carbon atoms. In general, for groups comprising two or more subgroups, the last named subgroup 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.

[0194] 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.

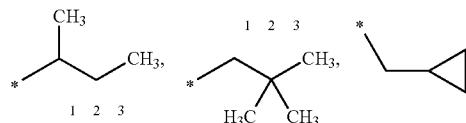
[0195] An asterisk may be used in sub-formulas to indicate the bond which is connected to the core molecule as defined.

[0196] The numeration of the atoms of a substituent starts with the atom which is closest to the core or the group to which the substituent is attached.

[0197] 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:



[0198] The asterisk may be used in sub-formulas to indicate the bond which is connected to the core molecule as defined.

[0199] 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 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.

[0200] 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 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 compound.

[0201] 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 human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, and commensurate with a reasonable benefit/risk ratio.

[0202] 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.

[0203] Salts of acids which for example are useful for purifying or isolating the compounds of the present invention are also part of the invention.

[0204] The term halogen generally denotes fluorine, chlorine, bromine and iodine.

[0205] The term “C<sub>1-n</sub>-alkyl”, wherein n is an integer from 2 to n, either alone or in 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—CH<sub>2</sub>—C(CH<sub>3</sub>)<sub>2</sub>—, H<sub>3</sub>C—C(CH<sub>3</sub>)<sub>2</sub>—CH<sub>2</sub>—, H<sub>3</sub>C—CH(CH<sub>3</sub>)—CH(CH<sub>3</sub>)— and H<sub>3</sub>C—CH<sub>2</sub>—CH(CH<sub>2</sub>CH<sub>3</sub>)—.

[0206] The term “C<sub>1-n</sub>-alkylene” wherein n is an integer from 2 to n, either alone or in combination with another radical, denotes an acyclic, straight-chain or branched divalent alkyl radical containing from 1 to n carbon atoms. For example, the term C<sub>1-4</sub>-alkylene includes —(CH<sub>2</sub>)—, —(CH<sub>2</sub>—CH<sub>2</sub>)—, —(CH(CH<sub>3</sub>))—, —(CH<sub>2</sub>—CH<sub>2</sub>—CH<sub>2</sub>)—, —(C(CH<sub>3</sub>)<sub>2</sub>)—, —(CH(CH<sub>2</sub>CH<sub>3</sub>))—, —(CH(CH<sub>3</sub>)—CH<sub>2</sub>)—, —(CH<sub>2</sub>—CH(CH<sub>3</sub>))—, —(CH<sub>2</sub>—CH<sub>2</sub>—CH<sub>2</sub>—CH<sub>2</sub>)—, —(CH<sub>2</sub>—CH<sub>2</sub>—CH(CH<sub>3</sub>))—, —(CH(CH<sub>3</sub>)—CH<sub>2</sub>—CH<sub>2</sub>)—, —(CH<sub>2</sub>—CH(CH<sub>3</sub>)—CH<sub>2</sub>)—, —(CH<sub>2</sub>—C(CH<sub>3</sub>)<sub>2</sub>)—, —(C(CH<sub>3</sub>)<sub>2</sub>—CH<sub>2</sub>)—, —(CH(CH<sub>3</sub>)—CH(CH<sub>3</sub>))—, —(CH<sub>2</sub>—CH(CH<sub>2</sub>CH<sub>3</sub>))—, —(CH(CH<sub>2</sub>CH<sub>3</sub>)—CH<sub>2</sub>)—, —(CH(CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>))—, —(CHCH(CH<sub>3</sub>)<sub>2</sub>)— and —C(CH<sub>3</sub>)(CH<sub>2</sub>CH<sub>3</sub>)—.

[0207] The term “C<sub>2-n</sub>-alkenyl”, is used for a group as defined in the definition for “C<sub>1-n</sub>-alkyl” with at least two carbon atoms, if at least two of those carbon atoms of said group are bonded to each other by a double bond. For example the term C<sub>2-3</sub>-alkenyl includes —CH=CH<sub>2</sub>—, —CH=CH—CH<sub>3</sub>—, —CH<sub>2</sub>—CH=CH<sub>2</sub>—.

[0208] The term “C<sub>2-n</sub>-alkenylene” is used for a group as defined in the definition for “C<sub>1-n</sub>-alkylene” with at least two carbon atoms, if at least two of those carbon atoms of said group are bonded to each other by a double bond. For example the term C<sub>2-3</sub>-alkenylene includes —CH=CH—, —CH=CH—CH<sub>2</sub>—, —CH<sub>2</sub>—CH=CH—.

[0209] The term “C<sub>2-n</sub>-alkynyl”, is used for a group as defined in the definition for “C<sub>1-n</sub>-alkyl” with at least two

carbon atoms, if at least two of those carbon atoms of said group are bonded to each other by a triple bond. For example the term C<sub>2-3</sub>-alkynyl includes —C≡CH, —C≡C—CH<sub>3</sub>, —CH<sub>2</sub>—C≡CH.

[0210] The term “C<sub>2-n</sub>-alkynylene” is used for a group as defined in the definition for “C<sub>1-n</sub>-alkylene” with at least two carbon atoms, if at least two of those carbon atoms of said group are bonded to each other by a triple bond. For example the term C<sub>2-3</sub>-alkynylene includes —C≡C—, —C≡C—CH<sub>2</sub>—, —CH<sub>2</sub>—C≡C—.

[0211] The term “C<sub>3-n</sub>-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 the term C<sub>3-10</sub>-carbocyclyl includes C<sub>3-10</sub>-cycloalkyl, C<sub>3-10</sub>-cycloalkenyl, octahydro-pentalenyl, octahydroindanyl, decahydronaphthyl, indanyl, tetrahydronaphthyl. Most preferably the term C<sub>3-n</sub>-carbocyclyl denotes C<sub>3-n</sub>-cycloalkyl, in particular C<sub>3-7</sub>-cycloalkyl.

[0212] 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, cyclododecyl, bicyclo[3.2.1]octyl, spiro[4.5]decyl, norpinyl, norbornyl, norcaryl, adamantyl, etc.

[0213] The term bicyclic includes spirocyclic.

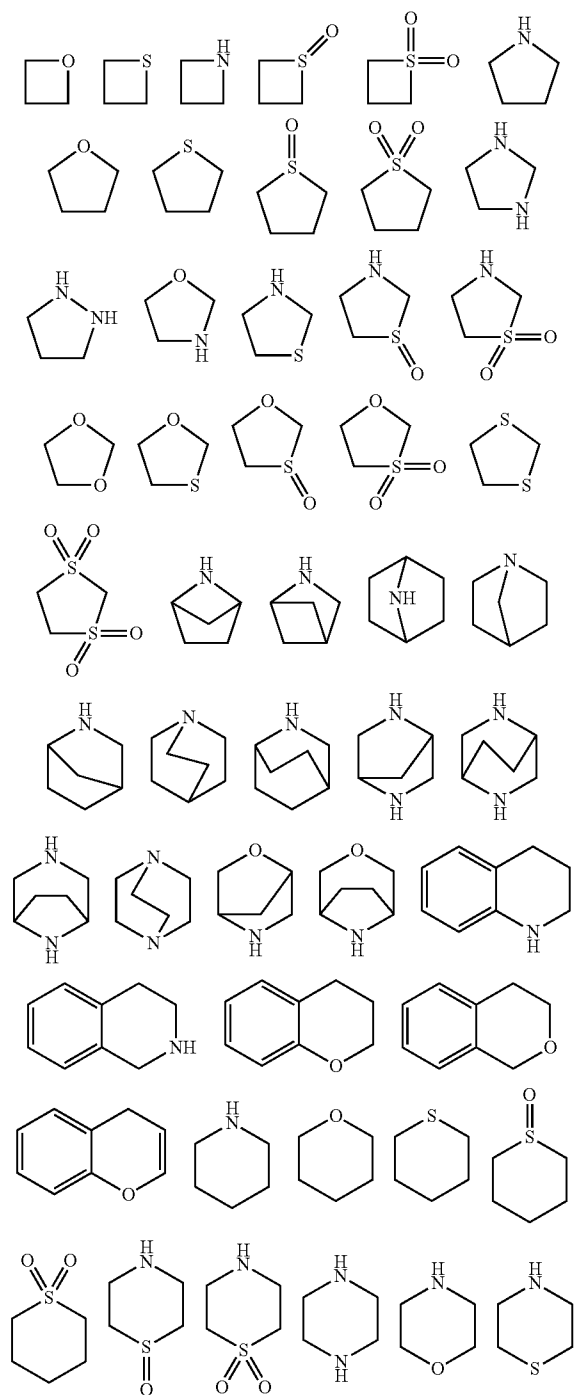
[0214] The term “C<sub>3-n</sub>-cycloalkenyl”, wherein n is an integer 3 to n, either alone or in combination with another radical, denotes a cyclic, unsaturated but nonaromatic, unbranched hydrocarbon radical with 3 to n C atoms, at least two of which are bonded to each other by a double bond. For example the term C<sub>3-7</sub>-cycloalkenyl includes cyclobutenyl, cyclopentenyl, cyclopentadienyl, cyclohexenyl, cyclohexadienyl, cycloheptenyl, cycloheptadienyl and cycloheptatrienyl.

[0215] 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 dihydronaphthyl. More preferably the term “aryl” as used herein, either alone or in combination with another radical, denotes phenyl or naphthyl, most preferably phenyl.

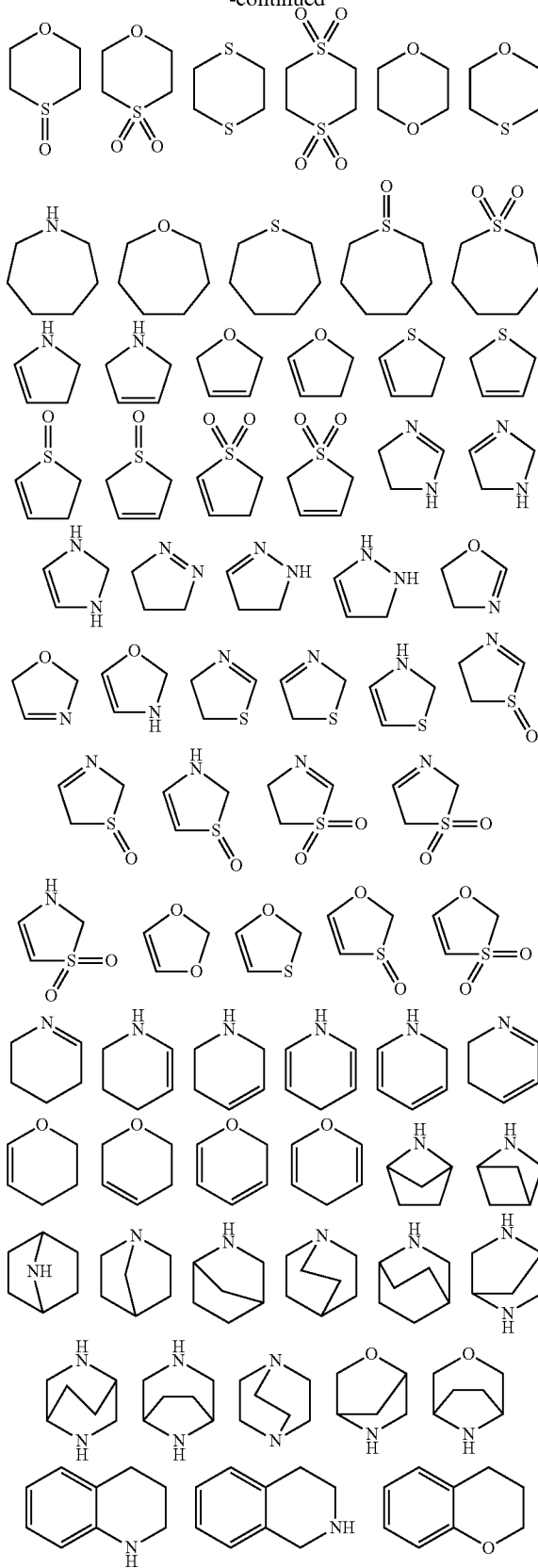
[0216] The term “heterocyclyl” means a saturated or unsaturated mono-, bi-, tri- or spirocarbocyclic, preferably mono-, bi- or spirocyclic-ring system containing one or more heteroatoms selected from N, O or S(O), with r=0, 1 or 2, which in addition may have a carbonyl group. More preferably the term “heterocyclyl” as used herein, either 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), 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, oxetanyl, pyr-

rolidinyl, tetrahydrofuranyl, piperidinyl, tetrahydropyranyl, azepanyl, piperazinyl, morpholinyl, tetrahydrofuranonyl, tetrahydropyranonyl, pyrrolidinonyl, piperidinonyl, piperazinonyl and morpholinonyl.

[0217] Thus, the term “heterocyclyl” includes the following exemplary structures which are not depicted as radicals as each form may be attached through a covalent bond to any atom so long as appropriate valences are maintained:

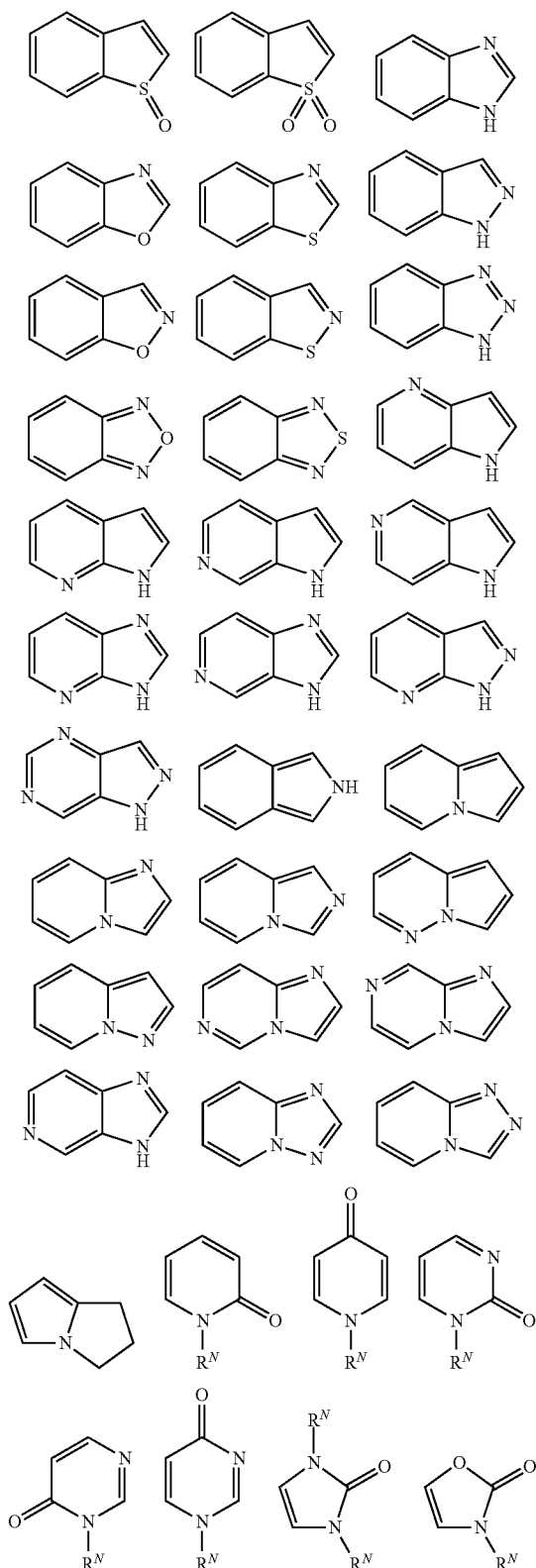


-continued





-continued

 $R^N$  = H or residue attached via a C atom

**[0220]** 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.

#### Pharmacological Activity

**[0221]** The activity of the compounds of the invention may be demonstrated using the following assay:

**[0222]** 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.

**[0223]** MIN6 cells [Miyazaki J et al. Endocrinology. 1990 July; 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, 50  $\mu$ M  $\beta$ -mercaptoethanol, 0.3 mg/mL Genitacin, 2 mM GlutaMAX at 37° C. 5% CO<sub>2</sub>. For the assay, the cells are seeded in Optiplates (white, 384-well, 160 W—barcoded, TC, sterile with lid, Cat. No. #6007688 (Perkin Elmer); 10000 cells/well; 50  $\mu$ l). The plates 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  $\mu$ l of the test compound are added, the compounds are diluted using stimulating buffer (140 mM NaCl, 3.6 mM KCl, 0.5 mM NaH<sub>2</sub>PO<sub>4</sub>, 0.5 mM MgSO<sub>4</sub>, 1.5 mM CaCl<sub>2</sub>, 10 mM Hepes, 5 mM NaHCO<sub>3</sub>; pH 7.4. 0.5 mM IBMX and 0.1% BSA, the final DMSO concentration is 1%). After 45 minutes incubation at room temperature (approx. 20° C.), the cAMP concentrations are determined using the AlphaScreen cAMP Assay Kit (Cat. No. #6760625R from PerkinElmer). 10  $\mu$ l of Biotin-cAMP (final concentration 1 U/well in lysing buffer (5 mM Hepes (pH 7.4), 0.1% BSA, 0.5% Tween) and 10  $\mu$ L Bead solution (final concentration 1 U/well in lysing buffer) are added. The plates are incubated for 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.

**[0224]** The compounds according to the invention typically have EC<sub>50</sub> values in the range from about 1 nM to about 10  $\mu$ M, preferably from 1 nM to 1  $\mu$ M, preferably less than 1  $\mu$ M, particularly preferably less than 500 nM, most particularly preferably less than 100 nM.

**[0225]** EC<sub>50</sub> values (cAMP assay) 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 No. | EC <sub>50</sub> [nM] | Example No. | EC <sub>50</sub> [nM] | Example No. | EC <sub>50</sub> [nM] | Example No. | EC <sub>50</sub> [nM] |
|-------------|-----------------------|-------------|-----------------------|-------------|-----------------------|-------------|-----------------------|
| 1           | 82                    | 2           | 213                   | 3           | 204                   | 4           | 1459                  |
| 5           | 62                    | 6           | 1297                  | 7           | 1198                  | 8           | 120                   |
| 9           | 224                   | 10          | 748                   | 11          | 136                   | 12          | 72                    |
| 13          | 132                   | 14          | 145                   | 15          | 157                   | 16          | 66                    |
| 17          | 680                   | 18          | 5                     | 19          | 21                    | 20          | 7                     |
| 21          | 33                    | 22          | 210                   | 23          | 18                    | 24          | 42                    |

-continued

| Example No. | EC <sub>50</sub> [nM] | Example No. | EC <sub>50</sub> [nM] | Example No. | EC <sub>50</sub> [nM] | Example No. | EC <sub>50</sub> [nM] |
|-------------|-----------------------|-------------|-----------------------|-------------|-----------------------|-------------|-----------------------|
| 25          | 97                    | 26          | 360                   | 27          | 1795                  | 28          | 159                   |
| 29          | 118                   | 30          | 176                   | 31          | 48                    | 32          | 35                    |
| 33          | 639                   | 34          | 86                    | 35          | 136                   | 36          | 358                   |
| 37          | 142                   | 38          | 9                     | 39          | 3                     | 40          | 7                     |
| 41          | 11                    | 42          | 2                     | 43          | 14                    | 44          | 47                    |
| 45          | 25                    | 46          | 3                     | 47          | 1862                  | 48          | 1342                  |
| 49          | 149                   | 50          | 505                   | 51          | 140                   | 52          | 211                   |
| 53          | 120                   | 54          | 129                   | 55          | 106                   | 56          | 2777                  |
| 57          | 3751                  | 58          | 2205                  | 59          | 167                   | 60          | 76                    |
| 61          | 13                    | 62          | 786                   | 63          | 42                    | 64          | 934                   |
| 65          | 1166                  | 66          | 636                   | 67          | 219                   | 68          | 544                   |
| 69          | 1117                  | 70          | 489                   | 71          | 90                    | 72          | 14                    |
| 73          | 1667                  | 74          | 1014                  | 75          | 170                   | 76          | 71                    |
| 77          | 55                    | 78          | 9                     | 79          | 210                   | 80          | 75                    |
| 81          | 98                    | 82          | 65                    | 83          | 15                    | 84          | 140                   |
| 85          | 46                    | 86          | 171                   | 87          | 443                   | 88          | 349                   |
| 89          | 240                   | 90          | 8                     | 91          | 44                    | 92          | 151                   |
| 93          | 209                   | 94          | 349                   | 95          | 229                   | 96          | 192                   |
| 97          | 59                    | 98          | 71                    | 99          | 37                    | 100         | 810                   |
| 101         | 441                   | 102         | 109                   | 103         | 168                   | 104         | 180                   |
| 105         | 144                   | 106         | 253                   | 107         | 114                   | 108         | 312                   |
| 109         | 85                    | 110         | 141                   | 111         | 64                    | 112         | 220                   |
| 113         | 597                   | 114         | 378                   | 115         | 164                   | 116         | 445                   |
| 117         | 275                   | 118         | 129                   | 119         | 147                   | 120         | 212                   |
| 121         | 180                   | 122         | 55                    | 123         | 637                   | 124         | 102                   |
| 125         | 180                   | 126         | 99                    | 127         | 108                   | 128         | 156                   |
| 129         | 548                   | 130         | 193                   | 131         | 175                   | 132         | 98                    |
| 133         | 516                   | 134         | 561                   | 135         | 914                   | 136         | 194                   |
| 137         | 264                   | 138         | 346                   | 139         | 263                   | 140         | 441                   |
| 141         | 231                   | 142         | 105                   | 143         | 168                   | 144         | 230                   |
| 145         | 1002                  | 146         | 64                    | 147         | 159                   | 148         | 395                   |
| 149         | 297                   | 150         | 238                   | 151         | 123                   | 152         | 109                   |
| 153         | 109                   | 154         | 508                   | 155         | 448                   | 156         | 114                   |
| 157         | 401                   | 158         | 359                   | 159         | 303                   | 160         | 229                   |
| 161         | 278                   | 162         | 501                   | 163         | 405                   | 164         | 221                   |
| 165         | 173                   | 166         | 359                   | 167         | 146                   | 168         | 261                   |
| 169         | 179                   | 170         | 208                   | 171         | 383                   | 172         | 226                   |
| 173         | 234                   | 174         | 170                   | 175         | 165                   | 176         | 346                   |
| 177         | 456                   | 178         | 237                   | 179         | 338                   | 180         | 289                   |
| 181         | 206                   | 182         | 319                   | 183         | 63                    | 184         | 149                   |
| 185         | 390                   | 186         | 617                   | 187         | 122                   | 188         | 311                   |
| 189         | 434                   | 190         | 820                   | 191         | 420                   | 192         | 421                   |
| 193         | 300                   | 194         | 325                   | 195         | 486                   | 196         | 215                   |
| 197         | 169                   | 198         | 715                   | 199         | 395                   | 200         | 449                   |
| 201         | 180                   | 202         | 171                   | 203         | 295                   | 204         | 302                   |
| 205         | 347                   | 206         | 312                   | 207         | 369                   | 208         | 181                   |
| 209         | 312                   | 210         | 593                   | 211         | 561                   | 212         | 350                   |
| 213         | 521                   | 214         | 418                   | 215         | 393                   | 216         | 424                   |
| 217         | 550                   | 218         | 216                   | 219         | 375                   | 220         | 183                   |
| 221         | 110                   | 222         | 545                   | 223         | 634                   | 224         | 157                   |
| 225         | 185                   | 226         | 179                   | 227         | 161                   | 228         | 379                   |
| 229         | 177                   | 230         | 297                   | 231         | 414                   | 232         | 422                   |
| 234         | 297                   | 235         | 307                   | 236         | 317                   | 237         | 408                   |
| 238         | 111                   | 239         | 424                   | 240         | 171                   | 241         | 245                   |
| 242         | 593                   | 243         | 309                   | 244         | 237                   | 245         | 322                   |
| 246         | 169                   | 247         | 51                    | 258         | 61                    |             |                       |

[0226] Alternatively, the effect of the compounds on the activation of GPR119 are determined as follows:

[0227] Quantitative detection of cAMP accumulation from cells expressing human GPR119 receptor is achieved using Perkin Elmer's LANCE cAMP-384 Kit (Cat#AD0264) according to the manufacturer's protocol. Briefly, HEK293 cells stably expressing a mutant form of the human GPR119 receptor as assay tool (Methionine 1 replaced with the amino acid sequence MKTIIALSYIFCLVFADYKDDDDA, and T327 & S329 changed to alanines; SEQ ID No. 1) are grown to 50-70% confluency in cell culture media (DMEM, 10% heat inactivated Fetal Bovine Serum, 50 I.U./mL penicillin, 50 µg/mL streptomycin, 10 mM HEPES, 20 µg/mL G418

Sulfate). On the day of the assay, GPR119 stable HEK293 cells are lifted from the tissue culture plate and 1000 cells/well are incubated along with various concentrations of test compounds for 20 min at 37° C. Detection Buffer (50 mM HEPES, 10 mM calcium chloride, 0.35% Triton X-100, 1 mg/mL BSA) containing cAMP-specific antibody is then added to all wells and allowed to equilibrate in the dark for 10 minutes at room temperature. Upon equilibration, Detection Buffer containing europium-labeled cAMP tracer complex is added to all wells and allowed to react for 1 hour at room temperature. After 1 hour, bound europium-labeled cAMP tracer is measured using a Perkin Elmer Envision plate reader. The quantity of cAMP generated in each well is derived from a standard curve. EC<sub>50</sub> is determined using nonlinear regression analysis of the cAMP values over a range of agonist concentration (12 points spanning the range from 30 µM to 100 µM).

[0228] EC<sub>50</sub> values (determined as described immediately above) 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 No. | EC <sub>50</sub> [nM] | Example No. | EC <sub>50</sub> [nM] | Example No. | EC <sub>50</sub> [nM] | Example No. | EC <sub>50</sub> [nM] |
|-------------|-----------------------|-------------|-----------------------|-------------|-----------------------|-------------|-----------------------|
| 248         | 54                    | 249         | 146                   | 250         | 45                    | 251         | 587                   |
| 252         | 193                   | 253         | 435                   | 254         | 518                   | 255         | 1547                  |
| 256         | 265                   | 257         | 801                   |             |                       |             |                       |

[0229] 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 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.

[0230] Accordingly, the present invention relates to a compound of general formula I as a medicament.

[0231] Furthermore, the present invention relates to the use of a compound of general formula I 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 human.

[0232] 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 need of such treatment a therapeutically effective amount of a compound or a pharmaceutical composition of the present invention.

[0233] Diseases and conditions mediated by agonists of the G-protein-coupled receptor GPR119 embrace metabolic diseases or conditions.

[0234] 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 macroangiopathies), metabolic acidosis or ketosis, reactive hypoglycaemia, hyperinsulinaemia, glucose

metabolic disorder, insulin resistance, metabolic syndrome, dyslipidaemias of different origins, atherosclerosis and related diseases, obesity, high blood pressure, chronic heart failure, oedema and hyperuricaemia.

**[0235]** 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 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.

**[0236]** Therefore according to another aspect the invention relates to compounds of formula I and pharmaceutical compositions according to the invention for use in preventing, delaying, slowing the progression of and/or treating metabolic diseases, particularly in improving the glycaemic control and/or beta cell function in the patient.

**[0237]** In another aspect the invention relates to compounds of formula I and pharmaceutical compositions according to the invention for use in preventing, delaying, slowing the progression of and/or treating type 2 diabetes, overweight, obesity, complications of diabetes and associated pathological conditions.

**[0238]** In addition the compounds and pharmaceutical compositions according to the invention are suitable for use in one or more of the following therapeutic processes:

**[0239]** 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, atherosclerosis, endothelial dysfunction or bone-related diseases (such as osteoporosis, rheumatoid arthritis or osteoarthritis);

**[0240]** for improving glycaemic control and/or reducing fasting plasma glucose, postprandial plasma glucose and/or the glycosylated haemoglobin HbA1c;

**[0241]** for preventing, delaying, slowing or reversing the progression of disrupted glucose tolerance, insulin resistance and/or metabolic syndrome to type 2 diabetes;

**[0242]** 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 retinopathy, nephropathy or neuropathies, diabetic foot, ulcers or macroangiopathies;

**[0243]** for reducing weight or preventing weight gain or assisting weight loss;

**[0244]** 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;

**[0245]** for maintaining and/or improving insulin sensitivity and/or preventing or treating hyperinsulinaemia and/or insulin resistance.

**[0246]** In particular, the compounds and pharmaceutical compositions according to the invention are suitable for the treatment of obesity, diabetes (comprising type 1 and 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).

**[0247]** The compounds according to the invention are most particularly suitable for treating type 2 diabetes mellitus.

**[0248]** The dose range of the compounds of general formula I applicable per day is usually from 0.001 to 10 mg, 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 mg, for example 0.5 to 500 mg.

**[0249]** 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 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.

**[0250]** 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.

#### Pharmaceutical Compositions

**[0251]** Suitable preparations for administering the compounds of formula I, optionally in 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 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.

**[0252]** 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, 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 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.

#### Combination Therapy

**[0253]** 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.

**[0254]** 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.

**[0255]** 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 $\beta$ -HSD1 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.

**[0256]** Therapeutic agents for the treatment of overweight and/or obesity are for example antagonists of the cannabinoid) receptor, MCH-1 receptor antagonists, MC4 receptor agonists, NPY5 or NPY2 antagonists,  $\beta$ 3-agonists, leptin or leptin mimetics, agonists of the 5HT2c receptor.

**[0257]** Therapeutic agents for the treatment of high blood pressure, chronic heart failure 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 prevention of high blood pressure and complications of diabetes, often combined with a diuretic such as hydrochlorothiazide.

**[0258]** The dosage for the combination partners mentioned above is usually  $\frac{1}{5}$  of the lowest dose normally recommended up to  $\frac{1}{1}$  of the normally recommended dose.

**[0259]** 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.

**[0260]** 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-protein-coupled receptor GPR119, in particular diseases or conditions as described hereinbefore and hereinafter.

**[0261]** 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

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 hereinbefore and hereinafter,

**[0262]** The use of the compound according to the invention in combination with the additional therapeutic agent may take place simultaneously or at staggered times.

**[0263]** 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.

**[0264]** 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.

**[0265]** 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

### Preliminary Remarks

**[0266]** As a rule,  $^1\text{H-NMR}$  and/or mass spectra have been obtained for the compounds prepared. The  $R_f$ -values are determined using Merck silica gel 60 F<sub>254</sub> plates and UV light at 254 nm. The terms "ambient temperature" and "room temperature" are used interchangeably and designate a temperature of about 20° C.

**[0267]** Parameters of analytical HPLC employed for characterization of products (TFA denotes trifluoroacetic acid, MeOH denotes methanol, EtOH denotes ethanol):

| Method:                        | 1  |                              |                  |                |
|--------------------------------|--|------------------------------|------------------|----------------|
| Device:                        | Agilent 1100 with DA- and MS-Detector              |                              |                  |                |
| Column:                        | XBridge C18, 4.6 $\times$ 30 mm, 3.5 $\mu\text{m}$ |                              |                  |                |
| Column Supplier:               | Waters   |                              |                  |                |
| Gradient/Solvent<br>Time [min] | % Sol<br>[H <sub>2</sub> O, 0.1%<br>TFA]           | % Sol<br>[MeOH, 0.1%<br>TFA] | Flow<br>[ml/min] | Temp<br>[° C.] |
| 0.00                           | 95   | 5                            | 4.0              | 60             |
| 0.15                           | 95   | 5                            | 4.0              | 60             |
| 1.70                           | 0  | 100                          | 4.0              | 60             |
| 2.25                           | 0  | 100                          | 4.0              | 60             |

| Method:                        | 2  |                              |                  |                |
|--------------------------------|--|------------------------------|------------------|----------------|
| Device:                        | Waters Alliance with DA- and MS-Detector           |                              |                  |                |
| Column:                        | XBridge C18, 4.6 $\times$ 30 mm, 3.5 $\mu\text{m}$ |                              |                  |                |
| Column Supplier:               | Waters   |                              |                  |                |
| Gradient/Solvent<br>Time [min] | % Sol<br>[H <sub>2</sub> O, 0.1%<br>TFA]           | % Sol<br>[MeOH, 0.1%<br>TFA] | Flow<br>[ml/min] | Temp<br>[° C.] |
| 0.00                           | 95   | 5                            | 4.0              | 60             |
| 0.20                           | 95   | 5                            | 4.0              | 60             |



-continued

|      |    |     |     |    |
|------|----|-----|-----|----|
| 1.50 | 0  | 100 | 4.0 | 60 |
| 1.75 | 0  | 100 | 4.0 | 60 |
| 1.85 | 95 | 5   | 4.0 | 60 |

|                  |  |
|------------------|--|
| Method:          | 3  |
| Device:          | Waters Alliance with DA- and MS-Detector |
| Column:          | XBridge C18, 4.6 × 30 mm, 3.5 μm         |
| Column Supplier: | Waters                                   |

| Gradient/Solvent<br>Time [min] | % Sol<br>[H <sub>2</sub> O, 0.1%<br>TFA] | % Sol<br>[MeOH, 0.1%<br>TFA] | Flow<br>[ml/min] | Temp<br>[° C.] |
|--------------------------------|--|------------------------------|------------------|----------------|
| 0.00                           | 95                                       | 5                            | 4.0              | 60             |
| 0.20                           | 95                                       | 5                            | 4.0              | 60             |
| 1.50                           | 0  | 100                          | 4.0              | 60             |
| 1.90                           | 0  | 100                          | 4.0              | 60             |
| 2.00                           | 95                                       | 5                            | 4.0              | 60             |

|                  |                                       |
|------------------|---------------------------------------|
| Method:          | 4                                     |
| Device:          | Agilent 1200 with DA- and MS-Detector |
| Column:          | XBridge C18, 3 × 30 mm, 2.5 μm        |
| Column Supplier: | Waters                                |

| Gradient/Solvent<br>Time [min] | % Sol<br>[H <sub>2</sub> O, 0.1% TFA] | % Sol<br>[MeOH] | Flow<br>[ml/min] | Temp<br>[° C.] |
|--------------------------------|---------------------------------------|-----------------|------------------|----------------|
| 0.00                           | 95                                    | 5               | 2.2              | 60.0           |
| 0.05                           | 95                                    | 5               | 2.2              | 60.0           |
| 1.40                           | 0                                     | 100             | 2.2              | 60.0           |
| 1.80                           | 0                                     | 100             | 2.9              | 60.0           |

|                  |                                       |
|------------------|---------------------------------------|
| Method:          | 5                                     |
| Device:          | Agilent 1100 with DA- and MS-Detector |
| Column:          | XBridge C18, 4.6 × 30 mm, 3.5 μm      |
| Column Supplier: | Waters                                |

| Gradient/Solvent<br>Time [min] | % Sol<br>[H <sub>2</sub> O, 0.1% HCOOH] | % Sol<br>[MeOH] | Flow<br>[ml/min] | Temp<br>[° C.] |
|--------------------------------|---|-----------------|------------------|----------------|
| 0.00                           | 95                                      | 5               | 4.0              | 60             |
| 0.15                           | 95                                      | 5               | 4.0              | 60             |
| 1.70                           | 0                                       | 100             | 4.0              | 60             |
| 2.25                           | 0                                       | 100             | 4.0              | 60             |

|                  |                                      |
|------------------|--------------------------------------|
| Method:          | 6                                    |
| Device:          | Waters 1525 with DA- and MS-Detector |
| Column:          | Sunfire C18_4.6 × 30 mm, 2.5 μm      |
| Column Supplier: | Waters                               |

| Gradient/Solvent<br>Time [min] | % Sol<br>[H <sub>2</sub> O, 0.1%<br>TFA] | % Sol<br>[MeOH, 0.1%<br>TFA] | Flow<br>[ml/min] | Temp<br>[° C.] |
|--------------------------------|--|------------------------------|------------------|----------------|
| 0.00                           | 95                                       | 5                            | 4.0              | 60             |
| 0.05                           | 95                                       | 5                            | 3.0              | 60             |
| 2.05                           | 0  | 100                          | 3.0              | 60             |
| 2.10                           | 0  | 100                          | 4.0              | 60             |
| 2.35                           | 0  | 100                          | 4.0              | 60             |

|                  |  |
|------------------|--|
| Method:          | 7  |
| Device:          | Waters Alliance with DA- and MS-Detector |
| Column:          | XBridge C18, 4.6 × 30 mm, 3.5 μm         |
| Column Supplier: | Waters                                   |

| Gradient/Solvent<br>Time [min] | % Sol<br>[H <sub>2</sub> O, 0.1% TFA] | % Sol<br>[MeOH] | Flow<br>[ml/min] | Temp<br>[° C.] |
|--------------------------------|---------------------------------------|-----------------|------------------|----------------|
| 0.00                           | 95                                    | 5               | 4.8              | 60             |
| 1.60                           | 0                                     | 100             | 4.8              | 60             |
| 1.85                           | 0                                     | 100             | 4.8              | 60             |
| 1.90                           | 95                                    | 5               | 4.8              | 60             |

|                  |                                       |
|------------------|---------------------------------------|
| Method:          | 8                                     |
| Device:          | Agilent 1100 with DA- and MS-Detector |
| Column:          | XBridge C18, 4.6 × 30 mm, 3.5 μm      |
| Column Supplier: | Waters                                |

| Gradient/<br>Solvent<br>Time [min] | % Sol<br>[H <sub>2</sub> O, 0.1%<br>NH <sub>4</sub> OH] | % Sol<br>[MeOH] | Flow<br>[ml/min] | Temp<br>[° C.] |
|------------------------------------|---|-----------------|------------------|----------------|
| 0.00                               | 95  | 5               | 4.0              | 60             |
| 0.15                               | 95  | 5               | 4.0              | 60             |
| 1.70                               | 0   | 100             | 4.0              | 60             |
| 2.25                               | 0   | 100             | 4.0              | 60             |

|                  |                                       |
|------------------|---------------------------------------|
| Method:          | 9                                     |
| Device:          | Agilent 1200 with DA- and MS-Detector |
| Column:          | XBridge C18, 3 × 30 mm, 2.5 μm        |
| Column Supplier: | Waters                                |

| Gradient/<br>Solvent<br>Time [min] | % Sol<br>[H <sub>2</sub> O, 0.1%<br>NH <sub>4</sub> OH] | % Sol<br>[MeOH] | Flow<br>[ml/min] | Temp<br>[° C.] |
|------------------------------------|---|-----------------|------------------|----------------|
| 0.00                               | 95  | 5               | 2.2              | 60.0           |
| 0.05                               | 95  | 5               | 2.2              | 60.0           |
| 1.40                               | 0   | 100             | 2.2              | 60.0           |
| 1.80                               | 0   | 100             | 2.9              | 60.0           |

|                  |                                      |
|------------------|--------------------------------------|
| Method:          | 10                                   |
| Device:          | Waters 1525 with DA- and MS-Detector |
| Column:          | Sunfire C18, 4.6 × 30 mm, 2.5 μm     |
| Column Supplier: | Waters                               |

| Gradient/Solvent<br>Time [min] | % Sol<br>[H <sub>2</sub> O, 0.1% TFA] | % Sol<br>[MeOH] | Flow<br>[ml/min] | Temp<br>[° C.] |
|--------------------------------|---------------------------------------|-----------------|------------------|----------------|
| 0.00                           | 95                                    | 5               | 4.0              | 60             |
| 0.05                           | 95                                    | 5               | 3.0              | 60             |
| 2.05                           | 0                                     | 100             | 3.0              | 60             |
| 2.10                           | 0                                     | 100             | 4.5              | 60             |
| 2.40                           | 0                                     | 100             | 4.5              | 60             |

|                  |                                       |
|------------------|---------------------------------------|
| Method:          | 11                                    |
| Device:          | Agilent 1200 with DA- and MS-Detector |
| Column:          | XBridge C18, 3.0 × 30 mm, 2.5 μm      |
| Column Supplier: | Waters                                |

-continued

| Gradient/Solvent<br>Time [min] | % Sol<br>[H <sub>2</sub> O, 0.1% NH <sub>4</sub> OH] | % Sol<br>[MeOH] | Flow<br>[ml/min] | Temp<br>[° C.] |
|--------------------------------|--|-----------------|------------------|----------------|
| 0.00                           | 95   | 5               | 2.2              | 60             |
| 0.30                           | 95   | 5               | 2.2              | 60             |
| 1.50                           | 0  | 100             | 2.2              | 60             |
| 1.55                           | 0  | 100             | 2.9              | 60             |
| 1.70                           | 0  | 100             | 2.9              | 60             |

Method: 12  
 Device: Agilent 1200 with DA- and MS-Detector  
 Column: Sunfire C18, 3.0 × 30 mm, 2.5 µm  
 Column Supplier: Waters

| Gradient/Solvent<br>Time [min] | % Sol<br>[H <sub>2</sub> O, 0.1% TFA] | % Sol<br>[MeOH] | Flow<br>[ml/min] | Temp<br>[° C.] |
|--------------------------------|---------------------------------------|-----------------|------------------|----------------|
| 0.00                           | 95                                    | 5               | 2.2              | 60             |
| 0.30                           | 95                                    | 5               | 2.2              | 60             |
| 1.50                           | 0                                     | 100             | 2.2              | 60             |
| 1.55                           | 0                                     | 100             | 2.9              | 60             |
| 1.65                           | 0                                     | 100             | 2.9              | 60             |

Method: 13  
 Device: Agilent 1200 with DA- and MS-Detector  
 Column: Sunfire C18, 3.0 × 30 mm, 2.5 µm  
 Column Supplier: Waters

| Gradient/Solvent<br>Time [min] | % Sol<br>[H <sub>2</sub> O, 0.1% TFA] | % Sol<br>[MeOH] | Flow<br>[ml/min] | Temp<br>[° C.] |
|--------------------------------|---------------------------------------|-----------------|------------------|----------------|
| 0.00                           | 95                                    | 5               | 1.8              | 60             |
| 0.25                           | 95                                    | 5               | 1.8              | 60             |
| 1.70                           | 0                                     | 100             | 1.8              | 60             |
| 1.75                           | 0                                     | 100             | 2.5              | 60             |
| 1.90                           | 0                                     | 100             | 2.5              | 60             |

Method: 14  
 Device: Waters ZQ2000 MS, Agilent HP100, binary Pump DAD 210-500 nm, Waters 2700 AS  
 Column: XBridge C18, 4.6 × 50 mm, 3.5 µm  
 Column Supplier: Waters

| Gradient/Solvent<br>Time [min] | % Sol<br>[H <sub>2</sub> O, 0.032%<br>NH <sub>4</sub> OH] | % Sol<br>[MeOH] | Flow<br>[ml/min] | Temp<br>[° C.] |
|--------------------------------|---|-----------------|------------------|----------------|
| 0.00                           | 95  | 5               | 1.5              | 40             |
| 2.00                           | 0   | 100             | 1.5              | 40             |

Method: 15  
 Device: Agilent 1100 with DA and Waters MS-Detector  
 Column: Sunfire C18\_4.6 × 50 mm, 3.5 µm  
 Column Supplier: Waters

| Gradient/Solvent<br>Time [min] | % Sol<br>[H <sub>2</sub> O, 0.1%<br>TFA] | % Sol<br>[CH <sub>3</sub> CN,<br>0.08% TFA] | Flow<br>[ml/min] | Temperature<br>[° C.] |
|--------------------------------|--|---|------------------|-----------------------|
| 0.00                           | 95                                       | 5   | 1.5              | 60                    |
| 2.00                           | 0  | 100   | 1.5              | 60                    |

-continued

|      |    |     |     |    |
|------|----|-----|-----|----|
| 2.50 | 0  | 100 | 1.5 | 60 |
| 2.60 | 95 | 5   | 1.5 | 60 |
| 0.00 | 95 | 5   | 1.5 | 60 |

Method: 16  
 Device: Waters ZQ2000 MS, Alliance 2695 PDA2996 210-500 nm, 2700 AS  
 Column: Sunfire C18, 4.6 × 50 mm, 3.5 µm  
 Column Supplier: Waters

| Gradient/Solvent<br>Time [min] | % Solvent<br>[H <sub>2</sub> O, 0.1%<br>TFA] | % Solvent<br>[MeOH] | Flow<br>[ml/min] | Temperature<br>[° C.] |
|--------------------------------|--|---------------------|------------------|-----------------------|
| 0.00                           | 80   | 20                  | 2.0              | 60                    |
| 1.70                           | 0  | 100                 | 2.0              | 60                    |
| 2.50                           | 0  | 100                 | 2.0              | 60                    |
| 2.60                           | 80   | 20                  | 2.0              | 60                    |

Method: 17  
 Device: Waters Acquity with DA- and MS-Detector  
 Column: Ascentis Express C18, 2.1 × 50 mm, 2.7 µm  
 Column Supplier: Supelco

| Gradient/Solvent<br>Time [min] | % Sol<br>[H <sub>2</sub> O, 0.1%<br>TFA] | % Sol<br>[CH <sub>3</sub> CN,<br>0.08% TFA] | Flow<br>[ml/min] | Temperature<br>[° C.] |
|--------------------------------|--|---|------------------|-----------------------|
| 0.00                           | 95                                       | 5   | 1.5              | 60                    |
| 0.70                           | 1  | 99  | 1.5              | 60                    |
| 0.80                           | 1  | 99  | 1.5              | 60                    |
| 0.81                           | 95                                       | 5   | 1.5              | 60                    |

Method: 18  
 Device: Waters Acquity with DA- and MS-Detector  
 Column: XBridge C18, 2.1 × 50 mm, 1.7 µm  
 Column Supplier: Waters

| Gradient/Solvent<br>Time [min] | % Sol<br>[H <sub>2</sub> O, 0.1%<br>NH <sub>4</sub> OH] | % Solvent<br>[CH <sub>3</sub> CN] | Flow<br>[ml/min] | Temperature<br>[° C.] |
|--------------------------------|---|-----------------------------------|------------------|-----------------------|
| 0.00                           | 95  | 5                                 | 1.5              | 60                    |
| 0.70                           | 0   | 100                               | 1.5              | 60                    |
| 0.80                           | 0   | 100                               | 1.5              | 60                    |
| 0.81                           | 95  | 5                                 | 1.5              | 60                    |
| 1.90                           | 95  | 5                                 | 0.2              | 60                    |
| 2.00                           | 0   | 100                               | 0.2              | 60                    |
| 3.00                           | 0   | 100                               | 0.2              | 60                    |

Method: 19  
 Device: Agilent 1200 with DA- and MS-Detector  
 Column: Sunfire C18, 3.0 × 30 mm, 2.5 µm  
 Column Supplier: Waters

| Gradient/Solvent<br>Time [min] | % Sol<br>[H <sub>2</sub> O, 0.1% HCOOH] | % Sol<br>[MeOH] | Flow<br>[ml/min] | Temp<br>[° C.] |
|--------------------------------|---|-----------------|------------------|----------------|
| 0.00                           | 95                                      | 5               | 1.8              | 60             |
| 0.25                           | 95                                      | 5               | 1.8              | 60             |

-continued

|      |   |     |     |    |
|------|---|-----|-----|----|
| 1.70 | 0 | 100 | 1.8 | 60 |
| 1.75 | 0 | 100 | 2.5 | 60 |
| 1.90 | 0 | 100 | 2.5 | 60 |

| Method:                            |  | 20   |                  |                       |
|------------------------------------|--|--|------------------|-----------------------|
| Column:                            |  | MAX-RP, 2 × 50 mm                                |                  |                       |
| Column Supplier:                   |  | Phenomenex Synergi                               |                  |                       |
| Gradient/<br>Solvent<br>Time [min] | % Solvent<br>[H <sub>2</sub> O, 0.025%<br>TFA] | % Solvent<br>[CH <sub>3</sub> CN,<br>0.025% TFA] | Flow<br>[ml/min] | Temperature<br>[° C.] |
| 0.00                               | 95   | 5  | 1.0              | 30                    |
| 2.50                               | 10   | 90   | 1.0              | 30                    |
| 3.50                               | 10   | 90   | 1.0              | 30                    |

| Method:                            |                                 | 21   |                  |                       |
|------------------------------------|---------------------------------|--|------------------|-----------------------|
| Device:                            |                                 | Berger/Thar/Waters Multi-gram II prep SFC system with UV detection |                  |                       |
| Column:                            |                                 | Chiralcel AD-H, 21 × 250 mm, 5 μm                                  |                  |                       |
| Column Supplier:                   |                                 | Chiral Technologies  |                  |                       |
| Gradient/<br>Solvent<br>Time [min] | % Solvent<br>[CO <sub>2</sub> ] | % Solvent<br>[EtOH + 0.5%<br>N,N-dimethyl-<br>ethylamine]          | Flow<br>[ml/min] | Temperature<br>[° C.] |
| 0.00                               | 90                              | 10   | 65               | 30                    |
| 15                                 | 90                              | 10   | 65               | 30                    |

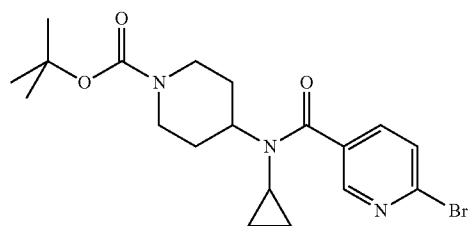
| Method:                            |  | 22   |                  |                       |
|------------------------------------|--|--|------------------|-----------------------|
| Column:                            |  | NX C18, 3 × 100 mm, 5 μm                                       |                  |                       |
| Column Supplier:                   |  | Phenomenex Gemini  |                  |                       |
| Gradient/<br>Solvent<br>Time [min] | % Solvent<br>[H <sub>2</sub> O, 0.04%<br>NH <sub>4</sub> OH] | % Solvent<br>[CH <sub>3</sub> CN, 0.04%<br>NH <sub>4</sub> OH] | Flow<br>[ml/min] | Temperature<br>[° C.] |
| 0.00                               | 95   | 5  | 2.0              | 30                    |
| 5.20                               | 5  | 95   | 2.0              | 30                    |

| Method:                            |   | 23                                    |                  |                       |
|------------------------------------|---|---------------------------------------|------------------|-----------------------|
| Device:                            |   | Agilent 1200 with DA- and MS-Detector |                  |                       |
| Column:                            |   | XBridge C18, 3 × 30 mm, 2.5 μm        |                  |                       |
| Column Supplier:                   |   | Waters                                |                  |                       |
| Gradient/<br>Solvent<br>Time [min] | % Solvent<br>[H <sub>2</sub> O, 0.1%<br>NH <sub>3</sub> ] | % Solvent<br>[Acetonitrile]           | Flow<br>[ml/min] | Temperature<br>[° C.] |
| 0.00                               | 97  | 3                                     | 2.2              | 60                    |
| 0.20                               | 97  | 3                                     | 2.2              | 60                    |
| 1.20                               | 0   | 100                                   | 2.2              | 60                    |
| 1.25                               | 0   | 100                                   | 3                | 60                    |
| 1.40                               | 0   | 100                                   | 3                | 60                    |

## Intermediate 1

4-[(6-Bromo-pyridine-3-carbonyl)-cyclopropyl-amino]-piperidine-1-carboxylic acid tert-butyl ester

[0268]

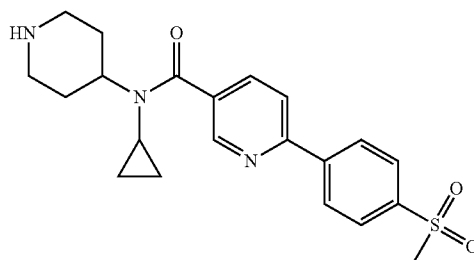


[0269] 2-(1H-Benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (2.80 g) is added to a mixture of 6-bromo-nicotinic acid (1.85 g) and triethylamine (1.28 mL) in N,N-dimethylformamide (25 mL) cooled in an ice bath. The mixture is stirred for 30 min prior to the addition of a solution of 4-cyclopropylamino-piperidine-1-carboxylic acid tert-butyl ester (2.00 g) in N,N-dimethylformamide (5 mL). The resulting mixture is stirred at room temperature overnight. Water and ethyl acetate are added and the organic phase is separated, washed with water, 1N aqueous NaOH solution, and brine, and dried over MgSO<sub>4</sub>. The solvent is evaporated in vacuo and the residue is triturated with diisopropyl ether to yield the title compound. LC (method 1): t<sub>R</sub>=1.59 min; Mass spectrum (ESI<sup>+</sup>): m/z=424 [M+H]<sup>+</sup>.

## Intermediate 2

N-Cyclopropyl-6-(4-methanesulfonyl-phenyl)-N-piperidin-4-yl-nicotinamide

[0270]

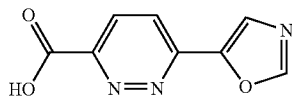


[0271] The title compound is prepared from 4-{cyclopropyl-[6-(4-methanesulfonyl-phenyl)-pyridine-3-carbonyl]-amino}-piperidine-1-carboxylic acid tert-butyl ester by treatment with trifluoroacetic acid in dichloromethane. LC (method 2): t<sub>R</sub>=0.70 min; Mass spectrum (ESI<sup>+</sup>): m/z=400 [M+H]<sup>+</sup>.

## Intermediate 3

6-Oxazol-5-yl-pyridazine-3-carboxylic acid

[0272]

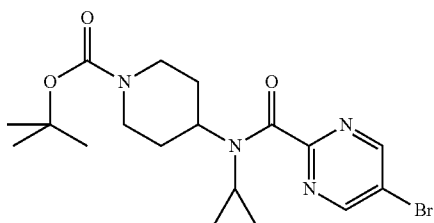


[0273] A mixture of 6-chloro-pyridazine-3-carboxylic acid (350 mg), 5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-2-triisopropylsilylanyl-oxazole (1.00 g),  $\text{PdCl}_2[1,1'$ -bis(diphenylphosphino)-ferrocene] $\cdot\text{CH}_2\text{Cl}_2$  complex (200 mg), and aqueous  $\text{Na}_2\text{CO}_3$  solution (2 M; 3.0 mL) in 1,4-dioxane (5 mL) and water (1 mL) is stirred overnight at 80° C. under an argon atmosphere. After cooling to room temperature, the reaction mixture is acidified with hydrochloric acid (4 N; 3 mL) and extracted with ethyl acetate. The combined extracts are washed with brine, dried over  $\text{MgSO}_4$  and concentrated in vacuo. The residue is dissolved in tetrahydrofuran, hydrochloric acid (4N; 4 mL) is added, and the mixture is stirred for 2 h at room temperature. The solvent is evaporated in vacuo and the residue is mixed with ethyl acetate and water. The aqueous phase is extracted with ethyl acetate and the combined extracts are washed with brine, dried over  $\text{MgSO}_4$ , and concentrated in vacuo. The residue is triturated with diethyl ether, filtered off and dried to give the title product. LC (method 2):  $t_R$ =0.45 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$ =192 [M+H]<sup>+</sup>.

## Intermediate 4

4-[(5-Bromopyrimidine-2-carbonyl)-cyclopropyl-amino]-piperidine-1-carboxylic acid tert-butyl ester

[0274]

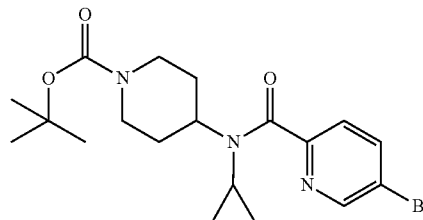


[0275] The title compound is prepared from 4-cyclopropylamino-piperidine-1-carboxylic acid tert-butyl ester and 5-bromo-pyrimidine-2-carboxylic acid following a procedure analogous to that described for Intermediate 1. LC (method 5):  $t_R$ =1.59 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$ =425 [M+H]<sup>+</sup>.

## Intermediate 5

4-[(5-Bromo-pyridine-2-carbonyl)-cyclopropyl-amino]-piperidine-1-carboxylic acid tert-butyl ester

[0276]

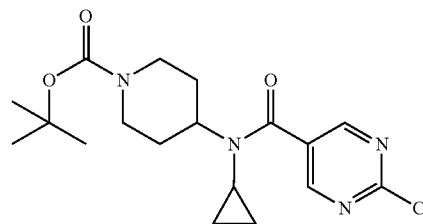


[0277] The title compound is prepared from 4-cyclopropylamino-piperidine-1-carboxylic acid tert-butyl ester and 5-bromo-pyridine-2-carboxylic acid following a procedure analogous to that described for Intermediate 1. LC (method 5):  $t_R$ =1.66 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$ =424 [M+H]<sup>+</sup>.

## Intermediate 6

4-[(2-Chloro-pyrimidine-5-carbonyl)-cyclopropyl-amino]-piperidine-1-carboxylic acid tert-butyl ester

[0278]

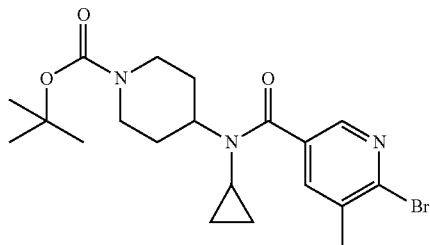


[0279] A mixture of 2-chloro-pyrimidine-5-carboxylic acid (2.0 g), chloro-N,N,N',N'-tetramethylformamidine hexafluorophosphate (4.12 g) and ethyldiisopropylamine (6.4 mL) in tetrahydrofuran (10 mL) is stirred at room temperature for 45 min. 4-Cyclopropylamino-piperidine-1-carboxylic acid tert-butyl ester (2.9 g) in tetrahydrofuran (5 mL) is added and stirring is continued for 1 h. The mixture is concentrated in vacuo and the residue is purified by preparative HPLC (C18 RP Sunfire,  $\text{H}_2\text{O}/\text{MeOH}+0.1\%$  TFA) to yield the desired product. LC (method 6):  $t_R$ =1.89 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$ =381 [M+H]<sup>+</sup>.

## Intermediate 7

4-[(6-Bromo-5-methyl-pyridine-3-carbonyl)-cyclopropyl-amino]-piperidine-1-carboxylic acid tert-butyl ester

[0280]

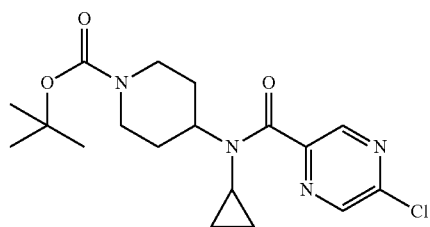


[0281] The title compound is prepared from 4-cyclopropylamino-piperidine-1-carboxylic acid tert-butyl ester and 6-bromo-5-methyl-nicotinic acid following a procedure analogous to that described for Intermediate 6. LC (method 4):  $t_R$ =1.24 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$ =438 [M+H]<sup>+</sup>.

## Intermediate 8

4-[(5-Chloro-pyrazine-2-carbonyl)-cyclopropyl-amino]-piperidine-1-carboxylic acid tert-butyl ester

[0282]

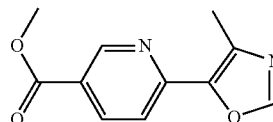


[0283] A catalytic amount of 4-dimethylaminopyridine is added to a mixture of 4-cyclopropylamino-piperidine-1-carboxylic acid tert-butyl ester (733 mg) and ethyldiisopropylamine (1.33 mL) in dichloromethane. 5-Chloro-pyrazine-2-carbonyl chloride (540 mg) in dichloromethane is added drop wise at room temperature and the resulting mixture is stirred for 2 h. Dichloromethane and water are added and the organic phase is separated, washed with water, dried over MgSO<sub>4</sub>, and concentrated in vacuo. The residue is chromatographed on silica gel (cyclohexane/ethyl acetate 2:1→1:2) to afford the title compound. LC (method 4):  $t_R$ =1.21 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$ =381 [M+H]<sup>+</sup>.

## Intermediate 9

6-(4-Methyl-oxazol-5-yl)-nicotinic acid methyl ester

[0284]

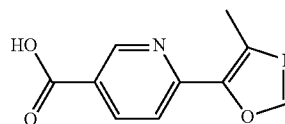


[0285] A mixture of 6-formyl-nicotinic acid methyl ester (500 mg), 1-(1-isocyano-ethanesulfonyl)-4-methyl-benzene (635 mg), and potassium carbonate (550 mg) in methanol (15 mL) is heated under reflux for 3 h. The reaction mixture is poured into water and extracted with dichloromethane. The combined extracts are dried over MgSO<sub>4</sub>, and concentrated in vacuo to give the title compound. LC (method 5):  $t_R$ =1.35 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$ =219 [M+H]<sup>+</sup>.

## Intermediate 10

6-(4-Methyl-oxazol-5-yl)-nicotinic acid

[0286]

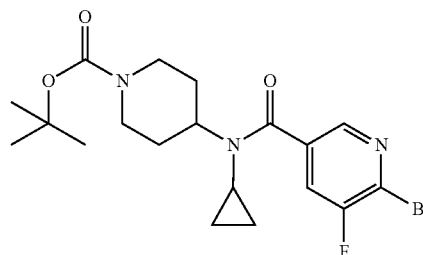


[0287] The title compound is prepared by treating 6-(4-methyl-oxazol-5-yl)-nicotinic acid methyl ester with aqueous NaOH solution in methanol. LC (method 5):  $t_R$ =1.11 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$ =205 [M+H]<sup>+</sup>.

## Intermediate 11

4-[(6-Bromo-5-fluoro-pyridine-3-carbonyl)-cyclopropyl-amino]-piperidine-1-carboxylic acid tert-butyl ester

[0288]

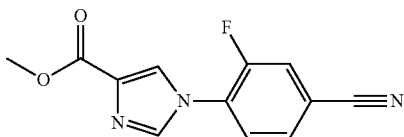


[0289] The title compound is prepared from 4-cyclopropylamino-piperidine-1-carboxylic acid tert-butyl ester and 6-bromo-5-fluoro-nicotinic acid following a procedure analogous to that described for Intermediate 6. LC (method 4):  $t_R$ =1.25 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$ =442 [M+H]<sup>+</sup>.

## Intermediate 12

1-(4-Cyano-2-fluoro-phenyl)-1H-imidazole-4-carboxylic acid methyl ester

[0290]

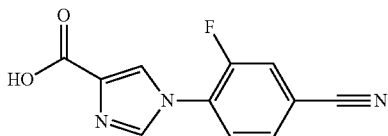


[0291] A mixture of 3,4-difluorobenzonitrile (193 mg), 1H-imidazole-4-carboxylic acid methyl ester (160 mg), and potassium carbonate (150 mg) in N-methyl-2-pyrrolidinone (4 mL) is heated to 150° C. for 30 min in a microwave oven. After cooling to room temperature, the reaction mixture is diluted with water and ethyl acetate. The aqueous phase is extracted with ethyl acetate and the combined extracts are dried over MgSO<sub>4</sub> and concentrated in vacuo. The residue is triturated with t-butyl methyl ether, filtered off, and dried to give the title compound. LC (method 4): t<sub>R</sub>=0.78 min; Mass spectrum (ESI<sup>+</sup>): m/z=246 [M+H]<sup>+</sup>.

## Intermediate 13

1-(4-Cyano-2-fluoro-phenyl)-1H-imidazole-4-carboxylic acid

[0292]

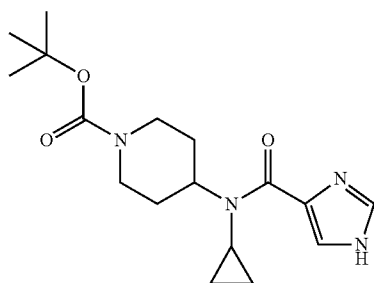


[0293] The title compound is prepared by treating 1-(4-cyano-2-fluoro-phenyl)-1H-imidazole-4-carboxylic acid methyl ester with aqueous NaOH solution in a mixture of tetrahydrofuran and methanol.

## Intermediate 14

4-[Cyclopropyl-(1H-imidazole-4-carbonyl)-amino]-piperidine-1-carboxylic acid tert-butyl ester

[0294]

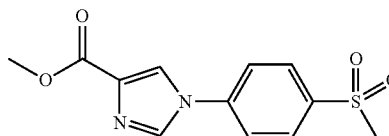


[0295] The title compound is prepared from 4-cyclopropylamino-piperidine-1-carboxylic acid tert-butyl ester and imidazole-4-carboxylic acid following a procedure analogous to that described for Intermediate 1. LC (method 4): t<sub>R</sub>=0.93 min; Mass spectrum (ESI<sup>+</sup>): m/z=335 [M+H]<sup>+</sup>.

## Intermediate 15

1-(4-Methanesulfonyl-phenyl)-1H-imidazole-4-carboxylic acid methyl ester

[0296]

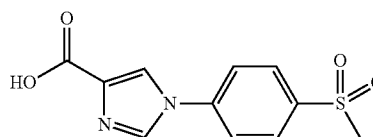


[0297] The title compound is prepared from 1-fluoro-4-methanesulfonyl-benzene and imidazole-4-carboxylic acid methyl ester following a procedure analogous to that described for Intermediate 12. The crude product is used without further purification. Mass spectrum (ESI<sup>+</sup>): m/z=281 [M+H]<sup>+</sup>.

## Intermediate 16

1-(4-Methanesulfonyl-phenyl)-1H-imidazole-4-carboxylic acid

[0298]

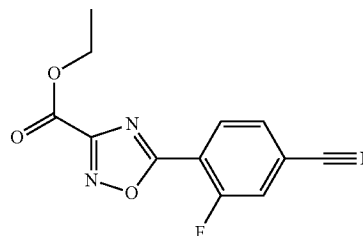


[0299] The title compound is prepared by treating 1-(4-methanesulfonyl-phenyl)-1H-imidazole-4-carboxylic acid methyl ester with aqueous NaOH solution in methanol. The crude product is used without further purification.

## Intermediate 17

5-(4-Cyano-2-fluoro-phenyl)-[1,2,4]oxadiazole-3-carboxylic acid ethyl ester

[0300]

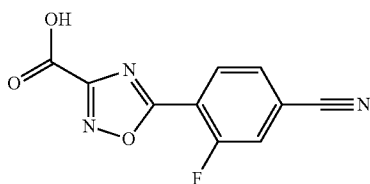


[0301] Amino-hydroxyimino-acetic acid ethyl ester (350 mg) is added to a mixture of 4-cyano-2-fluoro benzoyl chloride (450 mg) and 2,6-dimethylpyridine (1 mL) in dichloromethane (3 mL) and the mixture is stirred overnight at room temperature. The reaction mixture is diluted with water and the organic phase is separated, washed with 1 N hydrochloric acid, water, and brine, dried over  $\text{MgSO}_4$  and concentrated in vacuo. The residue is heated to  $170^\circ\text{C}$ . for 2 h to accomplish complete ring closure. The crude product is purified by silica gel chromatography (cyclohexane/ethyl acetate 65:35) to afford the title compound. LC (method 7):  $t_R=1.08$  min; Mass spectrum ( $\text{ESI}^+$ ):  $m/z=262$   $[\text{M}+\text{H}]^+$ .

Intermediate 18

5-(4-Cyano-2-fluoro-phenyl)-[1,2,4]oxadiazole-3-carboxylic acid

[0302]

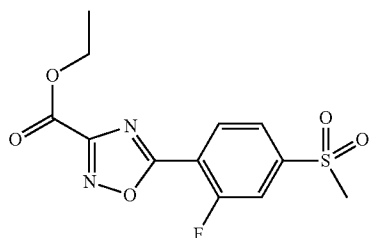


[0303] The title compound is prepared by treating 5-(4-cyano-2-fluoro-phenyl)-[1,2,4]oxadiazole-3-carboxylic acid ethyl ester with 1 M aqueous LiOH solution in a mixture of tetrahydrofuran and methanol. LC (method 7):  $t_R=0.69$  min; Mass spectrum ( $\text{ESI}^+$ ):  $m/z=234$   $[\text{M}+\text{H}]^+$ .

Intermediate 19

5-(2-Fluoro-4-methanesulfonyl-phenyl)-[1,2,4]oxadiazole-3-carboxylic acid ethyl ester

[0304]

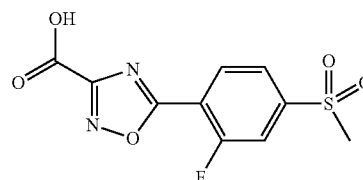


[0305] The title compound is prepared from 2-fluoro-4-methanesulfonyl-benzoyl chloride and amino-hydroxyimino-acetic acid ethyl ester following a procedure analogous to that described for Intermediate 17. LC (method 7):  $t_R=0.97$  min; Mass spectrum ( $\text{ESI}^+$ ):  $m/z=315$   $[\text{M}+\text{H}]^+$ .

Intermediate 20

5-(2-Fluoro-4-methanesulfonyl-phenyl)-[1,2,4]oxadiazole-3-carboxylic acid

[0306]

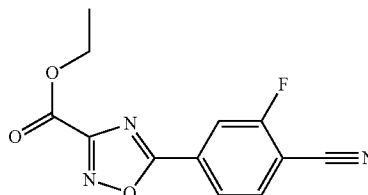


[0307] The title compound is prepared by treating 5-(2-fluoro-4-methanesulfonyl-phenyl)-[1,2,4]oxadiazole-3-carboxylic acid ethyl ester with 1 M aqueous LiOH solution tetrahydrofuran. LC (method 7):  $t_R=0.57$  min; Mass spectrum ( $\text{ESI}^+$ ):  $m/z=287$   $[\text{M}+\text{H}]^+$ .

Intermediate 21

5-(4-Cyano-3-fluoro-phenyl)-[1,2,4]oxadiazole-3-carboxylic acid ethyl ester

[0308]

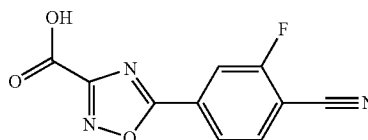


[0309] The title compound is prepared from 4-cyano-3-fluoro-benzoyl chloride and amino-hydroxyimino-acetic acid ethyl ester following a procedure analogous to that described for Intermediate 17. The ring closure is accomplished by heating in acetic acid and ethanol under reflux. LC (method 4):  $t_R=1.02$  min; Mass spectrum ( $\text{ESI}^+$ ):  $m/z=262$   $[\text{M}+\text{H}]^+$ .

Intermediate 22

5-(4-Cyano-3-fluoro-phenyl)-[1,2,4]oxadiazole-3-carboxylic acid

[0310]



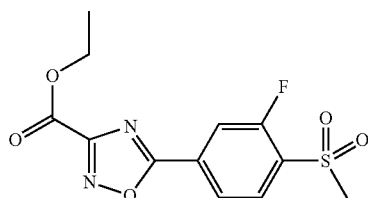
[0311] The title compound is prepared by treating 5-(4-cyano-3-fluoro-phenyl)-[1,2,4]oxadiazole-3-carboxylic acid

ethyl ester with 1 M aqueous LiOH solution in a tetrahydrofuran. LC (method 4):  $t_R=0.68$  min; Mass spectrum (ESI<sup>+</sup>):  $m/z=234$  [M+H]<sup>+</sup>.

## Intermediate 23

5-(3-Fluoro-4-methanesulfonyl-phenyl)-[1,2,4]oxadiazole-3-carboxylic acid ethyl ester

[0312]

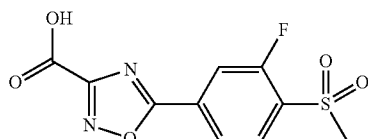


[0313] The title compound is prepared from 3-fluoro-4-methanesulfonyl-benzoyl chloride and amino-hydroxy-imino-acetic acid ethyl ester following a procedure analogous to that described for Intermediate 17. The ring closure is accomplished by heating in acetic acid and ethanol under reflux. LC (method 5):  $t_R=1.27$  min; Mass spectrum (ESI<sup>+</sup>):  $m/z=315$  [M+H]<sup>+</sup>.

## Intermediate 24

5-(3-Fluoro-4-methanesulfonyl-phenyl)-[1,2,4]oxadiazole-3-carboxylic acid

[0314]

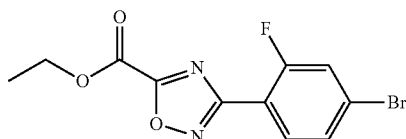


[0315] The title compound is prepared by treating 5-(3-fluoro-4-methanesulfonyl-phenyl)-[1,2,4]oxadiazole-3-carboxylic acid ethyl ester with 1 M aqueous LiOH solution tetrahydrofuran. LC (method 5):  $t_R=0.72$  min; Mass spectrum (ESI<sup>+</sup>):  $m/z=287$  [M+H]<sup>+</sup>.

## Intermediate 25

3-(4-Bromo-2-fluoro-phenyl)-[1,2,4]oxadiazole-5-carboxylic acid ethyl ester

[0316]

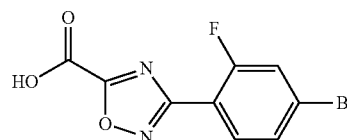


[0317] Ethyl oxalyl chloride (165  $\mu$ L) is added to a mixture of 4-bromo-2-fluoro-N-hydroxy-benzamidine (330 mg) and 2,6-dimethylpyridine (1 mL) in dichloromethane (4 mL) and the resulting mixture is stirred for 2 h at room temperature. The mixture is concentrated in vacuo and the residue is chromatographed on silica gel (cyclohexane/ethyl acetate 7:3) to afford the title compound. LC (method 5):  $t_R=1.60$  min; Mass spectrum (ESI<sup>+</sup>):  $m/z=315$  [M+H]<sup>+</sup>.

## Intermediate 26

3-(4-Bromo-2-fluoro-phenyl)-[1,2,4]oxadiazole-5-carboxylic acid

[0318]

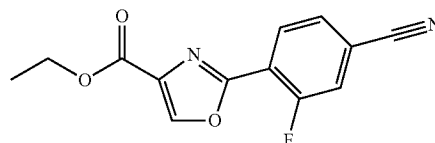


[0319] The title compound is prepared by treating 3-(4-bromo-2-fluoro-phenyl)-[1,2,4]oxadiazole-5-carboxylic acid ethyl ester with 1 M aqueous NaOH solution in a mixture of tetrahydrofuran and water. LC (method 5):  $t_R=1.30$  min; Mass spectrum (ESI<sup>-</sup>):  $m/z=285$  [M-H]<sup>-</sup>.

## Intermediate 27

2-(4-Cyano-2-fluoro-phenyl)-oxazole-4-carboxylic acid ethyl ester

[0320]



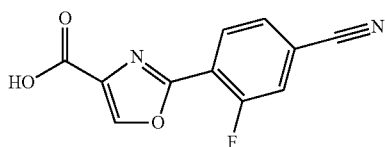
[0321] A mixture of 2-chloro-oxazole-4-carboxylic acid ethyl ester (250 mg), 4-cyano-2-fluorophenylboronic acid (277 mg), tetrakis-(triphenylphosphine)-palladium (115 mg), and aqueous Na<sub>2</sub>CO<sub>3</sub> solution (2 M; 1.84 mL) in 1,4-dioxane (10 mL) is heated to 150° C. under an argon atmosphere in a microwave oven. The reaction mixture is concentrated in vacuo. The residue is stirred in methanol for two days, filtered off and dried to give the title product. LC (method 8):  $t_R=1.41$  min; Mass spectrum (ESI<sup>+</sup>):  $m/z=261$  [M+H]<sup>+</sup>.



## Intermediate 28

2-(4-Cyano-2-fluoro-phenyl)-oxazole-4-carboxylic acid

[0322]

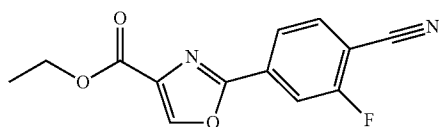


[0323] The title compound is prepared by treating 2-(4-cyano-2-fluoro-phenyl)-oxazole-4-carboxylic acid ethyl ester with 1 M aqueous NaOH solution in tetrahydrofuran. LC (method 8):  $t_R$ =1.42 min; Mass spectrum (ESI<sup>-</sup>):  $m/z$ =231 [M-H]<sup>-</sup>.

## Intermediate 29

2-(4-Cyano-3-fluoro-phenyl)-oxazole-4-carboxylic acid ethyl ester

[0324]

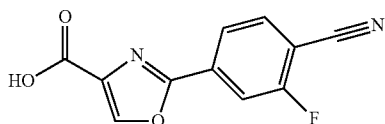


[0325] The title compound is prepared from 2-chloro-oxazole-4-carboxylic acid ethyl ester and 4-cyano-3-fluorophenylboronic acid following a procedure analogous to that described for Intermediate 27. LC (method 8):  $t_R$ =1.41 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$ =261 [M+H]<sup>+</sup>.

## Intermediate 30

2-(4-Cyano-3-fluoro-phenyl)-oxazole-4-carboxylic acid

[0326]

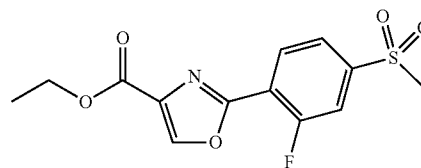


[0327] The title compound is prepared by treating 2-(4-cyano-3-fluoro-phenyl)-oxazole-4-carboxylic acid ethyl ester with 1 M aqueous NaOH solution in tetrahydrofuran. LC (method 8):  $t_R$ =1.19 min; Mass spectrum (ESI<sup>-</sup>):  $m/z$ =231 [M-H]<sup>-</sup>.

## Intermediate 31

2-(2-Fluoro-4-methanesulfonyl-phenyl)-oxazole-4-carboxylic acid ethyl ester

[0328]

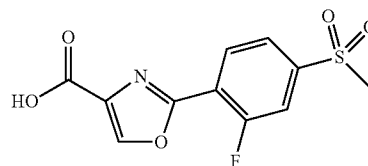


[0329] The title compound is prepared from 2-chloro-oxazole-4-carboxylic acid ethyl ester and 2-fluoro-4-methanesulfonyl-phenylboronic acid following a procedure analogous to that described for Intermediate 27. LC (method 8):  $t_R$ =1.30 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$ =314 [M+H]<sup>+</sup>.

## Intermediate 32

2-(2-Fluoro-4-methanesulfonyl-phenyl)-oxazole-4-carboxylic acid

[0330]

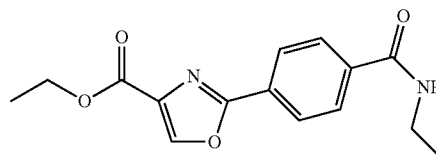


[0331] The title compound is prepared by treating 2-(2-fluoro-4-methanesulfonyl-phenyl)-oxazole-4-carboxylic acid ethyl ester with aqueous 1 M NaOH solution in tetrahydrofuran. LC (method 8):  $t_R$ =0.80 min; Mass spectrum (ESI<sup>-</sup>):  $m/z$ =284 [M-H]<sup>-</sup>.

## Intermediate 33

2-(4-Ethylcarbamoyl-phenyl)-oxazole-4-carboxylic acid ethyl ester

[0332]

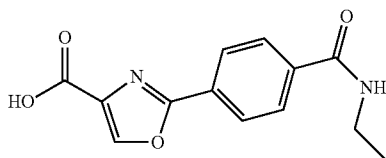


[0333] The title compound is prepared from 2-chloro-oxazole-4-carboxylic acid ethyl ester and 4-(ethylcarbamoyl)phenylboronic acid following a procedure analogous to that described for Intermediate 27. LC (method 8):  $t_R$ =1.36 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$ =289 [M+H]<sup>+</sup>.

## Intermediate 34

2-(4-Ethylcarbamoyl-phenyl)-oxazole-4-carboxylic acid

[0334]

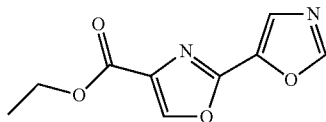


[0335] The title compound is prepared by treating 2-(4-ethylcarbamoyl-phenyl)-oxazole-4-carboxylic acid ethyl ester with 1 M aqueous NaOH solution in tetrahydrofuran. LC (method 9):  $t_R=0.37$  min; Mass spectrum (ESI<sup>-</sup>):  $m/z=259$  [M-H]<sup>-</sup>.

## Intermediate 35

[2,5']Bioxazolyl-4-carboxylic acid ethyl ester

[0336]

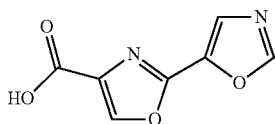


[0337] A mixture of 2-chloro-4-oxazolecarboxylic acid ethyl ester (200 mg), 5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-2-triisopropylsilyl-oxazole (596 mg) and aqueous Na<sub>2</sub>CO<sub>3</sub> solution (2 M; 1.49 mL) in N,N-dimethylformamide (8 mL) is sparged with argon for 10 minutes prior to the addition of PdCl<sub>2</sub>[1,1'-bis(diphenylphosphino)-ferrocene]\*CH<sub>2</sub>Cl<sub>2</sub> complex (93 mg). The reaction mixture is stirred overnight at 80° C. under an argon atmosphere. After cooling to room temperature, water and ethyl acetate 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 6:4→3:7) to afford the title compound. LC (method 8):  $t_R=1.09$  min; Mass spectrum (ESI<sup>+</sup>):  $m/z=209$  [M+H]<sup>+</sup>.

## Intermediate 36

[2,5']Bioxazolyl-4-carboxylic acid

[0338]

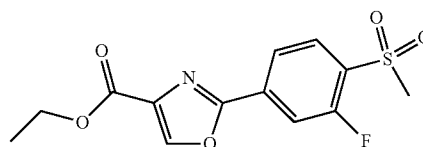


[0339] The title compound is prepared by treating [2,5']bioxazolyl-4-carboxylic acid ethyl ester with 1 M aqueous NaOH solution in tetrahydrofuran. LC (method 8):  $t_R=0.10$  min; Mass spectrum (ESI<sup>+</sup>):  $m/z=181$  [M+H]<sup>+</sup>.

## Intermediate 37

2-(3-Fluoro-4-methanesulfonyl-phenyl)-oxazole-4-carboxylic acid ethyl ester

[0340]

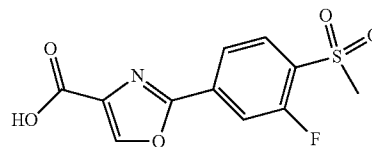


[0341] The title compound is prepared from 2-chloro-oxazole-4-carboxylic acid ethyl ester and 3-fluoro-4-methanesulfonyl-phenylboronic acid following a procedure analogous to that described for Intermediate 27. LC (method 8):  $t_R=1.29$  min; Mass spectrum (ESI<sup>+</sup>):  $m/z=314$  [M+H]<sup>+</sup>.

## Intermediate 38

2-(3-Fluoro-4-methanesulfonyl-phenyl)-oxazole-4-carboxylic acid

[0342]

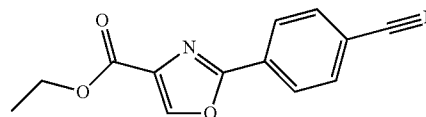


[0343] The title compound is prepared by treating 2-(3-fluoro-4-methanesulfonyl-phenyl)-oxazole-4-carboxylic acid ethyl ester with 1 M aqueous NaOH solution in tetrahydrofuran. LC (method 8):  $t_R=0.83$  min; Mass spectrum (ESI<sup>-</sup>):  $m/z=284$  [M-H]<sup>-</sup>.

## Intermediate 39

2-(4-Cyano-phenyl)-oxazole-4-carboxylic acid ethyl ester

[0344]

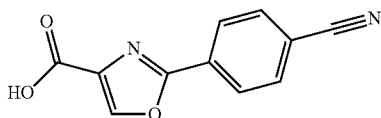


[0345] The title compound is prepared from 2-chloro-oxazole-4-carboxylic acid ethyl ester and 4-cyanophenylboronic acid following a procedure analogous to that described for Intermediate 27. LC (method 8):  $t_R=1.01$  min; Mass spectrum (ESI<sup>+</sup>):  $m/z=243$  [M+H]<sup>+</sup>.

## Intermediate 40

2-(4-Cyano-phenyl)-oxazole-4-carboxylic acid

[0346]

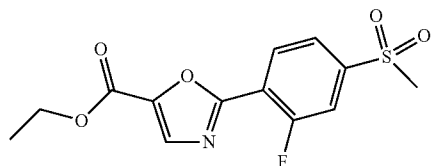


[0347] The title compound is prepared by treating 2-(4-cyano-phenyl)-oxazole-4-carboxylic acid ethyl ester with 1 M aqueous NaOH solution in tetrahydrofuran. LC (method 8):  $t_R$ =1.09 min; Mass spectrum (ESI<sup>-</sup>):  $m/z$ =213 [M-H]<sup>-</sup>.

## Intermediate 41

2-(2-Fluoro-4-methanesulfonyl-phenyl)-oxazole-5-carboxylic acid ethyl ester

[0348]

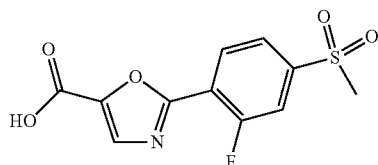


[0349] The title compound is prepared from 2-chloro-oxazole-5-carboxylic acid ethyl ester and 2-fluoro-4-methanesulfonyl-phenylboronic acid following a procedure analogous to that described for Intermediate 27. LC (method 8):  $t_R$ =1.34 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$ =314 [M+H]<sup>+</sup>.

## Intermediate 42

2-(2-Fluoro-4-methanesulfonyl-phenyl)-oxazole-5-carboxylic acid

[0350]

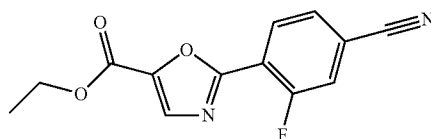


[0351] The title compound is prepared by treating 2-(2-fluoro-4-methanesulfonyl-phenyl)-oxazole-5-carboxylic acid ethyl ester with 1 M aqueous NaOH solution in tetrahydrofuran. LC (method 8):  $t_R$ =0.32 min; Mass spectrum (ESI<sup>-</sup>):  $m/z$ =284 [M-H]<sup>-</sup>.

## Intermediate 43

2-(4-Cyano-2-fluoro-phenyl)-oxazole-5-carboxylic acid ethyl ester

[0352]

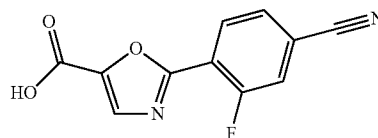


[0353] The title compound is prepared from 2-chloro-oxazole-5-carboxylic acid ethyl ester and 4-cyano-2-fluorophenylboronic acid following a procedure analogous to that described for Intermediate 27. LC (method 9):  $t_R$ =1.05 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$ =261 [M+H]<sup>+</sup>.

## Intermediate 44

2-(4-Cyano-2-fluoro-phenyl)-oxazole-5-carboxylic acid

[0354]

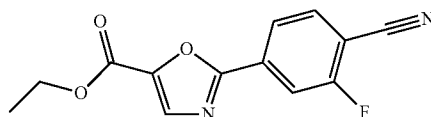


[0355] The title compound is prepared by treating 2-(4-cyano-2-fluoro-phenyl)-oxazole-4-carboxylic acid ethyl ester with 1 M aqueous NaOH solution in tetrahydrofuran. Mass spectrum (ESI<sup>+</sup>):  $m/z$ =233 [M+H]<sup>+</sup>.

## Intermediate 45

2-(4-Cyano-3-fluoro-phenyl)-oxazole-5-carboxylic acid ethyl ester

[0356]

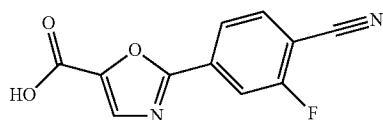


[0357] The title compound is prepared from 2-chloro-oxazole-5-carboxylic acid ethyl ester and 4-cyano-3-fluorophenylboronic acid following a procedure analogous to that described for Intermediate 27. LC (method 8):  $t_R$ =1.54 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$ =261 [M+H]<sup>+</sup>.

## Intermediate 46

2-(4-Cyano-3-fluoro-phenyl)-oxazole-5-carboxylic acid

[0358]

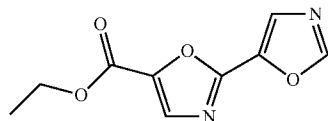


[0359] The title compound is prepared by treating 2-(4-cyano-3-fluoro-phenyl)-oxazole-4-carboxylic acid ethyl ester with 1 M aqueous NaOH solution in tetrahydrofuran. LC (method 8):  $t_R=1.13$  min; Mass spectrum (ESI<sup>-</sup>):  $m/z=231$  [M-H]<sup>-</sup>.

## Intermediate 47

[2,5']Bioxazolyl-5-carboxylic acid ethyl ester

[0360]

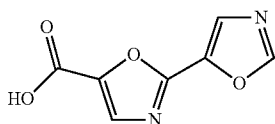


[0361] The title compound is prepared from 2-chloro-oxazole-5-carboxylic acid ethyl ester and 5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-2-triisopropylsilyl-oxazole following a procedure analogous to that described for Intermediate 36. LC (method 8):  $t_R=1.16$  min; Mass spectrum (ESI<sup>+</sup>):  $m/z=209$  [M+H]<sup>+</sup>.

## Intermediate 48

[2,5']Bioxazolyl-5-carboxylic acid

[0362]

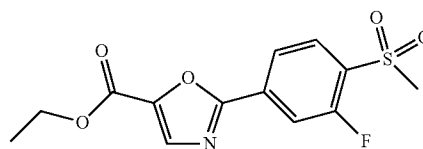


[0363] The title compound is prepared by treating [2,5']bioxazolyl-4-carboxylic acid ethyl ester with 1 M aqueous NaOH solution in tetrahydrofuran. Mass spectrum (ESI<sup>-</sup>):  $m/z=179$  [M-H]<sup>-</sup>.

## Intermediate 49

2-(3-Fluoro-4-methanesulfonyl-phenyl)-oxazole-5-carboxylic acid ethyl ester

[0364]

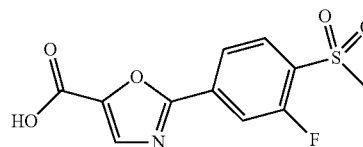


[0365] The title compound is prepared from 2-chloro-oxazole-5-carboxylic acid ethyl ester and 3-fluoro-4-methanesulfonyl-phenylboronic acid following a procedure analogous to that described for Intermediate 27. LC (method 8):  $t_R=1.37$  min; Mass spectrum (ESI<sup>+</sup>):  $m/z=314$  [M+H]<sup>+</sup>.

## Intermediate 50

2-(3-Fluoro-4-methanesulfonyl-phenyl)-oxazole-5-carboxylic acid

[0366]

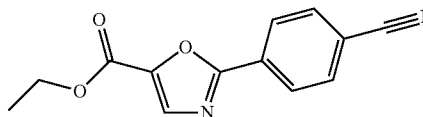


[0367] The title compound is prepared by treating 2-(3-fluoro-4-methanesulfonyl-phenyl)-oxazole-5-carboxylic acid ethyl ester with 1 M aqueous NaOH solution in tetrahydrofuran. LC (method 8):  $t_R=0.88$  min; Mass spectrum (ESI<sup>+</sup>):  $m/z=286$  [M+H]<sup>+</sup>.

## Intermediate 51

2-(4-Cyano-phenyl)-oxazole-5-carboxylic acid ethyl ester

[0368]

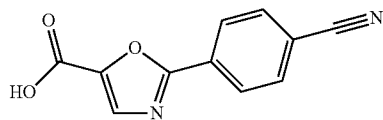


[0369] The title compound is prepared from 2-chloro-oxazole-5-carboxylic acid ethyl ester and 4-cyanophenylboronic acid following a procedure analogous to that described for Intermediate 27. LC (method 8):  $t_R=1.49$  min; Mass spectrum (ESI<sup>+</sup>):  $m/z=243$  [M+H]<sup>+</sup>.

## Intermediate 52

2-(4-Cyano-phenyl)-oxazole-5-carboxylic acid

[0370]

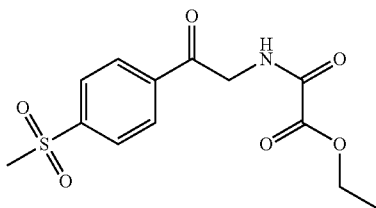


[0371] The title compound is prepared by treating 2-(4-cyano-phenyl)-oxazole-5-carboxylic acid ethyl ester with 1 M aqueous NaOH solution in tetrahydrofuran. LC (method 8):  $t_R$ =1.01 min; Mass spectrum (ESI<sup>-</sup>):  $m/z$ =213 [M-H]<sup>-</sup>.

## Intermediate 53

N-[2-(4-Methanesulfonyl-phenyl)-2-oxo-ethyl]-oxalamic acid ethyl ester

[0372]

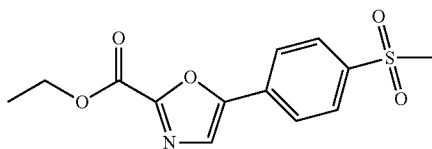


[0373] Chloro-oxo-acetic acid ethyl ester (805  $\mu$ L) is added drop wise under an argon atmosphere to a mixture of 2-amino-1-[4-(methylsulfonyl)phenyl]-ethanone hydrochloride (1.80 g) and triethylamine (2.01 mL) in dichloromethane (10 mL) at 0° C. The reaction mixture is stirred for 2.5 h at 0° C. Water is added and the aqueous phase is separated and extracted with dichloromethane. The combined organic phases are dried over MgSO<sub>4</sub> and concentrated in vacuo. The residue is chromatographed on silica gel (dichloromethane/methanol 99:1→95:5) to afford the title compound. LC (method 8):  $t_R$ =0.99 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$ =314 [M+H]<sup>+</sup>.

## Intermediate 54

5-(4-Methanesulfonyl-phenyl)-oxazole-2-carboxylic acid ethyl ester

[0374]



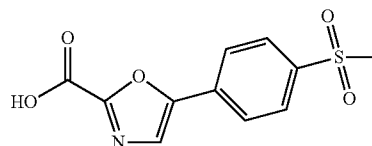
[0375] A mixture of N-[2-(4-methanesulfonyl-phenyl)-2-oxo-ethyl]-oxalamic acid ethyl ester (320 mg) and POCl<sub>3</sub> (975  $\mu$ L) is stirred under reflux for 11 h. After cooling to room

temperature, the mixture is poured onto ice water and stirred for 1 h. Dichloromethane is added and the aqueous phase is separated and extracted with dichloromethane. The combined organic phases are dried over MgSO<sub>4</sub> and concentrated in vacuo. The residue is chromatographed on silica gel (dichloromethane/methanol 99:1→90:10) to afford the title compound. LC (method 8):  $t_R$ =1.26 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$ =296 [M+H]<sup>+</sup>.

## Intermediate 55

5-(4-Methanesulfonyl-phenyl)-oxazole-2-carboxylic acid

[0376]

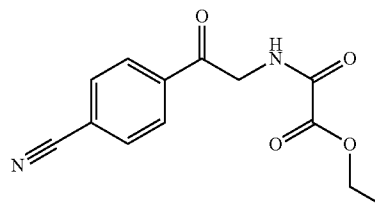


[0377] The title compound is prepared by treating 5-(4-methanesulfonyl-phenyl)-oxazole-2-carboxylic acid ethyl ester with 1 M aqueous NaOH solution in tetrahydrofuran. Mass spectrum (ESI<sup>-</sup>):  $m/z$ =266 [M-H]<sup>-</sup>.

## Intermediate 56

N-[2-(4-cyano-phenyl)-2-oxo-ethyl]-oxalamic acid ethyl ester

[0378]

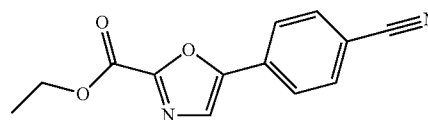


[0379] The title compound is prepared from 4-(2-amino-acetyl)-benzonitrile hydrochloride and chloro-oxo-acetic acid ethyl ester following a procedure analogous to that described for Intermediate 53. LC (method 8):  $t_R$ =1.13 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$ =261 [M+H]<sup>+</sup>.

## Intermediate 57

5-(4-Cyano-phenyl)-oxazole-2-carboxylic acid ethyl ester

[0380]

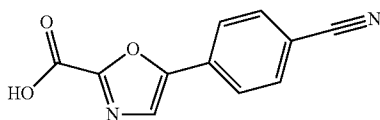


[0381] The title compound is prepared from N-[2-(4-cyano-phenyl)-2-oxo-ethyl]-oxalamic acid ethyl ester following a procedure analogous to that described for Intermediate 54. LC (method 8):  $t_R$ =1.42 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$ =243 [M+H]<sup>+</sup>.

## Intermediate 58

5-(4-Cyano-phenyl)-oxazole-2-carboxylic acid

[0382]

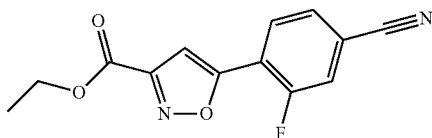


[0383] The title compound is prepared by treating 5-(4-cyano-phenyl)-oxazole-2-carboxylic acid ethyl ester with 1 M aqueous NaOH solution in tetrahydrofuran. LC (method 8):  $t_R$ =0.89 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$ =215 [M+H]<sup>+</sup>.

## Intermediate 59

5-(4-Cyano-2-fluoro-phenyl)-isoxazole-3-carboxylic acid ethyl ester

[0384]

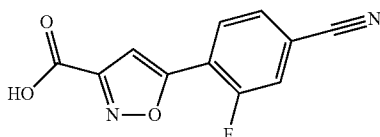


[0385] The title compound is prepared from 5-chloro-isoxazole-3-carboxylic acid ethyl ester and 4-cyano-2-fluorophenylboronic acid following a procedure analogous to that described for Intermediate 27. LC (method 8):  $t_R$ =1.09 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$ =261 [M+H]<sup>+</sup>.

## Intermediate 60

5-(4-Cyano-2-fluoro-phenyl)-isoxazole-3-carboxylic acid

[0386]

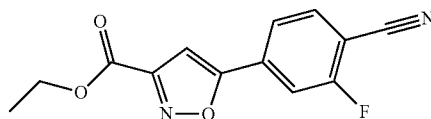


[0387] The title compound is prepared by treating 5-(4-cyano-2-fluoro-phenyl)-isoxazole-3-carboxylic acid ethyl ester with 1 M aqueous NaOH solution in tetrahydrofuran. LC (method 9):  $t_R$ =0.35 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$ =233 [M+H]<sup>+</sup>.

## Intermediate 61

5-(4-Cyano-3-fluoro-phenyl)-isoxazole-3-carboxylic acid ethyl ester

[0388]

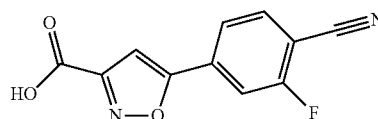


[0389] The title compound is prepared from 5-chloro-isoxazole-3-carboxylic acid ethyl ester and 4-cyano-3-fluorophenylboronic acid following a procedure analogous to that described for Intermediate 27. LC (method 8):  $t_R$ =1.09 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$ =261 [M+H]<sup>+</sup>.

## Intermediate 62

5-(4-Cyano-3-fluoro-phenyl)-isoxazole-3-carboxylic acid

[0390]

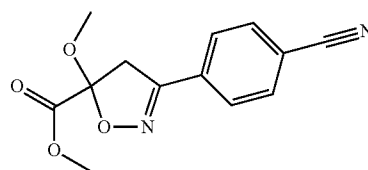


[0391] The title compound is prepared by treating 5-(4-cyano-3-fluoro-phenyl)-isoxazole-3-carboxylic acid ethyl ester with 1 M aqueous NaOH solution in tetrahydrofuran. LC (method 9):  $t_R$ =0.40 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$ =233 [M+H]<sup>+</sup>.

## Intermediate 63

3-(4-Cyano-phenyl)-5-methoxy-4,5-dihydro-isoxazole-5-carboxylic acid methyl ester

[0392]

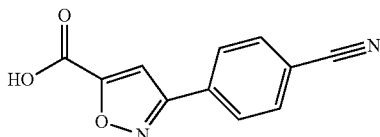


[0393] Triethylamine (288  $\mu$ L) is added drop wise to a mixture of 4-cyano-N-hydroxy-benzenecarboximidoyl chloride (150 mg) and 2-methoxy-acrylic acid methyl ester (116 mg) in dichloromethane (2 mL) under an argon atmosphere. The reaction mixture is stirred overnight at room temperature. Water is added and the aqueous phase is separated and extracted with ethyl acetate. The combined organic phases are washed with brine, dried over MgSO<sub>4</sub>, and concentrated in vacuo. The residue is chromatographed on silica gel (cyclo-

hexane/ethyl acetate 80:20→50:50) to afford the title compound. LC (method 9):  $t_R=0.92$  min; Mass spectrum (ESI<sup>+</sup>):  $m/z=261$  [M+H]<sup>+</sup>.

## Intermediate 64

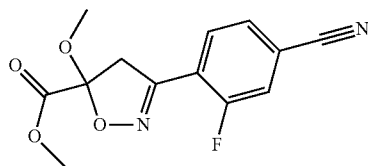
3-(4-Cyano-phenyl)-isoxazole-5-carboxylic acid  
[0394]



[0395] The title compound is prepared by treating 3-(4-cyano-phenyl)-5-methoxy-4,5-dihydro-isoxazole-5-carboxylic acid methyl ester with 1 M aqueous NaOH solution in tetrahydrofuran. LC (method 9):  $t_R=0.27$  min; Mass spectrum (ESI<sup>-</sup>):  $m/z=213$  [M-H]<sup>-</sup>.

## Intermediate 65

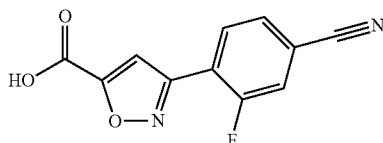
3-(4-Cyano-2-fluoro-phenyl)-5-methoxy-4,5-dihydro-isoxazole-5-carboxylic acid methyl ester  
[0396]



[0397] The title compound is prepared from 4-cyano-2-fluoro-N-hydroxy-benzenecarboximidoyl chloride and 2-methoxy-acrylic acid methyl ester acid following a procedure analogous to that described for Intermediate 63. LC (method 9):  $t_R=0.93$  min; Mass spectrum (ESI<sup>+</sup>):  $m/z=279$  [M+H]<sup>+</sup>.

## Intermediate 66

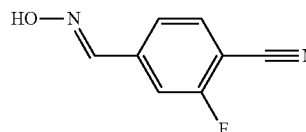
3-(4-Cyano-2-fluoro-phenyl)-isoxazole-5-carboxylic acid  
[0398]



[0399] The title compound is prepared by treating 3-(4-cyano-2-fluoro-phenyl)-5-methoxy-4,5-dihydro-isoxazole-5-carboxylic acid methyl ester with 1 M aqueous NaOH solution in tetrahydrofuran. LC (method 9):  $t_R=0.32$  min; Mass spectrum (ESI<sup>-</sup>):  $m/z=231$  [M-H]<sup>-</sup>.

## Intermediate 67

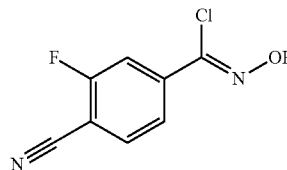
2-Fluoro-4-(hydroxyimino-methyl)-benzonitrile  
[0400]



[0401] Hydroxylamine sulfate (319 mg) is added to 2-fluoro-4-formyl-benzonitrile (500 mg) in methanol (3 mL) and the reaction mixture is stirred for 1.5 h at 70° C. After cooling to room temperature, water is added (3 mL) and the mixture is cooled in an ice bath. The precipitate is filtered off, washed with an ice cold methanol/water (2:1) mixture (7.5 mL) and with ice cold water (9 mL), and dried in an exsiccator to give the title compound. LC (method 9):  $t_R=0.58$  min; Mass spectrum (ESI<sup>-</sup>):  $m/z=163$  [M-H]<sup>-</sup>.

## Intermediate 68

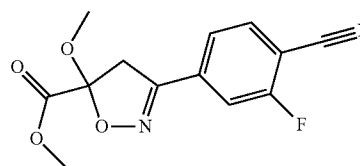
4-Cyano-3-fluoro-N-hydroxy-benzenecarboximidoyl chloride  
[0402]



[0403] N-Chlorosuccinimide (358 mg) is added to 2-fluoro-4-(hydroxyimino-methyl)-benzonitrile (367 mg) in N,N-dimethylformamide (4 mL) at room temperature and the reaction mixture is stirred overnight. The solvent is evaporated and water (4 mL) is added while stirring vigorously. The precipitate is filtered off, washed with water and dried in an exsiccator to give the title compound. LC (method 9):  $t_R=0.70$  min.

## Intermediate 69

3-(4-Cyano-3-fluoro-phenyl)-5-methoxy-4,5-dihydro-isoxazole-5-carboxylic acid methyl ester  
[0404]



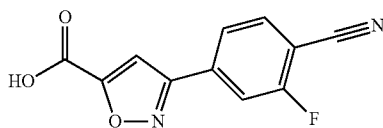
[0405] The title compound is prepared from 4-cyano-3-fluoro-N-hydroxy-benzenecarboximidoyl chloride and

2-methoxy-acrylic acid methyl ester acid following a procedure analogous to that described for Intermediate 63. LC (method 9):  $t_R$ =0.96 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$ =279 [M+H]<sup>+</sup>.

## Intermediate 70

3-(4-Cyano-3-fluoro-phenyl)-isoxazole-5-carboxylic acid

[0406]

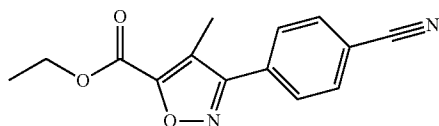


[0407] The title compound is prepared by treating 3-(4-cyano-3-fluoro-phenyl)-5-methoxy-4,5-dihydro-isoxazole-5-carboxylic acid methyl ester with 1 M aqueous NaOH solution in tetrahydrofuran. LC (method 9):  $t_R$ =0.40 min; Mass spectrum (ESI<sup>-</sup>):  $m/z$ =231 [M-H]<sup>-</sup>.

## Intermediate 71

5-(4-Cyano-phenyl)-4-methyl-isoxazole-3-carboxylic acid ethyl ester

[0408]

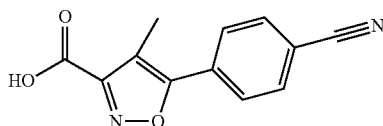


[0409] The title compound is prepared from 5-bromo-4-methyl-isoxazole-3-carboxylic acid ethyl ester and 4-cyano-phenylboronic acid following a procedure analogous to that described for Intermediate 27. LC (method 9):  $t_R$ =1.11 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$ =257 [M+H]<sup>+</sup>.

## Intermediate 72

5-(4-Cyano-phenyl)-4-methyl-isoxazole-3-carboxylic acid

[0410]

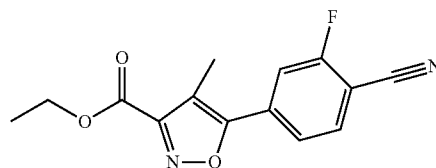


[0411] The title compound is prepared by treating 5-(4-cyano-phenyl)-4-methyl-isoxazole-3-carboxylic acid ethyl ester with 1 M aqueous NaOH solution in tetrahydrofuran. LC (method 9):  $t_R$ =0.41 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$ =229 [M+H]<sup>+</sup>.

## Intermediate 73

5-(4-Cyano-3-fluoro-phenyl)-4-methyl-isoxazole-3-carboxylic acid ethyl ester

[0412]

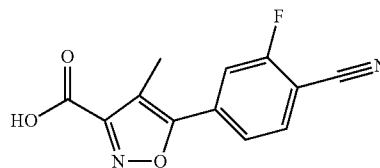


[0413] The title compound is prepared from 5-bromo-4-methyl-isoxazole-3-carboxylic acid ethyl ester and 4-cyano-3-fluoro-phenylboronic acid following a procedure analogous to that described for Intermediate 27. LC (method 9):  $t_R$ =1.14 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$ =275 [M+H]<sup>+</sup>.

## Intermediate 74

5-(4-Cyano-3-fluoro-phenyl)-4-methyl-isoxazole-3-carboxylic acid

[0414]

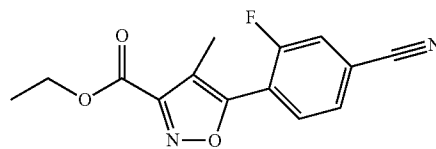


[0415] The title compound is prepared by treating 5-(4-cyano-3-fluoro-phenyl)-4-methyl-isoxazole-3-carboxylic acid ethyl ester with 1 M aqueous NaOH solution in tetrahydrofuran. LC (method 9):  $t_R$ =0.47 min; Mass spectrum (EI):  $m/z$ =246 [M]<sup>+</sup>.

## Intermediate 75

5-(4-Cyano-2-fluoro-phenyl)-4-methyl-isoxazole-3-carboxylic acid ethyl ester

[0416]



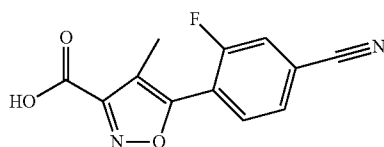
[0417] The title compound is prepared from 5-bromo-4-methyl-isoxazole-3-carboxylic acid ethyl ester and 4-cyano-2-fluoro-phenylboronic acid following a procedure analogous to that described for Intermediate 27. LC (method 9):  $t_R$ =1.13 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$ =275 [M+H]<sup>+</sup>.



## Intermediate 76

5-(4-Cyano-2-fluoro-phenyl)-4-methyl-isoxazole-3-carboxylic acid

[0418]

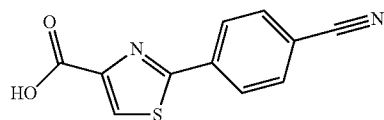


[0419] The title compound is prepared by treating 5-(4-cyano-2-fluoro-phenyl)-4-methyl-isoxazole-3-carboxylic acid ethyl ester with 1 M aqueous NaOH solution in tetrahydrofuran. LC (method 9):  $t_R$ =1.08 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$ =247 [M+H]<sup>+</sup>.

## Intermediate 77

2-(4-Cyano-phenyl)-thiazole-4-carboxylic acid

[0420]

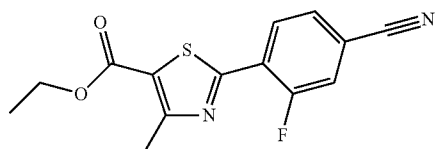


[0421] The title compound is prepared by treating 2-(4-cyano-phenyl)-thiazole-4-carboxylic acid tert-butyl ester with trifluoroacetic acid in dichloromethane. LC (method 9):  $t_R$ =0.44 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$ =231 [M+H]<sup>+</sup>.

## Intermediate 78

2-(4-Cyano-2-fluoro-phenyl)-4-methyl-thiazole-5-carboxylic acid ethyl ester

[0422]

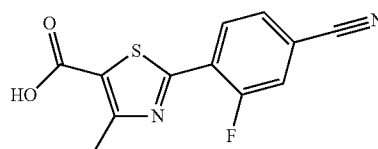


[0423] The title compound is prepared from 2-bromo-4-methyl-thiazole-5-carboxylic acid ethyl ester and 4-cyano-2-fluorophenylboronic acid following a procedure analogous to that described for Intermediate 27. LC (method 9):  $t_R$ =1.29 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$ =291 [M+H]<sup>+</sup>.

## Intermediate 79

2-(4-Cyano-2-fluoro-phenyl)-4-methyl-thiazole-5-carboxylic acid

[0424]

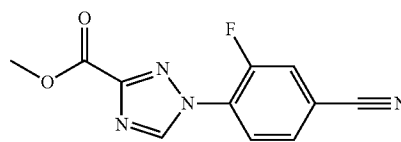


[0425] The title compound is prepared by treating 2-(4-cyano-2-fluoro-phenyl)-4-methyl-thiazole-5-carboxylic acid ethyl ester with 1 M aqueous NaOH solution in tetrahydrofuran. Mass spectrum (ESI<sup>-</sup>):  $m/z$ =261 [M-H]<sup>-</sup>.

## Intermediate 80

1-(4-Cyano-2-fluoro-phenyl)-1H-[1,2,4]triazole-3-carboxylic acid methyl ester

[0426]

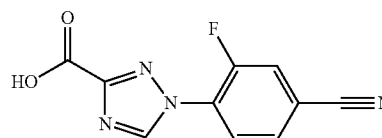


[0427] The title compound is prepared from 1H-[1,2,4]triazole-3-carboxylic acid methyl ester and 3,4-difluorobenzonitrile following a procedure analogous to that described for Intermediate 12. LC (method 9):  $t_R$ =0.74 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$ =247 [M+H]<sup>+</sup>.

## Intermediate 81

1-(4-Cyano-2-fluoro-phenyl)-1H-[1,2,4]triazole-3-carboxylic acid

[0428]

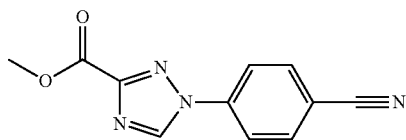


[0429] The title compound is prepared by 1-(4-cyano-2-fluoro-phenyl)-1H-[1,2,4]triazole-3-carboxylic acid methyl ester with 1 M aqueous NaOH solution in tetrahydrofuran. (ESI<sup>+</sup>):  $m/z$ =233 [M+H]<sup>+</sup>.

## Intermediate 82

1-(4-Cyano-phenyl)-1H-[1,2,4]triazole-3-carboxylic acid methyl ester

[0430]

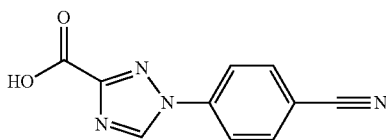


[0431] The title compound is prepared from 1H-[1,2,4]triazole-3-carboxylic acid methyl ester and 4-fluorobenzonitrile following a procedure analogous to that described for Intermediate 12. Mass spectrum (ESI<sup>+</sup>): m/z=229 [M+H]<sup>+</sup>.

## Intermediate 83

1-(4-Cyano-phenyl)-1H-[1,2,4]triazole-3-carboxylic acid

[0432]

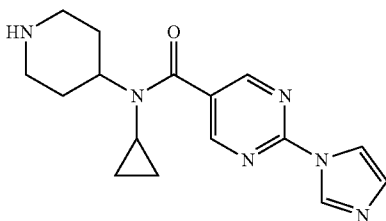


[0433] The title compound is prepared by 1-(4-cyano-phenyl)-1H-[1,2,4]triazole-3-carboxylic acid methyl ester with 1 M aqueous NaOH solution in tetrahydrofuran. LC (method 8): t<sub>R</sub>=0.19 min; (ESI<sup>+</sup>); m/z=215 [M+H]<sup>+</sup>.

## Intermediate 84

2-Imidazol-1-yl-pyrimidine-5-carboxylic acid cyclopropyl-piperidin-4-yl-amide

[0434]



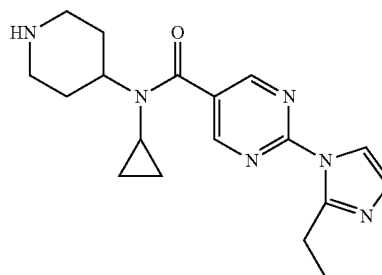
[0435] To 4-[cyclopropyl-(2-imidazol-1-yl-pyrimidine-5-carbonyl)-amino]-piperidine-1-carboxylic acid tert-butyl ester (2.1 g) in dichloromethane (5 mL) is added a total volume of 11 mL dichloromethane/trifluoroacetic acid (1:1). The mixture is stirred for 2 d at room temperature. After concentration in vacuo the residue is triturated with diethyl

ether to afford the title compound as a trifluoroacetic acid salt. LC (method 10): t<sub>R</sub>=0.68 min; Mass spectrum (ESI<sup>+</sup>): m/z=313 [M+H]<sup>+</sup>.

## Intermediate 85

2-(2-Ethyl-imidazol-1-yl)-pyrimidine-5-carboxylic acid cyclopropyl-piperidin-4-yl-amide

[0436]

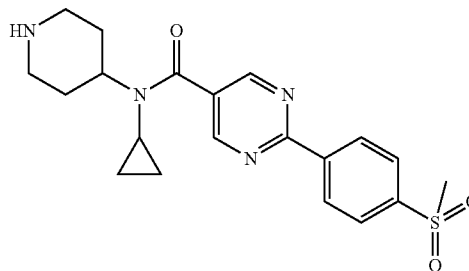


[0437] A mixture of 4-[(2-chloro-pyrimidine-5-carbonyl)-cyclopropyl-amino]-piperidine-1-carboxylic acid tert-butyl ester (3.0 g), 2-ethylimidazole (0.73 g) and ethyldiisopropylamine (2.0 mL) in N-methyl-2-pyrrolidinone (10 mL) is stirred for 12 h at 80° C. The solvent is removed in vacuo and the residue is purified by HPLC (C18 RP Sunfire, H<sub>2</sub>O/MeOH+0.1% TFA) to yield the boc-protected intermediate. The intermediate is dissolved in dichloromethane and dichloromethane/trifluoroacetic acid (1:1, 5% H<sub>2</sub>O) is added and the mixture is stirred for 5 h at room temperature. After concentration in vacuo the residue is triturated with diethyl ether to afford the title compound as a trifluoroacetic acid salt. LC (method 10): t<sub>R</sub>=1.56 min; Mass spectrum (ESI<sup>+</sup>): m/z=341 [M+H]<sup>+</sup>.

## Intermediate 86

2-(4-Methanesulfonyl-phenyl)-pyrimidine-5-carboxylic acid cyclopropyl-piperidin-4-yl-amide

[0438]

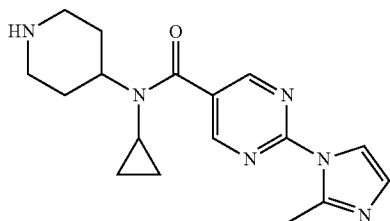


[0439] The title compound was prepared analogously to 2-imidazol-1-yl-pyrimidine-5-carboxylic acid cyclopropyl-piperidin-4-yl-amide (Intermediate 84), using 4-{cyclopropyl-[2-(4-methanesulfonyl-phenyl)-pyrimidine-5-carbonyl]-amino}-piperidine-1-carboxylic acid tert-butyl ester (Example 247) as starting material. LC (method 10): t<sub>R</sub>=1.20 min; Mass spectrum (ESI<sup>+</sup>): m/z=401 [M+H]<sup>+</sup>.

## Intermediate 87

2-(2-Methyl-imidazol-1-yl)-pyrimidine-5-carboxylic acid cyclopropyl-piperidin-4-yl-amide

[0440]

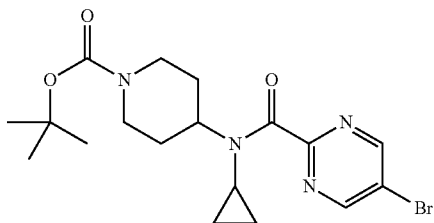


[0441] The title compound was prepared analogously to 2-(2-ethyl-imidazol-1-yl)-pyrimidine-5-carboxylic acid cyclopropyl-piperidin-4-yl-amide (Intermediate 85), using 2-methyl-imidazole as starting material. LC (method 10):  $t_R$ =0.56 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$ =327 [M+H]<sup>+</sup>.

## Intermediate 88

4-[(5-Bromo-pyrimidine-2-carbonyl)-cyclopropyl-amino]-piperidine-1-carboxylic acid tert-butyl ester

[0442]



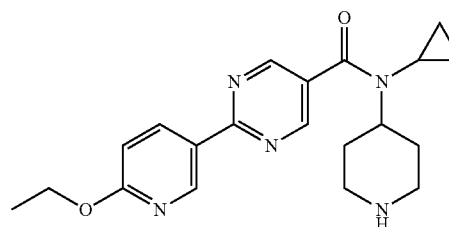
[0443] The title compound was prepared analogously to 4-[(2-chloro-pyrimidine-5-carbonyl)-cyclopropyl-amino]-piperidine-1-carboxylic acid tert-butyl ester (Intermediate 6),

using 5-bromopyrimidine-2-carboxylic acid as starting material. LC (method 11):  $t_R$ =1.22 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$ =425 [M+H]<sup>+</sup>.

## Intermediate 89

2-(6-Ethoxy-pyridin-3-yl)-pyrimidine-5-carboxylic acid cyclopropyl-piperidin-4-yl-amide

[0444]



[0445] Under an argon atmosphere an aqueous solution of Na<sub>2</sub>CO<sub>3</sub> (2 M, 1.0 mL) and bis(triphenylphosphine)-palladium(II) chloride (22 mg) are added to a mixture of 2-ethoxy-5-pyridineboronic acid (0.35 g) and 4-[(2-chloro-pyrimidine-5-carbonyl)-cyclopropyl-amino]-piperidine-1-carboxylic acid tert-butyl ester (0.4 g) in 1,4-dioxane (20 mL) and methanol (10 mL). The mixture is stirred for 12 h at 80° C. and concentrated in vacuo. To the residue is added dichloromethane and water. The organic phase is separated and the aqueous phase is extracted with dichloromethane. The combined extracts are dried over MgSO<sub>4</sub> and concentrated in vacuo and treated with dichloromethane/trifluoroacetic acid (1:1+5% H<sub>2</sub>O). The mixture is stirred at room temperature for 1 h, concentrated and purified by HPLC (C18 RP Sunfire, MeOH/H<sub>2</sub>O+0.1% TFA) to give the desired product as a trifluoroacetic acid salt. LC (method 12):  $t_R$ =0.99 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$ =368 [M+H]<sup>+</sup>.

[0446] The following compounds of table 1 are prepared analogously to Intermediate 89, the starting materials used being shown in the column headed "E 1" and "E 2":

TABLE 1

| Int. | Structure | E 1    | E 2 | ESI-MS<br>[m/z]             | HPLC $t_R$<br>[min]<br>(method) |
|------|-----------|--------|-----|-----------------------------|---------------------------------|
| 90   |           | Int. 6 |     | 362<br>[M + H] <sup>+</sup> | 0.85<br>(12)                    |

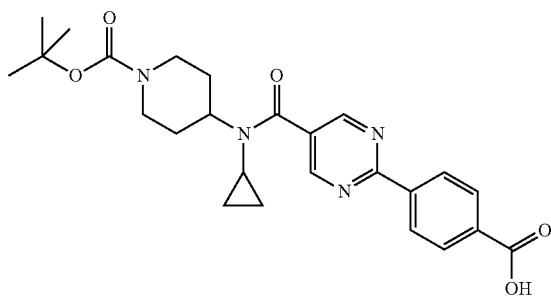
TABLE 1-continued

| Int. | Structure | E 1    | E 2 | ESI-MS<br>[m/z]             | HPLC $t_R$<br>[min]<br>(method) |
|------|-----------|--------|-----|-----------------------------|---------------------------------|
| 91   |           | Int. 6 |     | 366<br>[M + H] <sup>+</sup> | 0.97<br>(12)                    |

Intermediate 92

4-([2-(4-Carboxy-phenyl)-pyrimidine-5-carbonyl]-cyclopropyl-amino)-piperidine-1-carboxylic acid tert-butyl ester

[0447]

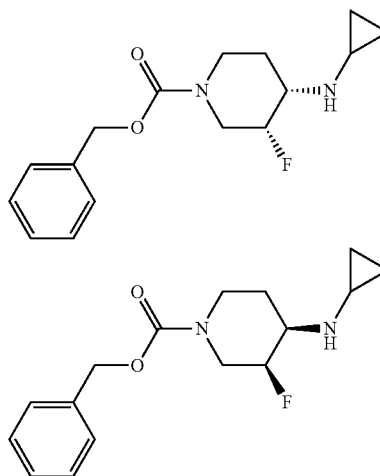


[0448] Under an argon atmosphere an aqueous solution of  $\text{Na}_2\text{CO}_3$  (2 M, 4.0 mL) and bis(triphenylphosphine)-palladium(II) chloride (83 mg) are added to a mixture of (4-methoxycarbonylphenyl)boronic acid (2.13 g) and 4-[(2-chloropyrimidine-5-carbonyl)-cyclopropyl-amino]-piperidine-1-carboxylic acid tert-butyl ester (1.55 g) in 1,4-dioxane (20 mL) and methanol (10 mL). The mixture is stirred for 12 h at 80° C. and concentrated in vacuo. To the residue is added dichloromethane and water. The organic phase is separated and the aqueous phase is extracted with dichloromethane. The combined extracts are dried over  $\text{MgSO}_4$  and concentrated in vacuo. The residue is taken up in methanol (20 mL), treated with NaOH solution (1 M, 10.2 mL) and the mixture is stirred for 3 h at 40° C. The mixture is slightly acidified using 1 M aqueous hydrochloric acid and the precipitate is collected and taken up in N,N-dimethylformamide. After addition of water the precipitate is collected and dried to yield the desired product. LC (method 13):  $t_R$ =1.46 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$ =467 [M+H]<sup>+</sup>.

Intermediates 93 and 94

Benzyl (3R,4S)-4-(cyclopropylamino)-3-fluoropiperidine-1-carboxylate Arbitrarily Assigned as Isomer 1 (First Eluting) and Benzyl (3S,4R)-4-(cyclopropylamino)-3-fluoropiperidine-1-carboxylate Arbitrarily Assigned as Isomer 2 (Second Eluting)

[0449]

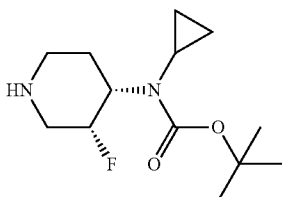


[0450] To a solution of benzyl-3-fluoro-4-oxopiperidine-1-carboxylate (10.0 g) and cyclopropylamine (2.5 g) in dichloromethane (100 mL) are added sodium triacetoxyborohydride (10.1 g) and glacial acetic acid (5.0 g). The reaction mixture is stirred at room temperature for 20 h. Then 60 mL of 2 N NaOH is added to reach pH 10. The mixture is extracted with dichloromethane (2×50 mL). The combined organic phases are dried over sodium sulfate, filtered and concentrated in vacuo and purified by silica gel chromatography (dichloromethane/methanol 90:10) to afford the desired product as a mixture of mainly cis isomers [LC (method 20):  $t_R$ =1.98 min; mass spectrum (AFCI):  $m/z$ =293 [M+H]<sup>+</sup>]. Chiral SFC separation (chiral SFC method 21) gives the separated title compounds (cis isomers of unknown absolute stereochemistry) arbitrarily assigned as Isomer 1 (first eluting; 7.25 min) and Isomer 2 (second eluting; 9.41 min).

## Intermediate 95

tert-Butyl N-cyclopropyl-N-[(3R,4S)-3-fluoropiperidin-4-yl]carbamate

[0451]

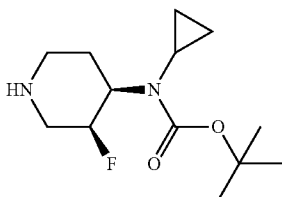


[0452] Benzyl (3R,4S)-4-(cyclopropylamino)-3-fluoropiperidine-1-carboxylate (Intermediate 93, absolute stereochemistry arbitrarily assigned) (3.0 g) is dissolved in 1:1 tetrahydrofuran/water (100 mL) and NaOH (800 mg, 20 mmol) is added followed by di-tert-butyl dicarbonate (2.6 g) and stirred rapidly at room temperature overnight. The reaction is heated to reflux and additional portions of di-tert-butyl dicarbonate are added over two days (3×2.6 g). The reaction is extracted with ethyl acetate and the organic extracts are washed with brine, dried over  $\text{MgSO}_4$  and concentrated. Chromatography on silica gel eluting with ethyl acetate/hexane gives the Boc-protected intermediate and elution with methanol/dichloromethane gives recovered amine. The intermediate is re-dissolved in ethyl acetate (30 mL) and 10% Pd/C (200 mg) is added and the reaction mixture stirred under a hydrogen atmosphere for 2 h at room temperature. Filtration through celite and concentration gives the title compound. LC (method 20):  $t_R$ =1.95 min; Mass spectrum (APCI):  $m/z$ =259  $[\text{M}+\text{H}]^+$ .

## Intermediate 96

tert-Butyl N-cyclopropyl-N-[(3S,4R)-3-fluoropiperidin-4-yl]carbamate

[0453]

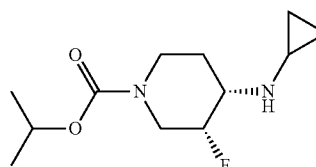


[0454] The title compound is prepared from benzyl (3S,4R)-4-(cyclopropylamino)-3-fluoropiperidine-1-carboxylate (Intermediate 94, absolute stereochemistry arbitrarily assigned) following a procedure analogous to that described for Intermediate 21. LC (method 20):  $t_R$ =2.02 min; Mass spectrum (APCI):  $m/z$ =259  $[\text{M}+\text{H}]^+$ .

## Intermediate 97

(3R,4S)-4-Cyclopropylamino-3-fluoro-piperidine-1-carboxylic acid isopropyl ester

[0455]

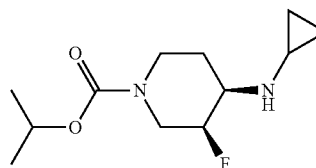


[0456] tert-Butyl N-cyclopropyl-N-[(3R,4S)-3-fluoropiperidin-4-yl]carbamate (Intermediate 95, absolute stereochemistry arbitrarily assigned) (60 mg) and triethylamine (47 mg) are combined in dichloromethane (2 mL) and isopropyl chloroformate (0.38 mL, 1 M in toluene) is added and stirred at room temperature overnight. Water is added and the organic phase is separated and dried over  $\text{MgSO}_4$  and concentrated. The crude material is dissolved in 20% trifluoroacetic acid/dichloromethane and stirred at room temperature for 1 h. After concentration dichloromethane (5 mL) and aqueous NaOH solution (2 M, 1 mL) is added and the organic layer separated and dried over  $\text{MgSO}_4$  and concentrated to give the title compound. LC (method 20):  $t_R$ =1.19 min; Mass spectrum (APCI):  $m/z$ =245  $[\text{M}+\text{H}]^+$ .

## Intermediate 98

(3S,4R)-4-Cyclopropylamino-3-fluoro-piperidine-1-carboxylic acid isopropyl ester

[0457]

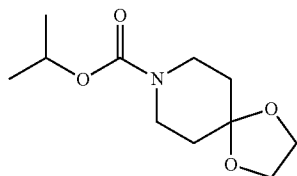


[0458] The title compound is prepared from tert-butyl N-cyclopropyl-N-[(3S,4R)-3-fluoropiperidin-4-yl]carbamate (Intermediate 96, absolute stereochemistry arbitrarily assigned) following a procedure analogous to that described for Intermediate 2. LC (method 20):  $t_R$ =1.20 min; Mass spectrum (APCI):  $m/z$ =245  $[\text{M}+\text{H}]^+$ .

## Intermediate 99

1,4-Dioxo-8-aza-spiro[4.5]decane-8-carboxylic acid  
isopropyl ester

[0459]

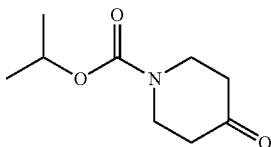


[0460] 1,4-Dioxo-8-aza-spiro[4.5]decane (5.0 g) is dissolved in dichloromethane (50 mL) under nitrogen and cooled to 0° C. Triethylamine (7.1 g) is added followed by isopropyl chloroformate (33.2 mL, 1.0 M solution in toluene) drop wise keeping the internal temperature below 5° C. then allowed to warm to room temperature overnight. The reaction is diluted with dichloromethane (100 mL) and washed with 0.5 M hydrochloric acid (100 mL) and water (100 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to give the title compound. LC (method 1): t<sub>R</sub>=1.93 min; Mass spectrum (APCI): m/z=230 [M+H]<sup>+</sup>.

## Intermediate 100

4-Oxo-piperidine-1-carboxylic acid isopropyl ester

[0461]

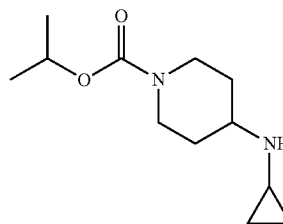


[0462] Propan-2-yl 1,4-dioxo-8-azaspiro[4.5]decane-8-carboxylate (3.8 g) is treated with 9 N hydrochloric acid (60 mL) and stirred at room temperature overnight. With cooling aqueous 4 M aqueous NaOH solution (110 mL) is added with stirring to pH 13-14. The resulting mixture is extracted with ethyl acetate (2×200 mL) and the organic extracts are combined, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated to give the title compound.

## Intermediate 101

4-Cyclopropylamino-piperidine-1-carboxylic acid  
isopropyl ester

[0463]

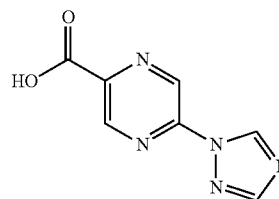


[0464] 4-Oxo-piperidine-1-carboxylic acid isopropyl ester (1.5 g) and cyclopropylamine (8.6 g) are combined in dichloromethane (25 mL) and glacial acetic acid (0.97 mL) is added. Sodium triacetoxyborohydride (2.1 g) is added under nitrogen and the mixture stirred at room temperature for 18 h. The mixture is diluted with dichloromethane (50 mL) and washed with 10% aqueous K<sub>2</sub>CO<sub>3</sub> solution (2×50 mL). The organic layer is extracted with 3 M hydrochloric acid (2×30 mL) and the organic layer discarded. The aqueous layer is made basic with 4 M NaOH and extracted with dichloromethane (2×50 mL) and the organic layers are combined, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated to give the title compound. LC (method 20): t<sub>R</sub>=1.46 min; Mass spectrum (APCI): m/z=227 [M+H]<sup>+</sup>.

## Intermediate 102

5-[1,2,4]Triazol-1-yl-pyrazine-2-carboxylic acid

[0465]

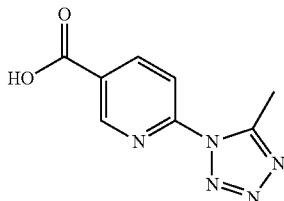


[0466] A mixture of methyl 5-chloropyrazine-2-carboxylate (0.75 g), K<sub>2</sub>CO<sub>3</sub> (1.8 g) and 1H-1,2,4-triazole (1.2 g) in N,N-dimethylformamide (6 mL) is heated to 100° C. overnight. Analysis of the crude mixture by LCMS shows saponified product. The product is acidified with 1 N hydrochloric acid and the precipitate is filtered and washed with water and diethyl ether to afford the title compound. LC (method 20): t<sub>R</sub>=1.06 min; Mass spectrum (APCI): m/z=192 [M+H]<sup>+</sup>.

## Intermediate 103

6-(5-Methyl-tetrazol-1-yl)-nicotinic acid

[0467]

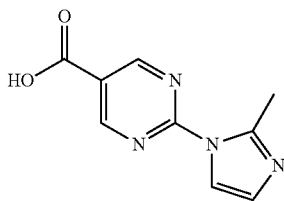


[0468] To a solution of methyl 6-aminopyridine-3-carboxylate (1.52 g) in dichloromethane (10 mL) and pyridine (3 mL) is added acetic anhydride (2 g) and stirred at room temperature overnight. After concentration water and in dichloromethane are added and the organic layer separated, washed with saturated aqueous  $\text{CuSO}_4$ , then water, dried over  $\text{MgSO}_4$  and concentrated. The N-acyl compound is dissolved in acetonitrile (20 mL) and sodium azide (4 g) and  $\text{SiCl}_4$  (4 mL) are added and the mixture stirred at room temperature overnight. The reaction is quenched by slow addition to an ice/ $\text{NaHCO}_3$  mixture and extracted with ethyl acetate. The organic extracts are dried over  $\text{MgSO}_4$  and concentrated. The crude ester is dissolved in methanol (30 mL) and 4 M aqueous NaOH solution (3 mL) is added and stirred at room temperature for 2 h. The mixture is neutralized to pH 7 with 6 M hydrochloric acid, concentrated and then acidified with 6 M hydrochloric acid and the precipitate is filtered off, washed with water, and dried by suction to give the title compound. LC (method 20):  $t_R=1.52$  min; Mass spectrum (APCI):  $m/z=206$   $[\text{M}+\text{H}]^+$ .

## Intermediate 104

2-(2-Methyl-imidazol-1-yl)-pyrimidine-5-carboxylic acid

[0469]

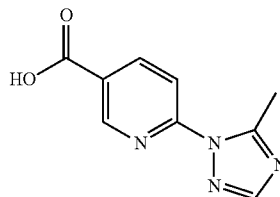


[0470] 2-Chloropyrimidine-5-carboxylic acid (0.75 g), 2-methyl imidazole (0.117 g) and potassium carbonate (1.96 g) in 3.75 mL of N,N-dimethylformamide are heated in microwave at  $50^\circ\text{C}$ . for 30 minutes, then cooled to room temperature and acidified with 3 mL of 1 N hydrochloric acid, followed by addition of conc. hydrochloric acid to pH 2. The precipitate is filtered, washed with a minimum amount of water and diethyl ether, and dried in vacuo to afford the title compound. LC (method 20):  $t_R=0.48$  min; Mass spectrum (APCI):  $m/z=205$   $[\text{M}+\text{H}]^+$ .

## Intermediate 105

6-(5-Methyl-[1,2,4]triazol-1-yl)-nicotinic acid

[0471]

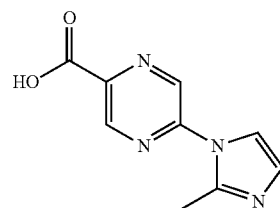


[0472] 2-Chloro-5-cyanopyridine (1.5 g) is dissolved in hydrazine (6 mL) at room temperature. An exothermic reaction occurs and a solid precipitate forms. Water is added and the solid is filtered off, washed with water, and dried by suction to give the hydrazine intermediate. The hydrazine is suspended in acetic acid (7 mL) and N-((dimethylamino)methylene)acetamide [made from acetamide and DMF-dimethyl-acetal by procedure in US2007/0111984A1] (700 mg) is added and the mixture is heated at  $90^\circ\text{C}$ . for 5.5 h. Additional N-((dimethylamino)methylene)acetamide (200 mg) is added and the mixture is heated at  $90^\circ\text{C}$ . for 3 h. After cooling and concentrating the residue is purified by chromatography on silica gel eluting with 0% to 100% ethyl acetate/hexane to give the intermediate nitrile. The nitrile is dissolved in methanol (10 mL) and 4 M aqueous NaOH solution (2 mL) is added and the mixture is heated at  $65^\circ\text{C}$ . for 16 h. The mixture is neutralized to pH 7 with 6 M hydrochloric acid, concentrated, and then acidified to pH 2 with 6 M hydrochloric acid. The precipitate is filtered off washing with water and dried by suction to give the title compound. LC (method 20):  $t_R=1.53$  min; Mass spectrum (APCI):  $m/z=205$   $[\text{M}+\text{H}]^+$ .

## Intermediate 106

5-(2-Methyl-imidazol-1-yl)-pyrazine-2-carboxylic acid

[0473]

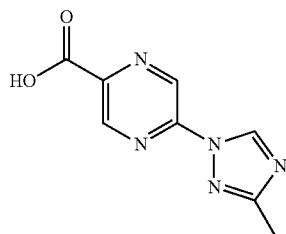


[0474] A mixture of methyl 5-chloropyrazine-2-carboxylate (0.75 g),  $\text{K}_2\text{CO}_3$  (1.8 g) and 2-methyl-1H-imidazole (1.3 g) in N,N-dimethylformamide (6 mL) is heated to  $100^\circ\text{C}$ . overnight. Analysis of the crude mixture by LCMS shows saponified product. The solvents are evaporated and the crude product is purified by HPLC. LC (method 20):  $t_R=0.27$  min; Mass spectrum (APCI):  $m/z=205$   $[\text{M}+\text{H}]^+$ .

## Intermediate 107

5-(3-Methyl-[1,2,4]triazol-1-yl)-pyrazine-2-carboxylic acid

[0475]

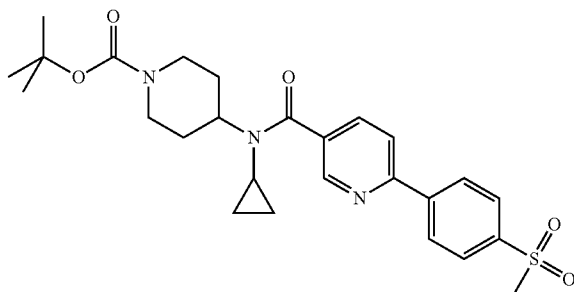


[0476] A mixture of methyl 5-chloropyrazine-2-carboxylate (0.75 g),  $K_2CO_3$  (1.8 g) and 3-methyl-1H-1,2,4-triazole (1.2 g) in N,N-dimethylformamide (6 mL) is heated to 100° C. overnight. Analysis of the crude mixture by LCMS shows saponified product. The product is acidified with 1 N hydrochloric acid and the precipitate is filtered and washed with water and diethyl ether to afford the title compound. LC (method 20):  $t_R$ =1.21 min; Mass spectrum (APCI):  $m/z$ =206  $[M+H]^+$ .

## Example 1

4-{Cyclopropyl-[6-(4-methanesulfonyl-phenyl)-pyridine-3-carbonyl]-amino}-piperidine-1-carboxylic acid tert-butyl ester

[0477]

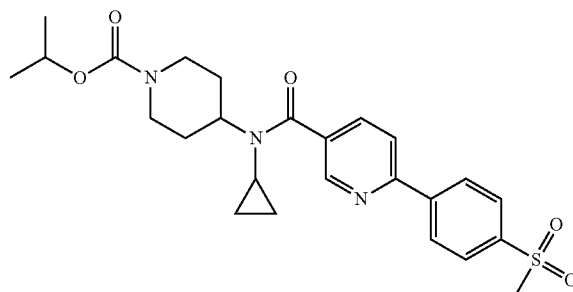


[0478] A 2 M aqueous  $Na_2CO_3$  solution (8.26 mL) is added to a mixture of 4-[(6-bromo-pyridine-3-carbonyl)-cyclopropyl-amino]-piperidine-1-carboxylic acid tert-butyl ester (500 mg) and 4-(methanesulfonyl)phenyl boronic acid (259 mg) in N,N-dimethyl-formamide (5 mL). The mixture is sparged with argon for 10 min and [1,1'-bis(diphenylphosphino)-ferrocene]dichloropalladium dichloromethane complex (96 mg) is added. The resulting mixture is stirred for 6 h at 90° C. After cooling to room temperature, water (50 mL) is added and the aqueous phase is extracted with ethyl acetate. The organic phase is dried over  $MgSO_4$ , the solvent is evaporated, and the residue is chromatographed on silica gel (ethyl acetate/cyclohexane 3:1→1:0) to afford the title compound. LC (method 2):  $t_R$ =1.17 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$ =500  $[M+H]^+$ .

## Example 2

4-{Cyclopropyl-[6-(4-methanesulfonyl-phenyl)-pyridine-3-carbonyl]-amino}-piperidine-1-carboxylic acid isopropyl ester

[0479]

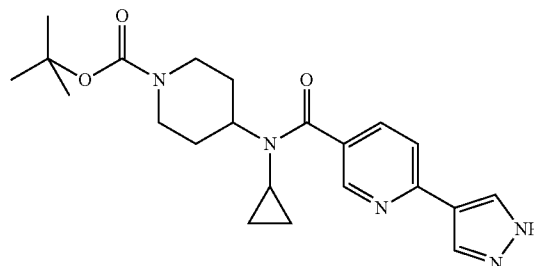


[0480] Isopropyl chloroformate (165  $\mu$ L) is added to an ice-cooled solution of N-cyclopropyl-6-(4-methanesulfonyl-phenyl)-N-piperidin-4-yl-nicotinamide (55 mg) and ethyldiisopropylamine (59  $\mu$ L) in dichloromethane (1 mL). The reaction mixture is stirred overnight at room temperature. The reaction mixture is washed with water, dried over  $MgSO_4$  and concentrated in vacuo to give the title compound. LC (method 2):  $t_R$ =1.10 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$ =486  $[M+H]^+$ .

## Example 3

4-{Cyclopropyl-[6-(1H-pyrazol-4-yl)-pyridine-3-carbonyl]-amino}-piperidine-1-carboxylic acid tert-butyl ester

[0481]



[0482] Potassium carbonate (65 mg) is added to a mixture of 4-[(6-bromo-pyridine-3-carbonyl)-cyclopropyl-amino]-piperidine-1-carboxylic acid tert-butyl ester (100 mg) and 4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-O-1H-pyrazole (91 mg) in 1,4-dioxane (3.6 mL) and water (0.9 mL). The mixture is sparged with argon for 10 min and [1,1'-bis(diphenylphosphino)-ferrocene]dichloropalladium dichloromethane complex (19 mg) is added. The resulting mixture is heated to 115° C. for 30 min in a microwave oven. After cooling to room temperature, the reaction mixture is diluted with methanol (5 mL) and filtered and the aqueous phase is extracted with ethyl acetate. The combined extracts are washed with brine, and dried over  $MgSO_4$  and concentrated in vacuo. The residue is purified by HPLC (MeOH/ $H_2O$ +0.

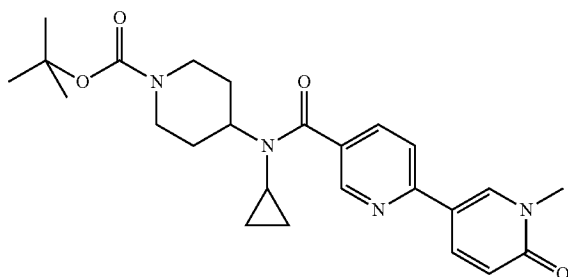


13%  $\text{NH}_4\text{OH}$ ) to afford the title compound. LC (method 3):  $t_R=1.05$  min; Mass spectrum (ESI<sup>+</sup>):  $m/z=412$   $[\text{M}+\text{H}]^+$ .

#### Example 4

4-[Cyclopropyl-(1'-methyl-6'-oxo-1',6'-dihydro-[2,3']bipyridinyl-5-carbonyl)-amino]-piperidine-1-carboxylic acid tert-butyl ester

[0483]

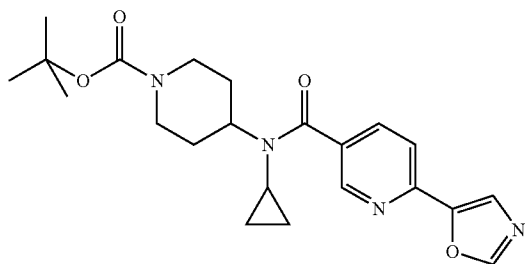


[0484] The title compound is prepared from 4-[(6-bromopyridine-3-carbonyl)-cyclopropyl-amino]-piperidine-1-carboxylic acid tert-butyl ester and 1-methyl-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1H-pyridin-2-one following a procedure analogous to that described in Example 1. LC (method 2):  $t_R=1.14$  min; Mass spectrum (ESI<sup>+</sup>):  $m/z=453$   $[\text{M}+\text{H}]^+$ .

#### Example 5

4-[Cyclopropyl-(6-oxazol-5-yl-pyridine-3-carbonyl)-amino]-piperidine-1-carboxylic acid tert-butyl ester

[0485]

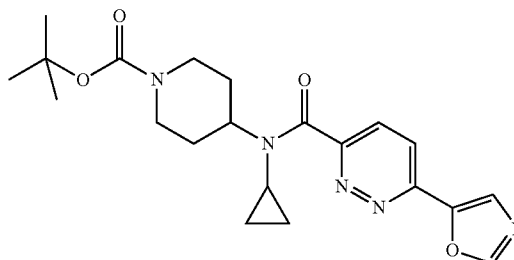


[0486] 2-(1H-Benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (410 mg) is added to a solution of 6-oxazol-5-yl-nicotinic acid (230 mg) and ethyldiisopropylamine (0.32 mL) in N,N-dimethylformamide (3 mL) at room temperature. 4-Cyclopropylamino-piperidine-1-carboxylic acid tert-butyl ester (291 mg) is added and the resulting mixture is stirred at room temperature overnight. Water and ethyl acetate are added and the organic phase is separated, washed with water, 1 N NaOH solution, and brine, dried over  $\text{MgSO}_4$  and concentrated in vacuo. The residue is purified by HPLC (MeOH/ $\text{H}_2\text{O}$ +0.13% TFA) to afford the title compound. LC (method 4):  $t_R=1.12$  min; Mass spectrum (ESI<sup>+</sup>):  $m/z=413$   $[\text{M}+\text{H}]^+$ .

#### Example 6

4-[Cyclopropyl-(6-oxazol-5-yl-pyridazine-3-carbonyl)-amino]-piperidine-1-carboxylic acid tert-butyl ester

[0487]

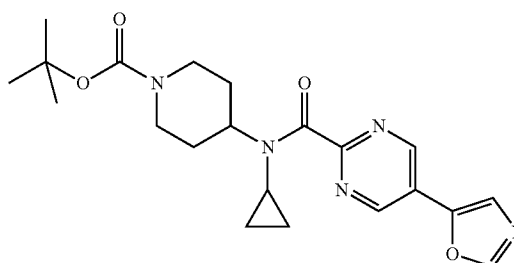


[0488] The title compound is prepared from 4-cyclopropylamino-piperidine-1-carboxylic acid tert-butyl ester and 6-oxazol-5-yl-pyridazine-3-carboxylic acid following a procedure analogous to that described in Example 5. LC (method 4):  $t_R=1.07$  min; Mass spectrum (ESI<sup>+</sup>):  $m/z=414$   $[\text{M}+\text{H}]^+$ .

#### Example 7

4-[Cyclopropyl-(5-oxazol-5-yl-pyrimidine-2-carbonyl)-amino]-piperidine-1-carboxylic acid tert-butyl ester

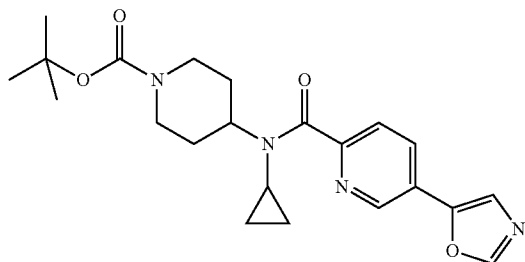
[0489]



[0490] A 2 M aqueous  $\text{Na}_2\text{CO}_3$  solution (1.00 mL) is added to a mixture of 4-[(5-bromopyrimidine-2-carbonyl)-cyclopropyl-amino]-piperidine-1-carboxylic acid tert-butyl ester (330 mg) and 5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-2-triisopropylsilyl-oxazole (410 mg) in N,N-dimethylformamide (5 mL). The mixture is sparged with argon and [1,1'-bis(diphenylphosphino)-ferrocene]dichloropalladium dichloromethane complex (65 mg) is added. The resulting mixture is stirred overnight at 80° C. After cooling to room temperature, water and ethyl acetate are added. The organic phase separated and washed with brine, dried over  $\text{MgSO}_4$ , and concentrated in vacuo. The residue is chromatographed on silica gel (ethyl acetate/methanol 100:0→80:20) to afford the title compound. LC (method 4):  $t_R=1.10$  min; Mass spectrum (ESI<sup>+</sup>):  $m/z=414$   $[\text{M}+\text{H}]^+$ .

## Example 8

[0491]



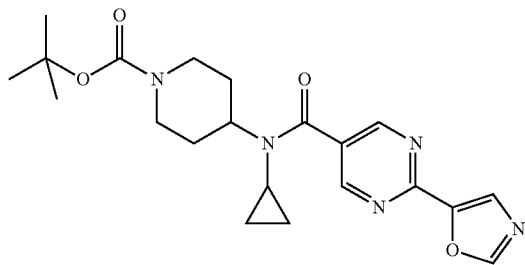
4-[Cyclopropyl-(5-oxazol-5-yl-pyridine-2-carbonyl)-amino]-piperidine-1-carboxylic acid tert-butyl ester

[0492] The title compound is prepared from 4-[(5-bromopyridine-2-carbonyl)-cyclopropyl-amino]-piperidine-1-carboxylic acid tert-butyl ester and 5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-2-triisopropylsilyl-oxazole following a procedure analogous to that described in Example 7. LC (method 4):  $t_R$ =1.10 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$ =413 [M+H]<sup>+</sup>.

## Example 9

4-[Cyclopropyl-(2-oxazol-5-yl-pyrimidine-5-carbonyl)-amino]-piperidine-1-carboxylic acid tert-butyl ester

[0493]

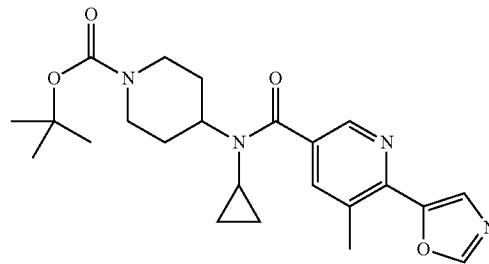


[0494] The title compound is prepared from 4-[(2-chloropyrimidine-5-carbonyl)-cyclopropyl-amino]-piperidine-1-carboxylic acid tert-butyl ester and 5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-2-triisopropylsilyl-oxazole following a procedure analogous to that described in Example 7. LC (method 4):  $t_R$ =1.21 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$ =414 [M+H]<sup>+</sup>.

## Example 10

4-[Cyclopropyl-(5-methyl-6-oxazol-5-yl-pyridine-3-carbonyl)-amino]-piperidine-1-carboxylic acid tert-butyl ester

[0495]

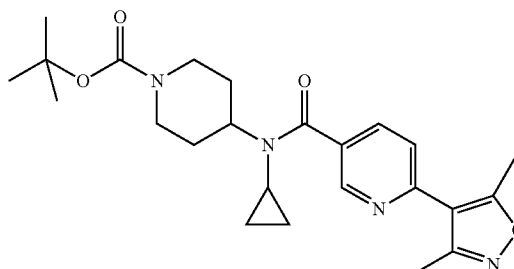


[0496] The title compound is prepared from 4-[(6-bromo-5-methyl-pyridine-3-carbonyl)-cyclopropyl-amino]-piperidine-1-carboxylic acid tert-butyl ester and 5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-2-triisopropylsilyl-oxazole following a procedure analogous to that described in Example 7. Since the cleavage of the triisopropylsilyl protecting group is not complete after the coupling reaction, the crude product is treated with tetrabutylammonium fluoride. LC (method 4):  $t_R$ =1.15 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$ =427 [M+H]<sup>+</sup>.

## Example 11

4-{Cyclopropyl-[6-(3,5-dimethyl-isoxazol-4-yl)-pyridine-3-carbonyl]-amino}-piperidine-1-carboxylic acid tert-butyl ester

[0497]

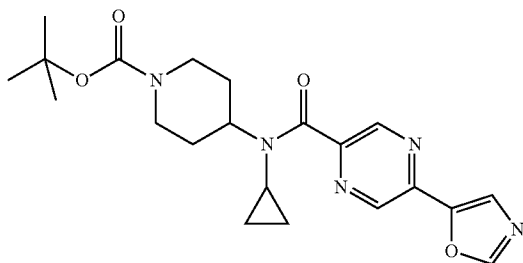


[0498] The title compound is prepared from 4-[(6-bromopyridine-3-carbonyl)-cyclopropyl-amino]-piperidine-1-carboxylic acid tert-butyl ester and 3,5-dimethylisoxazole-4-boronic acid following a procedure analogous to that described in Example 1. LC (method 4):  $t_R$ =1.21 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$ =441 [M+H]<sup>+</sup>.

## Example 12

4-[Cyclopropyl-(5-oxazol-5-yl-pyrazine-2-carbonyl)-amino]-piperidine-1-carboxylic acid tert-butyl ester

[0499]

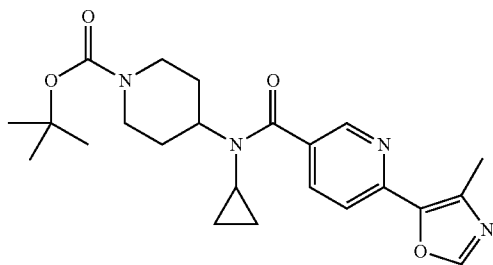


[0500] The title compound is prepared from 4-[(5-chloro-pyrazine-2-carbonyl)-cyclopropyl-amino]-piperidine-1-carboxylic acid tert-butyl ester and 5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-2-triisopropylsilyl-oxazole following a procedure analogous to that described in Example 7. LC (method 4):  $t_R$ =1.14 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$ =414 [M+H]<sup>+</sup>.

## Example 13

4-{Cyclopropyl-[6-(4-methyl-oxazol-5-yl)-pyridine-3-carbonyl]amino}-piperidine-1-carboxylic acid tert-butyl ester

[0501]



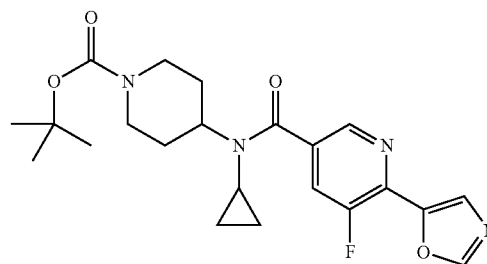
[0502] A mixture of 6-(4-methyl-oxazol-5-yl)-nicotinic acid (110 mg), chloro-N,N,N',N'-tetramethylformamidinium hexafluorophosphate (180 mg) and ethyldiisopropylamine (280  $\mu$ L) in tetrahydrofuran (2 mL) is stirred at room temperature for 45 min. 4-Cyclopropylamino-piperidine-1-carboxylic acid tert-butyl ester (130 mg) in tetrahydrofuran is added and stirring is continued overnight. Water and ethyl acetate are added and the organic phase is separated, washed with 1 N aqueous NaOH solution, 1 N hydrochloric acid, and brine, dried over MgSO<sub>4</sub>, and concentrated in vacuo. The residue is triturated with diisopropyl ether, filtered off, and

dried to give the title compound. LC (method 4):  $t_R$ =1.20 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$ =427 [M+H]<sup>+</sup>.

## Example 14

4-[Cyclopropyl-(5-fluoro-6-oxazol-5-yl-pyridine-3-carbonyl)-amino]-piperidine-1-carboxylic acid tert-butyl ester

[0503]

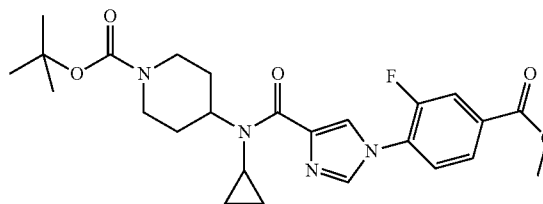


[0504] The title compound is prepared from 4-[(6-bromo-5-fluoro-pyridine-3-carbonyl)-cyclopropyl-amino]-piperidine-1-carboxylic acid tert-butyl ester and 5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-2-triisopropylsilyl-oxazole following a procedure analogous to that described in Example 7. LC (method 4):  $t_R$ =1.16 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$ =431 [M+H]<sup>+</sup>.

## Example 15

4-{Cyclopropyl-[1-(2-fluoro-4-methoxycarbonyl-phenyl)-1H-imidazole-4-carbonyl]amino}-piperidine-1-carboxylic acid tert-butyl ester

[0505]

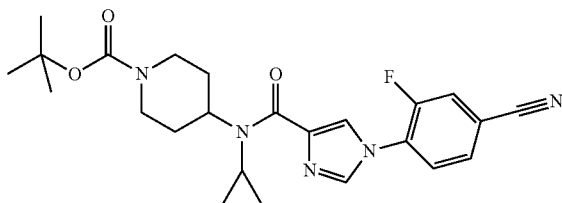


[0506] The title compound is prepared from 4-cyclopropylamino-piperidine-1-carboxylic acid tert-butyl ester and 1-(4-cyano-2-fluoro-phenyl)-1H-imidazole-4-carboxylic acid following a procedure analogous to that described in Example 5; the desired product containing the cyano group could not be isolated under these conditions. LC (method 4):  $t_R$ =1.24 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$ =487 [M+H]<sup>+</sup>.

## Example 16

4-[[1-(4-Cyano-2-fluoro-phenyl)-1H-imidazole-4-carbonyl]-cyclopropyl-amino]-piperidine-1-carboxylic acid tert-butyl ester

[0507]

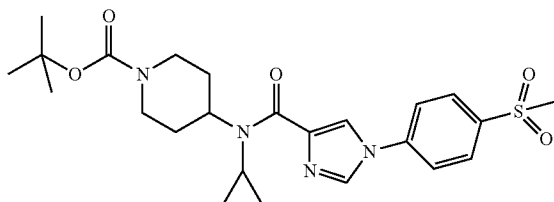


[0508] A mixture of 3,4-difluorobenzonitrile (50 mg), 4-[cyclopropyl-(1H-imidazole-4-carbonyl)-amino]-piperidine-1-carboxylic acid tert-butyl ester (100 mg), and potassium carbonate (65 mg) in dimethylsulfoxide (3 mL) is heated to 70° C. for 2 h. After cooling to room temperature, the reaction mixture is diluted with water and extracted with ethyl acetate. The combined extracts are dried over MgSO<sub>4</sub> and concentrated in vacuo. The residue is chromatographed on silica gel (cyclohexane/ethyl acetate 7:3→3:7) to afford the title compound. LC (method 4):  $t_R$ =1.16 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$ =454 [M+H]<sup>+</sup>.

## Example 17

4-{Cyclopropyl-[1-(4-methanesulfonyl-phenyl)-1H-imidazole-4-carbonyl]-amino}-piperidine-1-carboxylic acid tert-butyl ester

[0509]

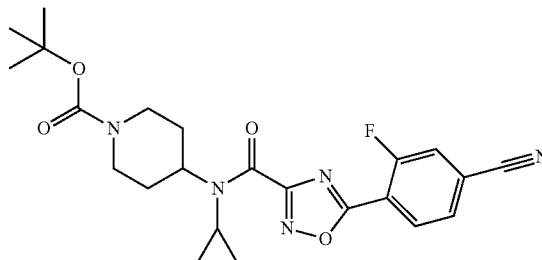


[0510] The title compound is prepared from 4-cyclopropylamino-piperidine-1-carboxylic acid tert-butyl ester and 1-(4-methanesulfonyl-phenyl)-1H-imidazole-4-carboxylic acid following a procedure analogous to that described in Example 5. LC (method 4):  $t_R$ =1.08 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$ =489 [M+H]<sup>+</sup>.

## Example 18

4-[[5-(4-Cyano-2-fluoro-phenyl)-[1,2,4]oxadiazole-3-carbonyl]-cyclopropyl-amino]-piperidine-1-carboxylic acid tert-butyl ester

[0511]

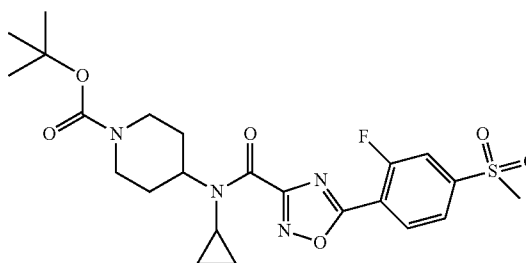


[0512] Oxalyl chloride (45  $\mu$ L) is added to 5-(4-cyano-2-fluoro-phenyl)-[1,2,4]oxadiazole-3-carboxylic acid (30 mg) in dichloromethane (2 mL) while cooling the mixture in a cold water bath. One drop of N,N-dimethylformamide is added and the reaction mixture is stirred for 1 h at room temperature. The mixture is concentrated in vacuo and the crude acid chloride is dissolved in tetrahydrofuran. 4-Cyclopropylamino-piperidine-1-carboxylic acid tert-butyl ester (31 mg) and triethylamine (35  $\mu$ L) are added and the reaction mixture is stirred for two days at room temperature. The mixture is concentrated in vacuo and the residue is chromatographed on silica gel (cyclohexane/ethyl acetate 6:4). The crude product is stirred in n-hexane overnight, filtered off, and dried to afford the title compound. LC (method 7):  $t_R$ =1.36 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$ =400 [M+2H-t-Bu]<sup>+</sup>.

## Example 19

4-{Cyclopropyl-[5-(2-fluoro-4-methanesulfonyl-phenyl)-[1,2,4]oxadiazole-3-carbonyl]-amino}-piperidine-1-carboxylic acid tert-butyl ester

[0513]

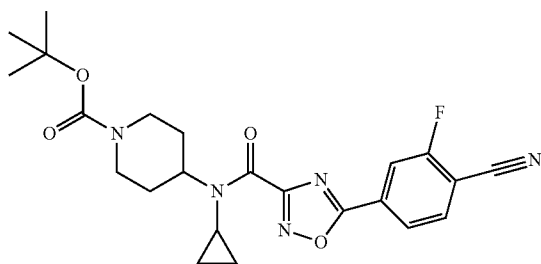


[0514] The title compound is prepared from 5-(2-fluoro-4-methanesulfonyl-phenyl)-[1,2,4]oxadiazole-3-carboxylic acid and 4-cyclopropylamino-piperidine-1-carboxylic acid tert-butyl ester following a procedure analogous to that described in Example 18. LC (method 7):  $t_R$ =1.33 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$ =526 [M+NH<sub>4</sub>]<sup>+</sup>.

## Example 20

4-{{[5-(4-Cyano-3-fluoro-phenyl)-[1,2,4]oxadiazole-3-carbonyl]-cyclopropyl-amino}-piperidine-1-carboxylic acid tert-butyl ester

[0515]

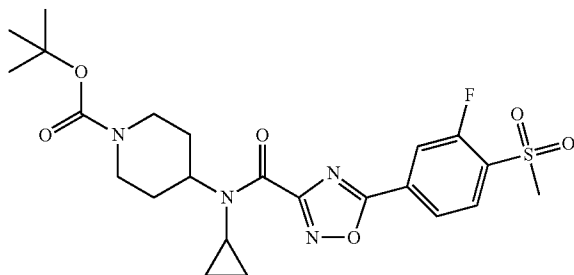


[0516] The title compound is prepared from 5-(4-cyano-3-fluoro-phenyl)-[1,2,4]oxadiazole-3-carboxylic acid and 4-cyclopropylamino-piperidine-1-carboxylic acid tert-butyl ester following a procedure analogous to that described in Example 18. LC (method 5):  $t_R$ =1.71 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$ =473 [M+NH<sub>4</sub>]<sup>+</sup>.

## Example 21

4-{Cyclopropyl-[5-(3-fluoro-4-methanesulfonyl-phenyl)-[1,2,4]oxadiazole-3-carbonyl]-amino}-piperidine-1-carboxylic acid tert-butyl ester

[0517]

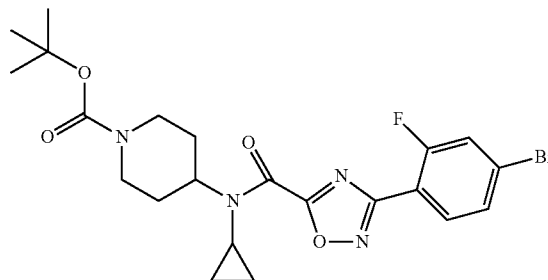


[0518] The title compound is prepared from 5-(3-fluoro-4-methanesulfonyl-phenyl)-[1,2,4]oxadiazole-3-carboxylic acid and 4-cyclopropylamino-piperidine-1-carboxylic acid tert-butyl ester following a procedure analogous to that described in Example 18. LC (method 4):  $t_R$ =1.61 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$ =526 [M+NH<sub>4</sub>]<sup>+</sup>.

## Example 22

4-{{[3-(4-Bromo-2-fluoro-phenyl)-[1,2,4]oxadiazole-5-carbonyl]-cyclopropyl-amino}-piperidine-1-carboxylic acid tert-butyl ester

[0519]

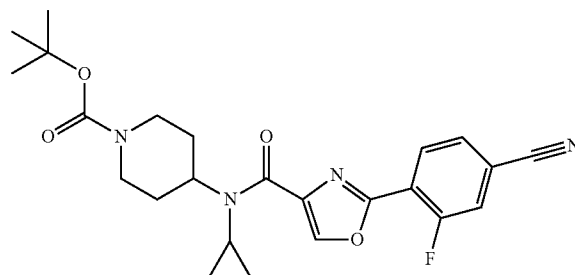


[0520] The title compound is prepared from 3-(4-bromo-2-fluoro-phenyl)-[1,2,4]oxadiazole-5-carboxylic acid and 4-cyclopropylamino-piperidine-1-carboxylic acid tert-butyl ester following a procedure analogous to that described in Example 18. LC (method 5):  $t_R$ =1.85 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$ =509 [M+H]<sup>+</sup>.

## Example 23

4-{{[2-(4-Cyano-2-fluoro-phenyl)-oxazole-4-carbonyl]-cyclopropyl-amino}-piperidine-1-carboxylic acid tert-butyl ester

[0521]

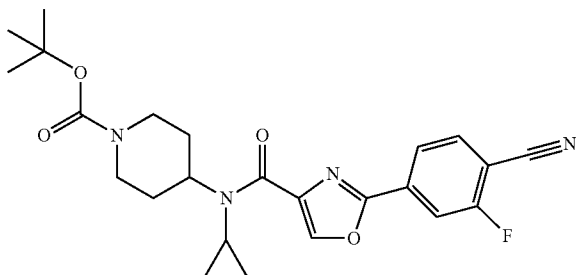


[0522] The title compound is prepared from 2-(4-cyano-2-fluoro-phenyl)-oxazole-4-carboxylic acid and 4-cyclopropylamino-piperidine-1-carboxylic acid tert-butyl ester following a procedure analogous to that described in Example 18. LC (method 8):  $t_R$ =1.68 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$ =455 [M+H]<sup>+</sup>.

## Example 24

4-{{2-(4-Cyano-3-fluoro-phenyl)-oxazole-4-carbonyl}-cyclopropyl-amino}-piperidine-1-carboxylic acid tert-butyl ester

[0523]

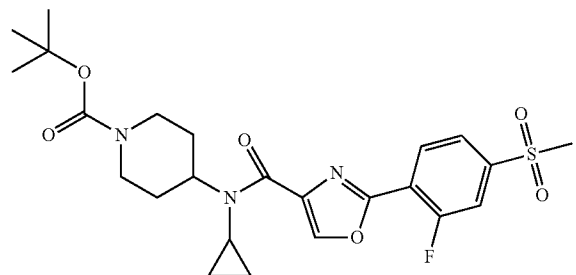


[0524] The title compound is prepared from 2-(4-cyano-3-fluoro-phenyl)-oxazole-4-carboxylic acid and 4-cyclopropylamino-piperidine-1-carboxylic acid tert-butyl ester following a procedure analogous to that described in Example 18. LC (method 8):  $t_R$ =1.71 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$ =455 [M+H]<sup>+</sup>.

## Example 25

4-{{(Cyclopropyl)-[2-(2-fluoro-4-methanesulfonyl-phenyl)-oxazole-4-carbonyl]-amino}-piperidine-1-carboxylic acid tert-butyl ester

[0525]

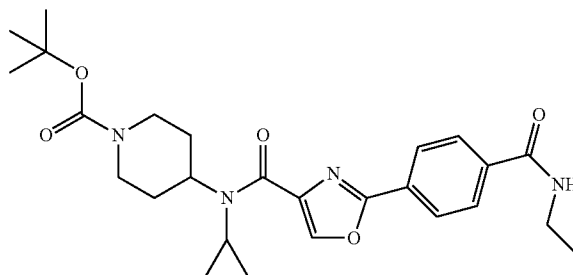


[0526] The title compound is prepared from 2-(2-fluoro-4-methanesulfonyl-phenyl)-oxazole-4-carboxylic acid and 4-cyclopropylamino-piperidine-1-carboxylic acid tert-butyl ester following a procedure analogous to that described in Example 18. LC (method 8):  $t_R$ =1.60 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$ =508 [M+H]<sup>+</sup>.

## Example 26

4-{Cyclopropyl-[2-(4-ethylcarbamoyl-phenyl)-oxazole-4-carbonyl]-amino}-piperidine-1-carboxylic acid tert-butyl ester

[0527]

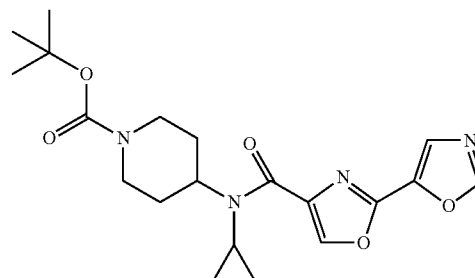


[0528] 2-(7-Aza-1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (178 mg) and 1-hydroxy-7-azabenzotriazole (28 mg) are added to a solution of 2-(4-ethylcarbamoyl-phenyl)-oxazole-4-carboxylic acid (81 mg) and ethyldiisopropylamine (208  $\mu$ L) in N,N-dimethylformamide (8 mL) at room temperature. 4-Cyclopropylamino-piperidine-1-carboxylic acid tert-butyl ester (75 mg) is added and the resulting mixture is stirred at room temperature overnight. Water and ethyl acetate are added and the organic phase is separated, washed with water and brine, dried over MgSO<sub>4</sub> and concentrated in vacuo. The residue is chromatographed on silica gel (dichloromethane/methanol 99:1→90:10). The crude product is triturated with diethyl ether, filtered off, and dried to afford the title compound. LC (method 8):  $t_R$ =1.63 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$ =483 [M+H]<sup>+</sup>.

## Example 27

4-[[[2,5']Bioxazolyl-4-carbonyl]-cyclopropyl-amino]-piperidine-1-carboxylic acid tert-butyl ester

[0529]

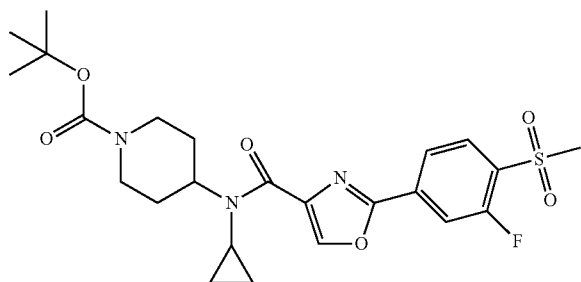


[0530] The title compound is prepared from [2,5']bioxazolyl-4-carboxylic acid and 4-cyclopropylamino-piperidine-1-carboxylic acid tert-butyl ester following a procedure analogous to that described in Example 26. LC (method 8):  $t_R$ =1.53 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$ =403 [M+H]<sup>+</sup>.

## Example 28

4-{Cyclopropyl-[2-(3-fluoro-4-methanesulfonyl-phenyl)-oxazole-4-carbonyl]-amino}-piperidine-1-carboxylic acid tert-butyl ester

[0531]

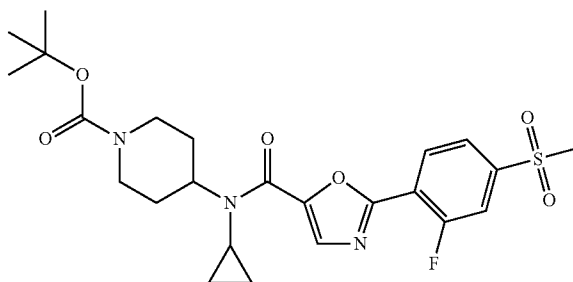


[0532] The title compound is prepared from 2-(3-fluoro-4-methanesulfonyl-phenyl)-oxazole-4-carboxylic acid and 4-cyclopropylamino-piperidine-1-carboxylic acid tert-butyl ester following a procedure analogous to that described in Example 18. LC (method 8):  $t_R$ =1.61 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$ =508 [M+H]<sup>+</sup>.

## Example 30

4-{Cyclopropyl-[2-(2-fluoro-4-methanesulfonyl-phenyl)-oxazole-5-carbonyl]-amino}-piperidine-1-carboxylic acid tert-butyl ester

[0535]

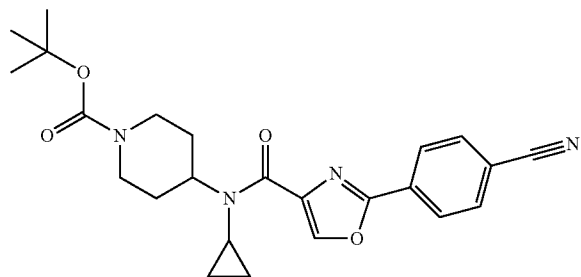


[0536] The title compound is prepared from 2-(2-fluoro-4-methanesulfonyl-phenyl)-oxazole-5-carboxylic acid and 4-cyclopropylamino-piperidine-1-carboxylic acid tert-butyl ester following a procedure analogous to that described in Example 18. LC (method 8):  $t_R$ =1.61 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$ =508 [M+H]<sup>+</sup>.

## Example 29

4-{[2-(4-Cyano-phenyl)-oxazole-4-carbonyl]-cyclopropyl-amino}-piperidine-1-carboxylic acid tert-butyl ester

[0533]

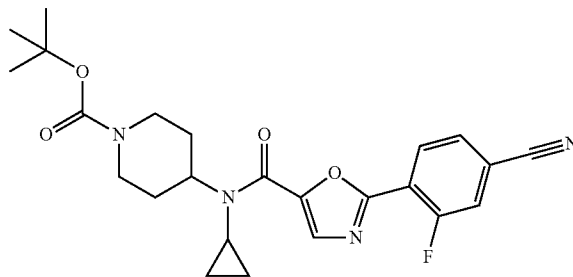


[0534] The title compound is prepared from 2-(4-cyano-phenyl)-oxazole-4-carboxylic acid and 4-cyclopropylamino-piperidine-1-carboxylic acid tert-butyl ester following a procedure analogous to that described in Example 18. LC (method 8):  $t_R$ =1.68 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$ =437 [M+H]<sup>+</sup>.

## Example 31

4-{[2-(4-Cyano-2-fluoro-phenyl)-oxazole-5-carbonyl]-cyclopropyl-amino}-piperidine-1-carboxylic acid tert-butyl ester

[0537]

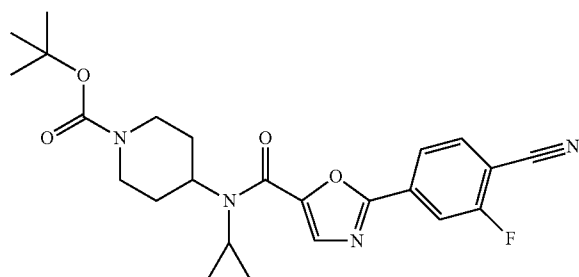


[0538] The title compound is prepared from 2-(4-cyano-2-fluoro-phenyl)-oxazole-5-carboxylic acid and 4-cyclopropylamino-piperidine-1-carboxylic acid tert-butyl ester following a procedure analogous to that described in Example 18. LC (method 8):  $t_R$ =1.68 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$ =455 [M+H]<sup>+</sup>.

## Example 32

4-{{2-(4-Cyano-3-fluoro-phenyl)-oxazole-5-carbonyl}-cyclopropyl-amino}-piperidine-1-carboxylic acid tert-butyl ester

[0539]

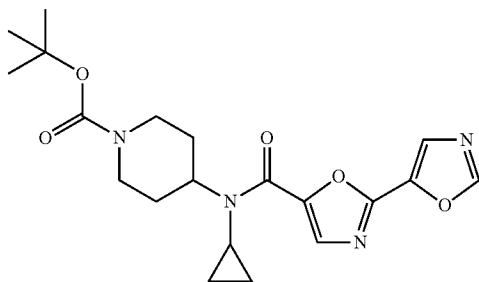


[0540] The title compound is prepared from 2-(4-cyano-3-fluoro-phenyl)-oxazole-5-carboxylic acid and 4-cyclopropylamino-piperidine-1-carboxylic acid tert-butyl ester following a procedure analogous to that described in Example 18. LC (method 8):  $t_R$ =1.71 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$ =455 [M+H]<sup>+</sup>.

## Example 33

4-([2,5']Bioxazolyl-5-carbonyl)-cyclopropyl-amino]-piperidine-1-carboxylic acid tert-butyl ester

[0541]

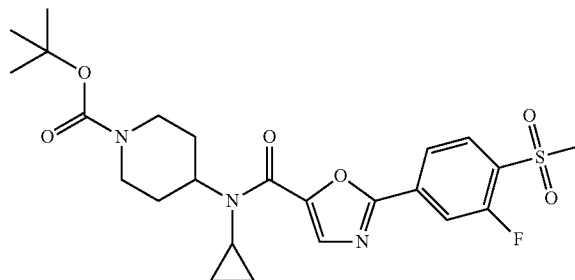


[0542] The title compound is prepared from [2,5']bioxazolyl-5-carboxylic acid and 4-cyclopropylamino-piperidine-1-carboxylic acid tert-butyl ester following a procedure analogous to that described in Example 26. LC (method 8):  $t_R$ =1.53 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$ =403 [M+H]<sup>+</sup>.

## Example 34

4-{Cyclopropyl-[2-(3-fluoro-4-methanesulfonyl-phenyl)-oxazole-5-carbonyl]-amino}-piperidine-1-carboxylic acid tert-butyl ester

[0543]

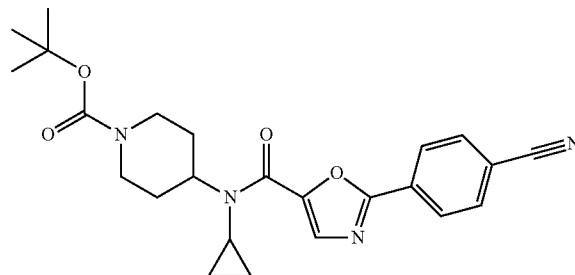


[0544] The title compound is prepared from 2-(3-fluoro-4-methanesulfonyl-phenyl)-oxazole-5-carboxylic acid and 4-cyclopropylamino-piperidine-1-carboxylic acid tert-butyl ester following a procedure analogous to that described in Example 18. LC (method 8):  $t_R$ =1.61 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$ =508 [M+H]<sup>+</sup>.

## Example 35

4-{{2-(4-Cyano-phenyl)-oxazole-5-carbonyl]-cyclopropyl-amino}-piperidine-1-carboxylic acid tert-butyl ester

[0545]



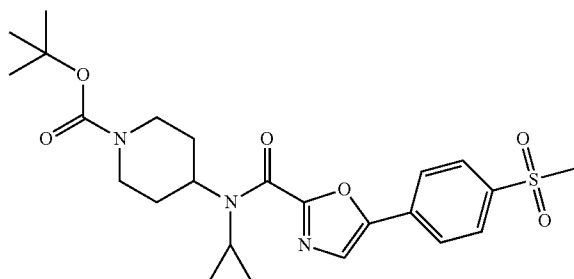
[0546] The title compound is prepared from 2-(4-cyano-phenyl)-oxazole-5-carboxylic acid and 4-cyclopropylamino-piperidine-1-carboxylic acid tert-butyl ester following a procedure analogous to that described in Example 18. LC (method 8):  $t_R$ =1.67 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$ =437 [M+H]<sup>+</sup>.



## Example 36

4-{Cyclopropyl-[5-(4-methanesulfonyl-phenyl)-oxazole-2-carbonyl]-amino}-piperidine-1-carboxylic acid tert-butyl ester

[0547]

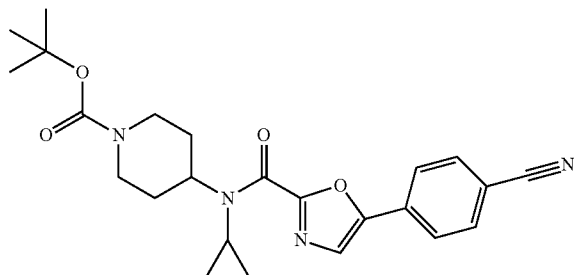


[0548] The title compound is prepared from 5-(4-methanesulfonyl-phenyl)-oxazole-2-carboxylic acid and 4-cyclopropylamino-piperidine-1-carboxylic acid tert-butyl ester following a procedure analogous to that described in Example 18. LC (method 8):  $t_R$ =1.58 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$ =490 [M+H]<sup>+</sup>.

## Example 37

4-{[5-(4-Cyano-phenyl)-oxazole-2-carbonyl]-cyclopropyl-amino}-piperidine-1-carboxylic acid tert-butyl ester

[0549]

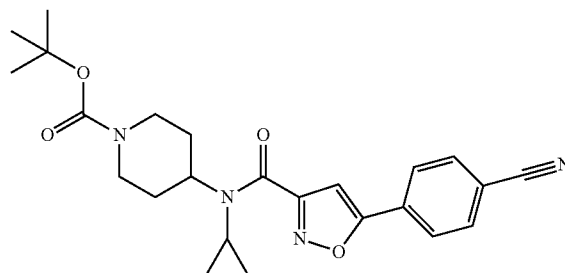


[0550] The title compound is prepared from 5-(4-cyano-phenyl)-oxazole-2-carboxylic acid and 4-cyclopropylamino-piperidine-1-carboxylic acid tert-butyl ester following a procedure analogous to that described in Example 18. LC (method 8):  $t_R$ =1.66 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$ =437 [M+H]<sup>+</sup>.

## Example 38

4-{[5-(4-Cyano-phenyl)-isoxazole-3-carbonyl]-cyclopropyl-amino}-piperidine-1-carboxylic acid tert-butyl ester

[0551]

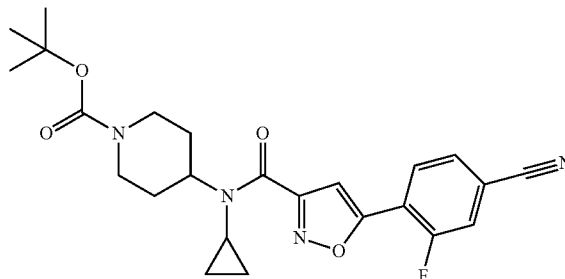


[0552] The title compound is prepared from 5-(4-cyano-phenyl)-isoxazole-3-carboxylic acid and 4-cyclopropylamino-piperidine-1-carboxylic acid tert-butyl ester following a procedure analogous to that described in Example 18. LC (method 8):  $t_R$ =1.69 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$ =437 [M+H]<sup>+</sup>.

## Example 39

4-{[5-(4-Cyano-2-fluoro-phenyl)-isoxazole-3-carbonyl]-cyclopropyl-amino}-piperidine-1-carboxylic acid tert-butyl ester

[0553]

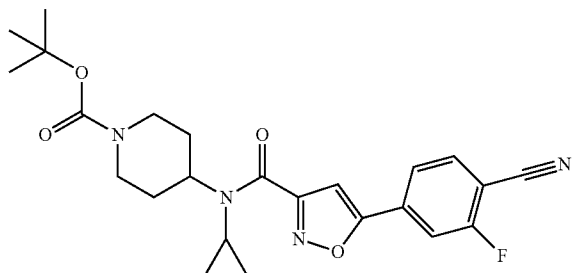


[0554] The title compound is prepared from 5-(4-cyano-2-fluoro-phenyl)-isoxazole-3-carboxylic acid and 4-cyclopropylamino-piperidine-1-carboxylic acid tert-butyl ester following a procedure analogous to that described in Example 18. LC (method 9):  $t_R$ =1.07 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$ =455 [M+H]<sup>+</sup>.

## Example 40

4-{{[5-(4-Cyano-3-fluoro-phenyl)-isoxazole-3-carbonyl]-cyclopropyl-amino}-piperidine-1-carboxylic acid tert-butyl ester

[0555]

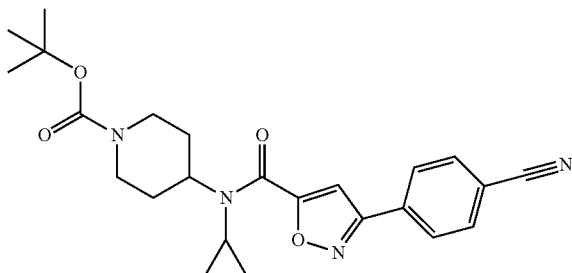


[0556] The title compound is prepared from 5-(4-cyano-3-fluoro-phenyl)-isoxazole-3-carboxylic acid and 4-cyclopropylamino-piperidine-1-carboxylic acid tert-butyl ester following a procedure analogous to that described in Example 18. LC (method 9):  $t_R$ =1.08 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$ =455 [M+H]<sup>+</sup>.

## Example 41

4-{{[3-(4-Cyano-phenyl)-isoxazole-5-carbonyl]-cyclopropyl-amino}-piperidine-1-carboxylic acid tert-butyl ester

[0557]

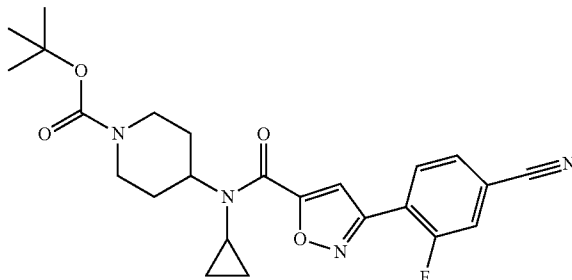


[0558] The title compound is prepared from 3-(4-cyano-phenyl)-isoxazole-5-carboxylic acid and 4-cyclopropylamino-piperidine-1-carboxylic acid tert-butyl ester following a procedure analogous to that described in Example 18. LC (method 9):  $t_R$ =1.27 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$ =437 [M+H]<sup>+</sup>.

## Example 42

4-{{[3-(4-Cyano-2-fluoro-phenyl)-isoxazole-5-carbonyl]-cyclopropyl-amino}-piperidine-1-carboxylic acid tert-butyl ester

[0559]

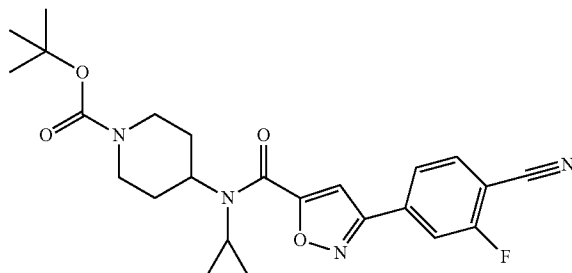


[0560] The title compound is prepared from 3-(4-cyano-2-fluoro-phenyl)-isoxazole-5-carboxylic acid and 4-cyclopropylamino-piperidine-1-carboxylic acid tert-butyl ester following a procedure analogous to that described in Example 18. LC (method 9):  $t_R$ =1.28 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$ =455 [M+H]<sup>+</sup>.

## Example 43

4-{{[3-(4-Cyano-3-fluoro-phenyl)-isoxazole-5-carbonyl]-cyclopropyl-amino}-piperidine-1-carboxylic acid tert-butyl ester

[0561]

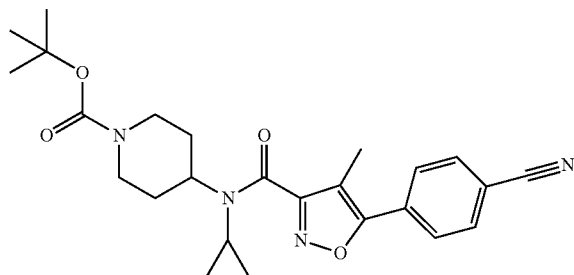


[0562] The title compound is prepared from 3-(4-cyano-3-fluoro-phenyl)-isoxazole-5-carboxylic acid and 4-cyclopropylamino-piperidine-1-carboxylic acid tert-butyl ester following a procedure analogous to that described in Example 18. LC (method 9):  $t_R$ =1.30 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$ =455 [M+H]<sup>+</sup>.

## Example 44

4-{[5-(4-Cyano-phenyl)-4-methyl-isoxazole-3-carbonyl]-cyclopropyl-amino}-piperidine-1-carboxylic acid tert-butyl ester

[0563]

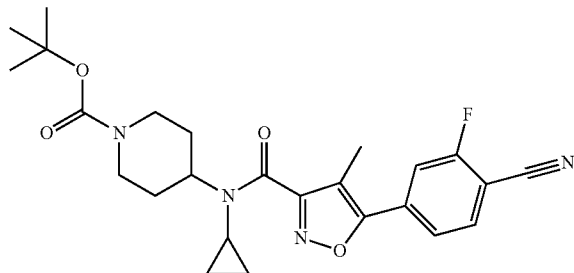


[0564] The title compound is prepared from 5-(4-cyano-phenyl)-4-methyl-isoxazole-3-carboxylic acid and 4-cyclopropylamino-piperidine-1-carboxylic acid tert-butyl ester following a procedure analogous to that described in Example 18. LC (method 9):  $t_R$ =1.29 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$ =451 [M+H]<sup>+</sup>.

## Example 45

4-{[5-(4-Cyano-3-fluoro-phenyl)-4-methyl-isoxazole-3-carbonyl]-cyclopropyl-amino}-piperidine-1-carboxylic acid tert-butyl ester

[0565]

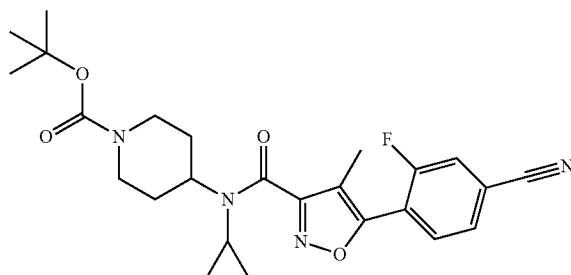


[0566] The title compound is prepared from 5-(4-cyano-3-fluoro-phenyl)-4-methyl-isoxazole-3-carboxylic acid and 4-cyclopropylamino-piperidine-1-carboxylic acid tert-butyl ester following a procedure analogous to that described in Example 18. LC (method 9):  $t_R$ =1.30 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$ =469 [M+H]<sup>+</sup>.

## Example 46

4-{[5-(4-Cyano-2-fluoro-phenyl)-4-methyl-isoxazole-3-carbonyl]-cyclopropyl-amino}-piperidine-1-carboxylic acid tert-butyl ester

[0567]

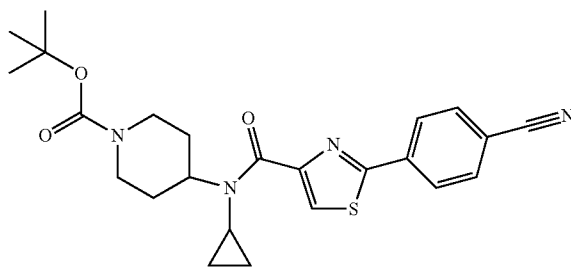


[0568] The title compound is prepared from 5-(4-cyano-2-fluoro-phenyl)-4-methyl-isoxazole-3-carboxylic acid and 4-cyclopropylamino-piperidine-1-carboxylic acid tert-butyl ester following a procedure analogous to that described in Example 18. LC (method 9):  $t_R$ =1.29 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$ =469 [M+H]<sup>+</sup>.

## Example 47

4-{[2-(4-Cyano-phenyl)-thiazole-4-carbonyl]-cyclopropyl-amino}-piperidine-1-carboxylic acid tert-butyl ester

[0569]

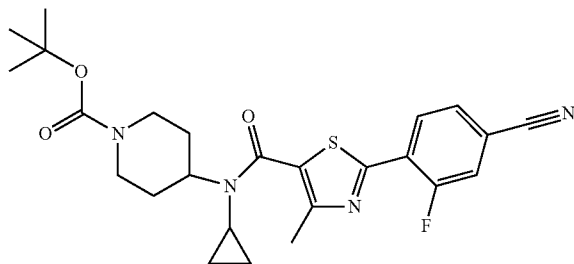


[0570] The title compound is prepared from 2-(4-cyano-phenyl)-thiazole-4-carboxylic acid and 4-cyclopropylamino-piperidine-1-carboxylic acid tert-butyl ester following a procedure analogous to that described in Example 18. LC (method 9):  $t_R$ =1.27 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$ =475 [M+Na]<sup>+</sup>.

## Example 48

4-{{[2-(4-Cyano-2-fluoro-phenyl)-4-methyl-thiazole-5-carbonyl]-cyclopropyl-amino}-piperidine-1-carboxylic acid tert-butyl ester

[0571]

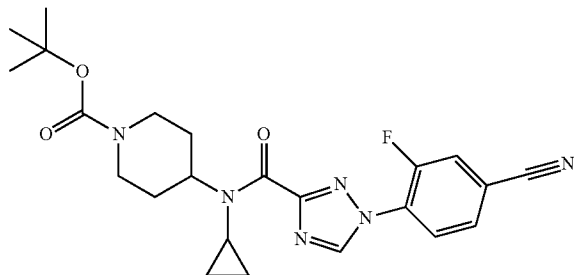


[0572] The title compound is prepared from 2-(4-cyano-2-fluoro-phenyl)-4-methyl-thiazole-5-carboxylic acid and 4-cyclopropylamino-piperidine-1-carboxylic acid tert-butyl ester following a procedure analogous to that described in Example 18. LC (method 9):  $t_R$ =1.33 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$ =485 [M+H]<sup>+</sup>.

## Example 49

4-{{[1-(4-Cyano-2-fluoro-phenyl)-1H-[1,2,4]triazole-3-carbonyl]-cyclopropyl-amino}-piperidine-1-carboxylic acid tert-butyl ester

[0573]

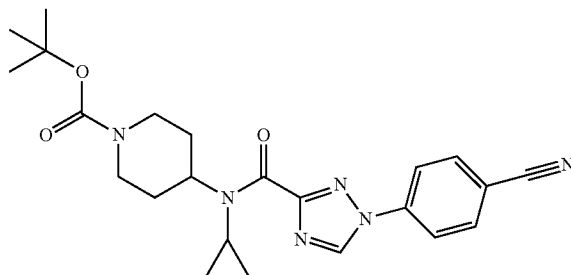


[0574] The title compound is prepared from 1-(4-cyano-2-fluoro-phenyl)-1H-[1,2,4]triazole-3-carboxylic acid and 4-cyclopropylamino-piperidine-1-carboxylic acid tert-butyl ester following a procedure analogous to that described in Example 18. LC (method 9):  $t_R$ =1.19 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$ =455 [M+H]<sup>+</sup>.

## Example 50

4-{{[1-(4-Cyano-phenyl)-1H-[1,2,4]triazole-3-carbonyl]-cyclopropyl-amino}-piperidine-1-carboxylic acid tert-butyl ester

[0575]

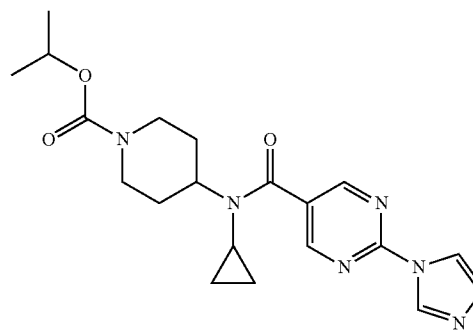


[0576] The title compound is prepared from 1-(4-cyano-phenyl)-1H-[1,2,4]triazole-3-carboxylic acid and 4-cyclopropylamino-piperidine-1-carboxylic acid tert-butyl ester following a procedure analogous to that described in Example 18. LC (method 9):  $t_R$ =1.18 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$ =437 [M+H]<sup>+</sup>.

## Example 51

4-[Cyclopropyl-(2-imidazol-1-yl-pyrimidine-5-carbonyl)-amino]-piperidine-1-carboxylic acid isopropyl ester

[0577]

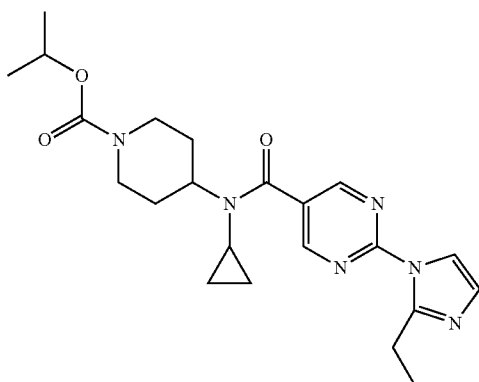


[0578] To 2-imidazol-1-yl-pyrimidine-5-carboxylic acid cyclopropyl-piperidin-4-yl-amide (43 mg) in tetrahydrofuran (2 mL) is added N,N-diisopropylethylamine (43  $\mu$ L). The mixture is cooled to 0° C. and isopropyl chloroformate (150  $\mu$ L) is added. The mixture is stirred for 12 h at room temperature. The solvent is removed in vacuo and the residue is purified by HPLC (C18 RP Sunfire, H<sub>2</sub>O/MeOH+0.1% TFA) to yield the desired product. LC (method 10):  $t_R$ =1.50 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$ =399 [M+H]<sup>+</sup>.

## Example 52

4-{Cyclopropyl-[2-(2-ethyl-imidazol-1-yl)-pyrimidine-5-carbonyl]-amino}-piperidine-1-carboxylic acid isopropyl ester

[0579]

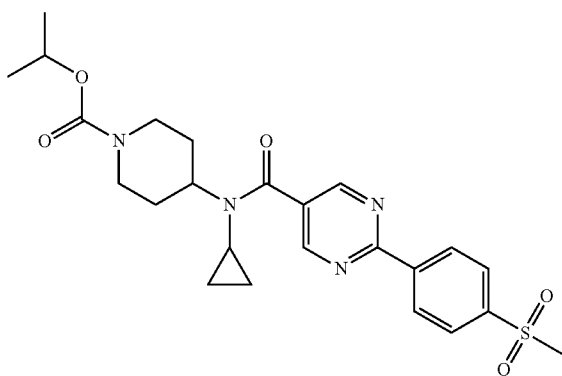


**[0580]** The title compound was prepared analogously to 4-[cyclopropyl-(2-imidazol-1-yl-pyrimidine-5-carbonyl)-amino]-piperidine-1-carboxylic acid isopropyl ester (Example 51), using 2-(2-ethyl-imidazol-1-yl)-pyrimidine-5-carboxylic acid cyclopropyl-piperidin-4-yl-amide as starting material. LC (method 10):  $t_R$ =1.54 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$ =427 [M+H]<sup>+</sup>.

## Example 53

4-{Cyclopropyl-[2-(4-methanesulfonyl-phenyl)-pyrimidine-5-carbonyl]-amino}-piperidine-1-carboxylic acid isopropyl ester

[0581]

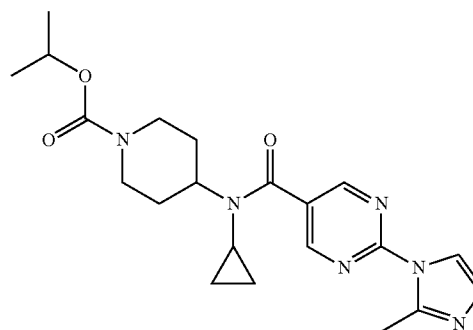


**[0582]** The title compound was prepared analogously to 4-[cyclopropyl-(2-imidazol-1-yl-pyrimidine-5-carbonyl)-amino]-piperidine-1-carboxylic acid isopropyl ester (Example 51), using 2-(2-ethyl-imidazol-1-yl)-pyrimidine-5-carboxylic acid cyclopropyl-piperidin-4-yl-amide as starting material. LC (method 10):  $t_R$ =1.86 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$ =487 [M+H]<sup>+</sup>.

## Example 54

4-{Cyclopropyl-[2-(2-methyl-imidazol-1-yl)-pyrimidine-5-carbonyl]-amino}-piperidine-1-carboxylic acid isopropyl ester

[0583]

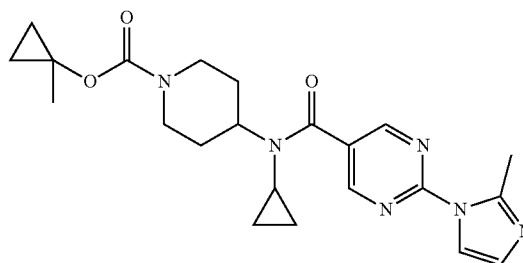


**[0584]** The title compound was prepared analogously to 4-[cyclopropyl-(2-imidazol-1-yl-pyrimidine-5-carbonyl)-amino]-piperidine-1-carboxylic acid isopropyl ester (Example 51), using 2-(2-methyl-imidazol-1-yl)-pyrimidine-5-carboxylic acid cyclopropyl-piperidin-4-yl-amide as starting material. LC (method 11):  $t_R$ =1.19 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$ =413 [M+H]<sup>+</sup>.

## Example 55

4-{Cyclopropyl-[2-(2-methyl-imidazol-1-yl)-pyrimidine-5-carbonyl]-amino}-piperidine-1-carboxylic acid 1-methyl-cyclopropyl ester

[0585]

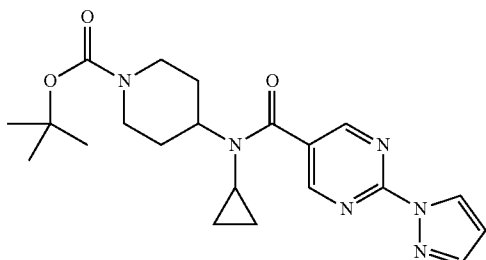


**[0586]** 2-(2-Methyl-imidazol-1-yl)-pyrimidine-5-carboxylic acid cyclopropyl-piperidin-4-yl-amide (trifluoroacetic acid salt, 35 mg), carbonic acid 1-methyl-cyclopropyl ester 4-nitro-phenyl ester (24 mg) and ethyldiisopropylamine (19  $\mu$ L) in dichloromethane (2 mL) are stirred for 12 h at 50° C. N,N-dimethylformamide (1 mL) is added and stirring is continued for 2 h at 50° C. The mixture is concentrated in vacuo and the residue is purified by HPLC (H<sub>2</sub>O/MeOH+0.1% TFA) to yield the desired product. LC (method 11):  $t_R$ =0.48 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$ =425 [M+H]<sup>+</sup>.

## Example 56

4-[Cyclopropyl-(2-pyrazol-1-yl-pyrimidine-5-carbonyl)-amino]-piperidine-1-carboxylic acid tert-butyl ester

[0587]



**[0588]** A mixture of 4-[(2-chloro-pyrimidine-5-carbonyl)-cyclopropyl-amino]-piperidine-1-carboxylic acid tert-butyl ester, pyrazole (22 mg) and ethyldiisopropylamine (41  $\mu$ L) in dimethylacetamide (2.0 mL) is stirred for 5 days at 100° C. The mixture is then purified by HPLC (C18 RP XBridge, MeOH/H<sub>2</sub>O+0.1% NH<sub>4</sub>OH) to yield the desired product. LC (method 14):  $t_R$ =2.47 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$ =413 [M+H]<sup>+</sup>.

**[0589]** The following compounds of table 2 are prepared analogously to Example 56, the starting materials used being shown in the column headed “E 1” and “E 2”:

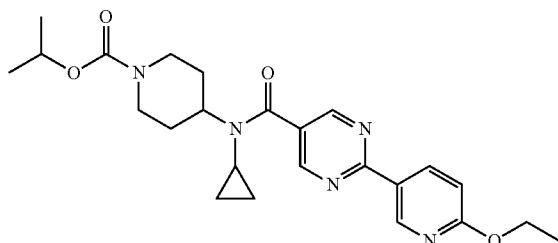
TABLE 2

| Ex. | Structure   | E 1    | E 2                         | ESI-MS<br>[m/z]             | HPLC $t_R$<br>[min]<br>(method) |
|-----|---|--------|-----------------------------|-----------------------------|---------------------------------|
| 57  | <p>4-{Cyclopropyl-[2-(3,5-dimethylpyrazol-1-yl)-pyrimidine-5-carbonyl]-amino}-piperidine-1-carboxylic acid tert-butyl ester</p>         | Int. 6 | 3,5-dimethylpyrazole        | 441<br>[M + H] <sup>+</sup> | 2.61<br>(14)                    |
| 58  | <p>4-(Cyclopropyl-[2-[4-(2-hydroxy-ethyl)-pyrazol-1-yl]-pyrimidine-5-carbonyl]-amino)-piperidine-1-carboxylic acid tert-butyl ester</p> | Int. 6 | 2-(1H-pyrazol-4-yl)-ethanol | 457<br>[M + H] <sup>+</sup> | 2.40<br>(14)                    |

## Example 59

4-{Cyclopropyl-[2-(6-ethoxy-pyridin-3-yl)-pyrimidine-5-carbonyl]-amino}-piperidine-1-carboxylic acid isopropyl ester

[0590]



[0591] To 2-(6-ethoxy-pyridin-3-yl)-pyrimidine-5-carboxylic acid cyclopropyl-piperidin-4-yl-amide (39 mg) in tetrahydrofuran (2 mL) is added ethyldiisopropylamine (43  $\mu$ L). The mixture is cooled to 0° C. and isopropyl chloroformate (144  $\mu$ L) is added. The mixture is stirred for 3 h at room temperature. The solvent is removed in vacuo and the residue is purified by HPLC (C18 RP Sunfire, H<sub>2</sub>O/MeOH+0.1% TFA) to yield the desired product. LC (method 6):  $t_R$ =2.01 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$ =454 [M+H]<sup>+</sup>.

[0592] The following compounds of table 3 are prepared analogously to Example 59, the starting material used being shown in the column headed "E 1":

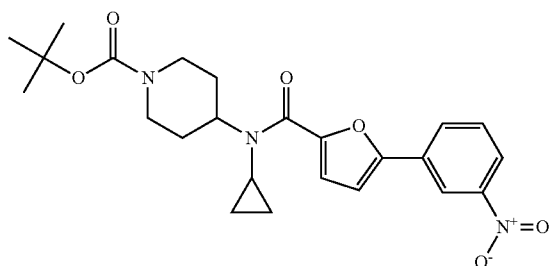
TABLE 3

| Ex. | Structure   | E 1     | ESI-MS<br>[m/z]             | HPLC $t_R$<br>[min]<br>(method) |
|-----|---|---------|-----------------------------|---------------------------------|
| 60  | <p>4-[[2-(4-Cyanomethyl-phenyl)-pyrimidine-5-carbonyl]-cyclopropyl-amino]-piperidine-1-carboxylic acid isopropyl ester</p>    | Int. 90 | 448<br>[M + H] <sup>+</sup> | 1.92<br>(6)                     |
| 61  | <p>4-[[2-(4-Cyano-3-fluoro-phenyl)-pyrimidine-5-carbonyl]-cyclopropyl-amino]-piperidine-1-carboxylic acid isopropyl ester</p> | Int. 91 | 452<br>[M + H] <sup>+</sup> | 2.07<br>(6)                     |

## Example 62

4-{Cyclopropyl-[5-(3-nitro-phenyl)-furan-2-carbonyl]-amino}-piperidine-1-carboxylic acid tert-butyl ester

[0593]



**[0594]** To 5-(3-nitro-phenyl)-furan-2-carboxylic acid (23 mg) in N,N-dimethylformamide (2 mL) is added 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (32 mg) and ethyldiisopropylamine (34  $\mu$ L) and the mixture is stirred for 15 min at room temperature. 4-Cyclopropylamino-piperidine-1-carboxylic acid tert-butyl ester (24 mg) is added and stirring is continued for 12 h at room temperature. The mixture is filtered through basic aluminum oxide, followed by washing with N,N-dimethylformamide/methanol (9:1) and concentration. The residue is purified by HPLC (XBridge, MeOH/H<sub>2</sub>O+0.1% NH<sub>4</sub>OH) to yield the desired product. LC (method 14):  $t_R$ =1.84 min; Mass spectrum (ESI<sup>+</sup>):  $m/z$ =456 [M+H]<sup>+</sup>.

**[0595]** The following compounds of table 4 are prepared analogously to Example 62, the starting material and the reagent used being shown in the column headed "E 2" and "Reagent" (TBTU denotes 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate and TCFH denotes chloro-N,N,N',N'-tetramethylformamidinium hexafluorophosphate):

TABLE 4

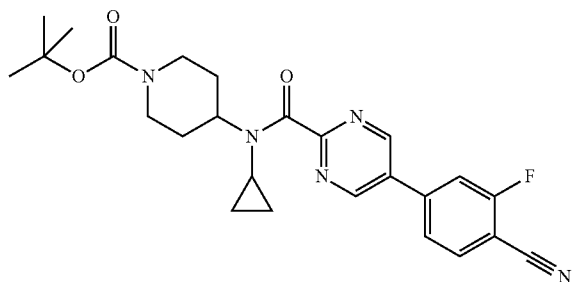
| Ex. | Structure | E 2 | Reagent | ESI-MS<br>[m/z]             | HPLC $t_R$<br>[min]<br>(method) |
|-----|-----------|-----|---------|-----------------------------|---------------------------------|
| 63  |           |     | TCFH    | 424<br>[M + H] <sup>+</sup> | 1.40<br>(15)                    |
| 64  |           |     | TBTU    | 456<br>[M + H] <sup>+</sup> | 1.75<br>(14)                    |
| 65  |           |     | TBTU    | 456<br>[M + H] <sup>+</sup> | 1.72<br>(14)                    |



## Example 66

4-{[5-(4-Cyano-3-fluoro-phenyl)-pyrimidine-2-carbonyl]-cyclopropyl-amino}-piperidine-1-carboxylic acid tert-butyl ester

[0596]



**[0597]** Under an argon atmosphere an aqueous solution of  $\text{Na}_2\text{CO}_3$  (2 M, 0.15 mL) and bis(triphenylphosphine)-palladium(II) chloride (3.1 mg) is added to a mixture of 4-cyano-3-fluorophenylboronic acid (74 mg) and 4-[(5-bromo-pyrimidine-2-carbonyl)-cyclopropyl-amino]-piperidine-1-carboxylic acid tert-butyl ester in 1,4-dioxane (1.3 mL) and methanol (0.67 mL). The mixture is stirred for 12 h at  $80^\circ\text{C}$ . The solvents are removed in vacuo. The residue is taken up in N,N-dimethylformamide filtered and purified by HPLC (C18 RP XBridge, MeOH/ $\text{H}_2\text{O}$ +0.1%  $\text{NH}_4\text{OH}$ ) to yield the desired product. LC (method 11):  $t_R$ =1.24 min; Mass spectrum ( $\text{ESI}^+$ ):  $m/z$ =464  $[\text{M}-\text{H}]^-$ .

**[0598]** The following compounds of table 5 are prepared analogously to Example 66, the starting materials used being shown in the column headed "E 1" and "E 2":

TABLE 5

| Ex. | Structure   | E 1        | E 2 | ESI-MS<br>[m/z]             | HPLC $t_R$<br>[min]<br>(method) |
|-----|---|------------|-----|-----------------------------|---------------------------------|
| 67  | <p>4-{Cyclopropyl-[5-(4-prop-2-ynyl-phenyl)-pyrimidine-2-carbonyl]-amino}-piperidine-1-carboxylic acid tert-butyl ester</p>     | Int.<br>88 |     | 460<br>[M - H] <sup>-</sup> | 1.21<br>(11)                    |
| 68  | <p>4-{Cyclopropyl-[5-(4-methanesulfonyl-phenyl)-pyrimidine-2-carbonyl]-amino}-piperidine-1-carboxylic acid tert-butyl ester</p> | Int.<br>88 |     | 499<br>[M - H] <sup>-</sup> | 1.16<br>(11)                    |

TABLE 5-continued

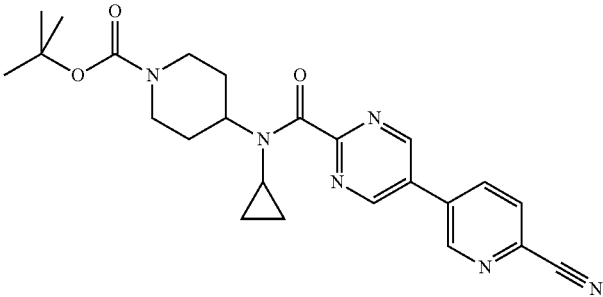
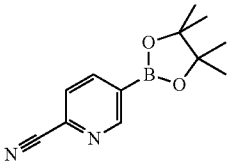
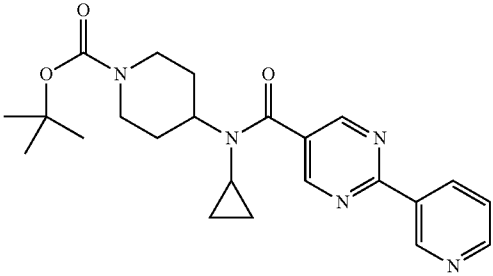
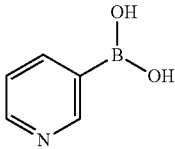
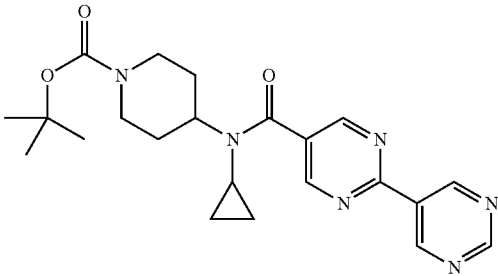
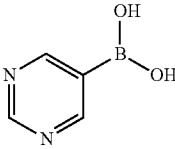
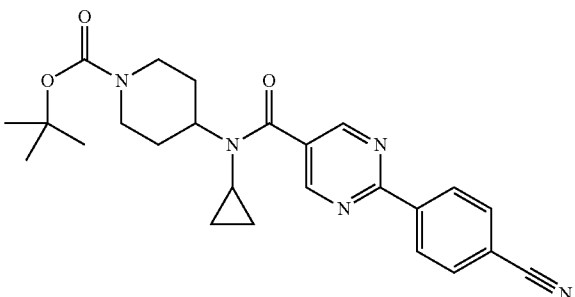
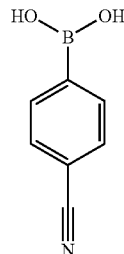
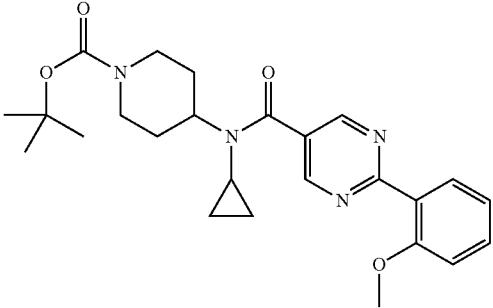
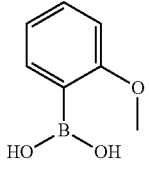
| Ex. | Structure  | E 1        | E 2  | ESI-MS<br>[m/z]             | HPLC $t_R$<br>[min]<br>(method) |
|-----|--|------------|--|-----------------------------|---------------------------------|
| 69  |  <p>4-([5-(6-Cyano-pyridin-3-yl)-pyrimidin-2-carbonyl]-cyclopropyl-amino)-piperidine-1-carboxylic acid tert-butyl ester</p> | Int.<br>88 |    | 477<br>[M - H] <sup>-</sup> | 1.16<br>(11)                    |
| 70  |  <p>4-[Cyclopropyl-(2-pyridin-3-yl-pyrimidine-5-carbonyl)-amino]-piperidine-1-carboxylic acid tert-butyl ester</p>        | Int.<br>6  |  | 424<br>[M + H] <sup>+</sup> | 1.88<br>(16)                    |
| 71  |  <p>4-([(2,5']Bipyrimidinyl-5-carbonyl)-cyclopropyl-amino]-piperidine-1-carboxylic acid tert-butyl ester</p>              | Int.<br>6  |  | 425<br>[M + H] <sup>+</sup> | 2.08<br>(16)                    |

TABLE 5-continued

| Ex. | Structure   | E 1       | E 2  | ESI-MS<br>[m/z]             | HPLC $t_R$<br>[min]<br>(method) |
|-----|---|-----------|--|-----------------------------|---------------------------------|
| 72  |  <p>4-([2-(4-Cyano-phenyl)-pyrimidine-5-carbonyl]-cyclopropyl-amino)-piperidine-1-carboxylic acid tert-butyl ester</p>     | Int.<br>6 |   | 448<br>[M + H] <sup>+</sup> | 2.25<br>(16)                    |
| 73  |  <p>4-{Cyclopropyl-[2-(2-methoxy-phenyl)-pyrimidine-5-carbonyl]-amino}-piperidine-1-carboxylic acid tert-butyl ester</p> | Int.<br>6 |  | 377<br>[M + H] <sup>+</sup> | 2.03<br>(16)                    |

## Examples 74-93

General Procedure for the Synthesis of the Bis-Aryls in Table 6 from 4-[(2-chloro-pyrimidine-5-carbonyl)-cyclopropyl-amino]-piperidine-1-carboxylic acid tert-butyl ester and their Respective Boronic Acids or Boronic Acid Pinacol Esters

**[0599]** Under an argon atmosphere an aqueous solution of Na<sub>2</sub>CO<sub>3</sub> (2 M, 0.10 mL) and bis(triphenylphosphine)-palladium(II) chloride (2.1 mg) is added to a mixture of the respec-

tive boronic acid (or boronic acid pinacol ester) (0.16 mmol) and 4-[(2-chloro-pyrimidine-5-carbonyl)-cyclopropyl-amino]-piperidine-1-carboxylic acid tert-butyl ester (38 mg, 0.1 mmol) in 1,4-dioxane (0.67 mL) and methanol (0.33 mL). The mixture is stirred for 6 h at 90° C. The mixture is subsequently filtered through basic aluminum oxide followed by washing with N,N-dimethylformamide/methanol (9:1). The solvents are removed in vacuo. The residue is taken up in N,N-dimethylformamide and purified by HPLC (C18 RP XBridge, MeOH/H<sub>2</sub>O+0.1% NH<sub>4</sub>OH) to yield the desired product.

TABLE 6

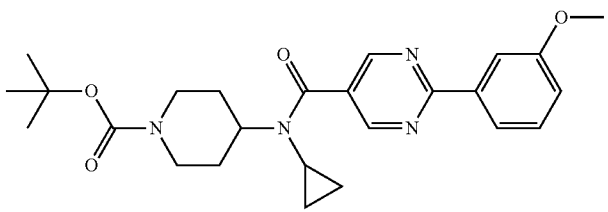
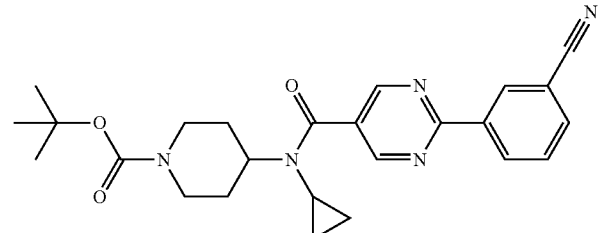
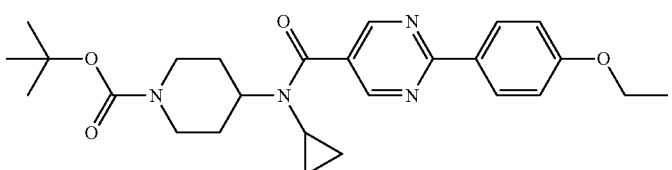
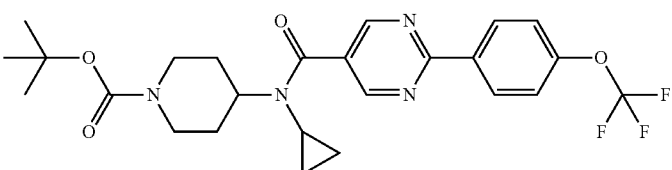
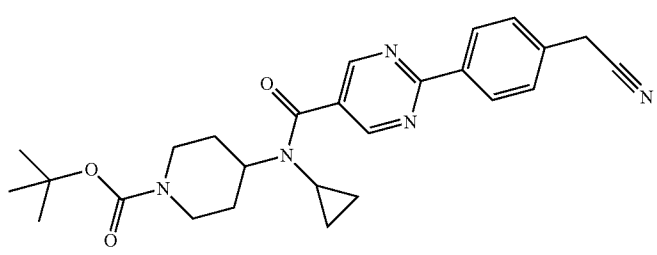
| Ex. | Structure   | ESI-MS<br>[m/z]             | HPLC $t_R$<br>[min]<br>(method) |
|-----|---|-----------------------------|---------------------------------|
| 74  | <br>4-((Cyclopropyl-[2-(3-methoxy-phenyl)-pyrimidine-5-carbonyl]-amino)-piperidine-1-carboxylic acid tert-butyl ester            | 453<br>[M + H] <sup>+</sup> | 0.61 (17)                       |
| 75  | <br>4-[[2-(3-Cyano-phenyl)-pyrimidine-5-carbonyl]-cyclopropyl-amino]-piperidine-1-carboxylic acid tert-butyl ester               | 448<br>[M + H] <sup>+</sup> | 0.59 (17)                       |
| 76  | <br>4-((Cyclopropyl-[2-(4-ethoxy-phenyl)-pyrimidine-5-carbonyl]-amino)-piperidine-1-carboxylic acid tert-butyl ester           | 467<br>[M + H] <sup>+</sup> | 0.64 (17)                       |
| 77  | <br>4-((Cyclopropyl-[2-(4-trifluoromethoxy-phenyl)-pyrimidine-5-carbonyl]-amino)-piperidine-1-carboxylic acid tert-butyl ester | 507<br>[M + H] <sup>+</sup> | 0.69 (17)                       |
| 78  | <br>4-[[2-(4-Cyanomethyl-phenyl)-pyrimidine-5-carbonyl]-cyclopropyl-amino]-piperidine-1-carboxylic acid tert-butyl ester       | 462<br>[M + H] <sup>+</sup> | 0.56 (17)                       |

TABLE 6-continued

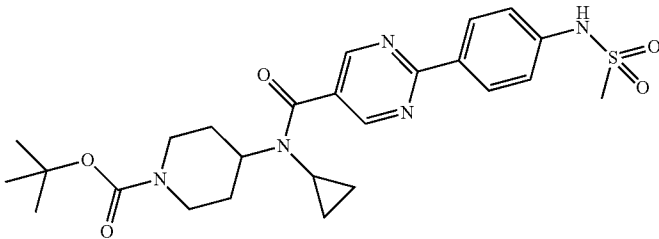
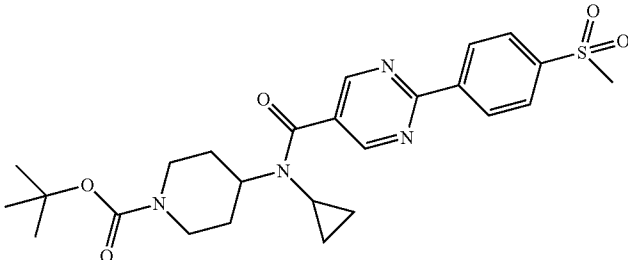
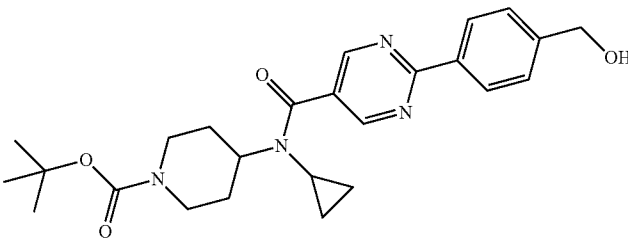
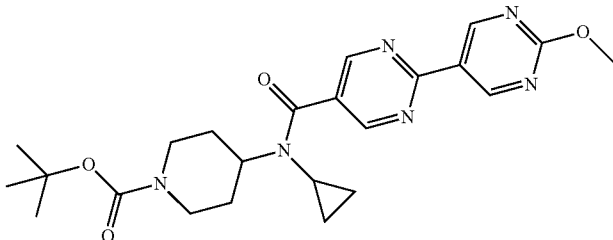
| Ex. | Structure   | ESI-MS<br>[m/z]             | HPLC t <sub>R</sub><br>[min]<br>(method) |
|-----|---|-----------------------------|--|
| 79  |  <p>4-[(Cyclopropyl-[2-(4-methanesulfonylamino-phenyl)-pyrimidin-5-carbonyl]-amino)-piperidin-1-carboxylic acid tert-butyl ester</p> | 516<br>[M + H] <sup>+</sup> | 0.52 ('17)                               |
| 80  |  <p>4-[(Cyclopropyl-[2-(4-methanesulfonyl-phenyl)-pyrimidin-5-carbonyl]-amino)-piperidin-1-carboxylic acid tert-butyl ester</p>     | 501<br>[M + H] <sup>+</sup> | 0.53 (17)                                |
| 81  |  <p>4-[(Cyclopropyl-[2-(4-hydroxymethyl-phenyl)-pyrimidin-5-carbonyl]-amino)-piperidin-1-carboxylic acid tert-butyl ester</p>      | 453<br>[M + H] <sup>+</sup> | 0.50 (17)                                |
| 82  |  <p>4-[(Cyclopropyl-[2'-methoxy-[2,5']bipyrimidin-5-carbonyl]-amino)-piperidin-1-carboxylic acid tert-butyl ester</p>              | 455<br>[M + H] <sup>+</sup> | 0.53 (17)                                |

TABLE 6-continued

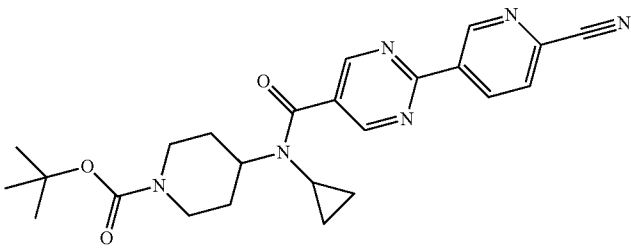
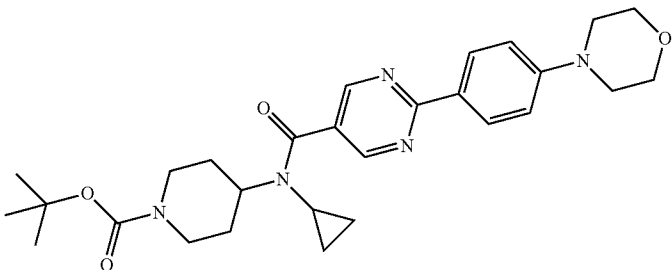
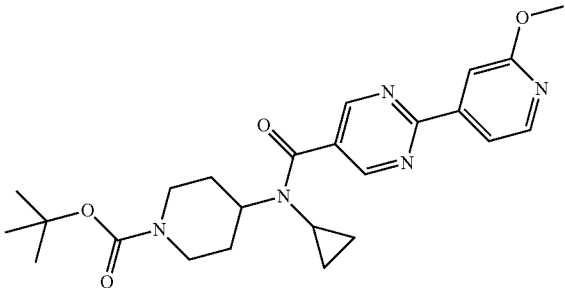
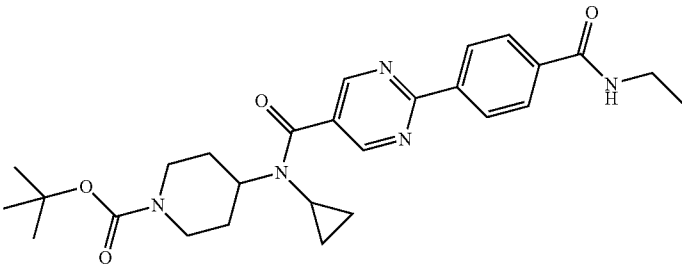
| Ex. | Structure  | ESI-MS<br>[m/z]             | HPLC $t_R$<br>[min]<br>(method) |
|-----|--|-----------------------------|---------------------------------|
| 83  |  <p>4-([2-(6-Cyano-pyridin-3-yl)-pyrimidine-5-carbonyl]-cyclopropyl-amino)-piperidine-1-carboxylic acid tert-butyl ester</p>      | 449<br>[M + H] <sup>+</sup> | 0.56 (17)                       |
| 84  |  <p>4-{Cyclopropyl-[2-(4-morpholin-4-yl-phenyl)-pyrimidine-5-carbonyl]-amino}-piperidine-1-carboxylic acid tert-butyl ester</p>  | 508<br>[M + H] <sup>+</sup> | 0.58 (17)                       |
| 85  |  <p>4-{Cyclopropyl-[2-(2-methoxy-pyridin-4-yl)-pyrimidine-5-carbonyl]-amino}-piperidine-1-carboxylic acid tert-butyl ester</p>  | 454<br>[M + H] <sup>+</sup> | 0.57 (17)                       |
| 86  |  <p>4-{Cyclopropyl-[2-(4-ethylcarbamoyl-phenyl)-pyrimidine-5-carbonyl]-amino}-piperidine-1-carboxylic acid tert-butyl ester</p> | 494<br>[M + H] <sup>+</sup> | 0.52 (17)                       |

TABLE 6-continued

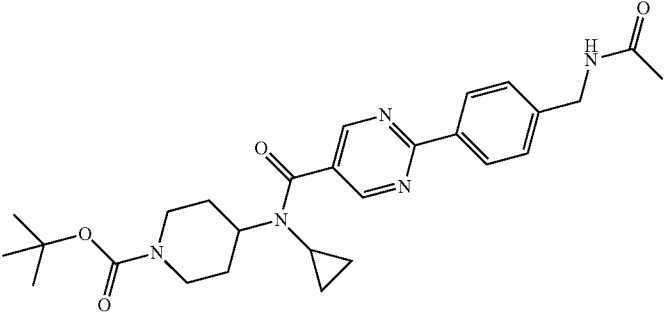
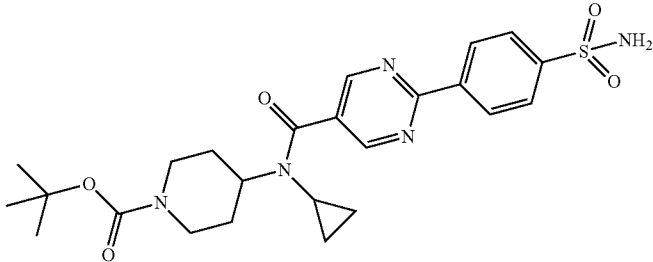
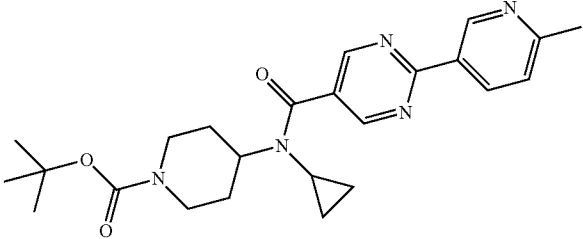
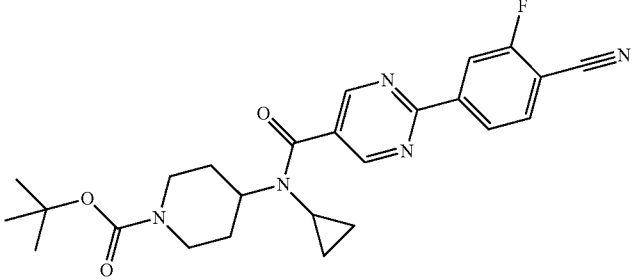
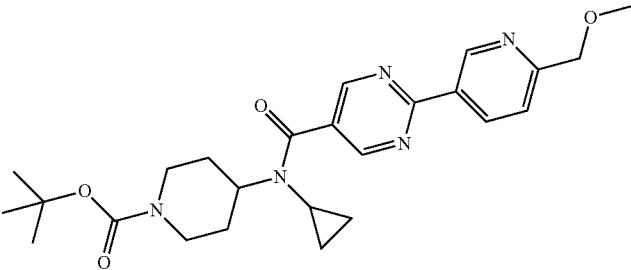
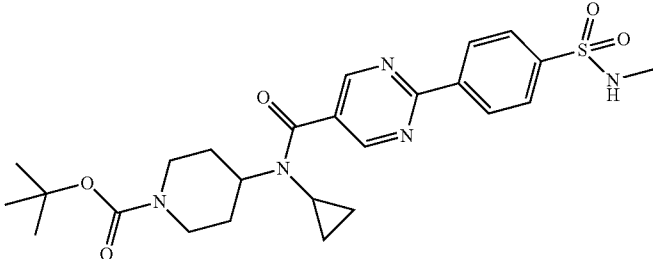
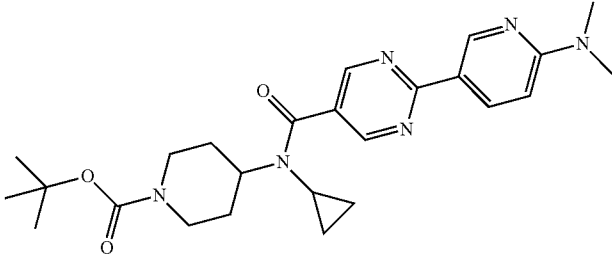
| Ex. | Structure  | ESI-MS<br>[m/z]             | HPLC $t_R$<br>[min]<br>(method) |
|-----|--|-----------------------------|---------------------------------|
| 87  |  <p>4-({2-[4-(Acetylamino-methyl)-phenyl]-pyrimidine-5-carbonyl}-cyclopropyl-amino)-piperidine-1-carboxylic acid tert-butyl ester</p> | 494<br>[M + H] <sup>+</sup> | 0.49 (17)                       |
| 88  |  <p>4-{Cyclopropyl-[2-(4-sulfamoyl-phenyl)-pyrimidine-5-carbonyl]-amino}-piperidine-1-carboxylic acid tert-butyl ester</p>           | 502<br>[M + H] <sup>+</sup> | 0.49 (17)                       |
| 89  |  <p>4-{Cyclopropyl-[2-(6-methyl-pyridin-3-yl)-pyrimidine-5-carbonyl]-amino}-piperidine-1-carboxylic acid tert-butyl ester</p>       | 438<br>[M + H] <sup>+</sup> | 0.40 (17)                       |
| 90  |  <p>4-{[2-(4-Cyano-3-fluoro-phenyl)-pyrimidine-5-carbonyl]-cyclopropyl-amino}-piperidine-1-carboxylic acid tert-butyl ester</p>     | 466<br>[M + H] <sup>+</sup> | 0.62 (17)                       |

TABLE 6-continued

| Ex. | Structure   | ESI-MS<br>[m/z]             | HPLC $t_R$<br>[min]<br>(method) |
|-----|---|-----------------------------|---------------------------------|
| 91  |  <p>4-{Cyclopropyl-[2-(6-ethoxy-pyridin-3-yl)-pyrimidine-5-carbonyl]-amino}-piperidine-1-carboxylic acid tert-butyl ester</p>          | 468<br>[M + H] <sup>+</sup> | 0.61 (17)                       |
| 92  |  <p>4-{Cyclopropyl-[2-(4-methanesulfamoyl-phenyl)-pyrimidine-5-carbonyl]-amino}-piperidine-1-carboxylic acid tert-butyl ester</p>     | 516<br>[M + H] <sup>+</sup> | 0.53 (17)                       |
| 93  |  <p>4-{Cyclopropyl-[2-(6-dimethylamino-pyridin-3-yl)-pyrimidine-5-carbonyl]-amino}-piperidine-1-carboxylic acid tert-butyl ester</p> | 467<br>[M + H] <sup>+</sup> | 0.42 (17)                       |

## Examples 94-100

General Procedure for the Synthesis of the N-Linked Bis-Aryls in Table 7 from 4-[(2-chloro-pyrimidine-5-carbonyl)-cyclopropyl-amino]-piperidine-1-carboxylic acid tert-butyl ester and Their Respective Boronic Acids or Boronic Acid Pinacol Esters

**[0600]** Under an argon atmosphere an aqueous solution of Na<sub>2</sub>CO<sub>3</sub> (2 M, 0.10 mL) and bis(triphenylphosphine)-palladium(II) chloride (2.1 mg) is added to a mixture of the respec-

tive boronic acid (or boronic acid pinacol ester) (0.16 mmol) and 4-[(2-chloro-pyrimidine-5-carbonyl)-cyclopropyl-amino]-piperidine-1-carboxylic acid tert-butyl ester (38 mg, 0.1 mmol) in 1,4-dioxane (0.67 mL) and methanol (0.33 mL). The mixture is stirred for 6 h at 90° C. The mixture is subsequently filtered through basic aluminum oxide followed by washing with N,N-dimethylformamide/methanol (9:1). The solvents are removed in vacuo. The residue is taken up in N,N-dimethylformamide and purified by HPLC (C18 RP XBridge, MeOH/H<sub>2</sub>O+0.1% NH<sub>4</sub>OH) to yield the desired product.



TABLE 7

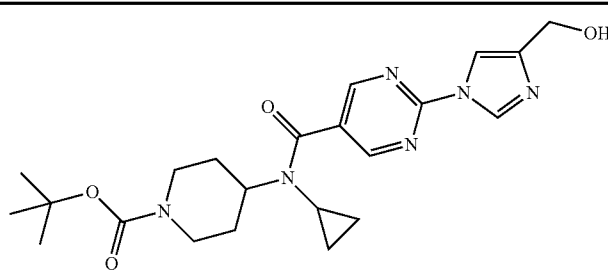
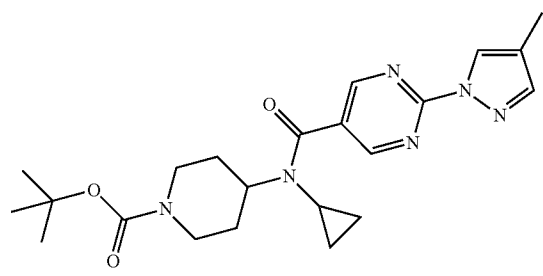
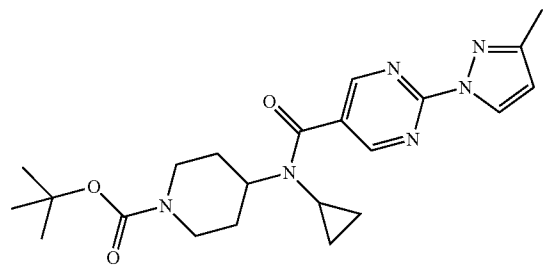
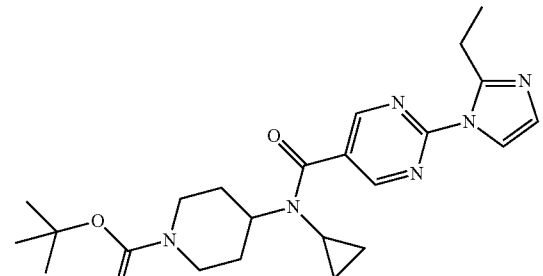
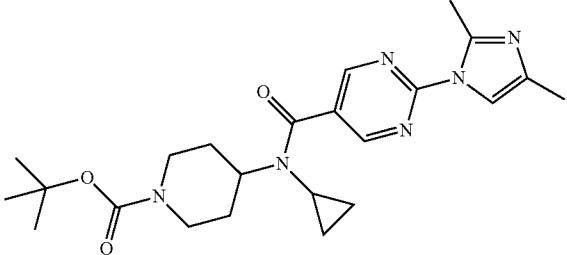
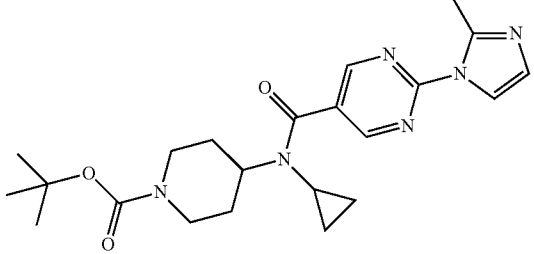
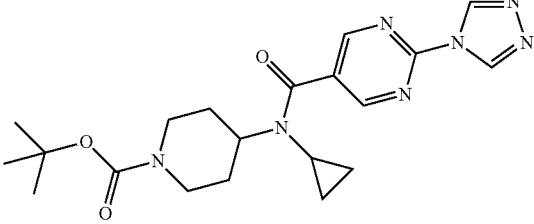
| Ex. | Structure  | ESI-MS<br>[m/z]             | HPLC $t_R$<br>[min]<br>(method) |
|-----|--|-----------------------------|---------------------------------|
| 94  |  <p>4-{Cyclopropyl-[2-(4-hydroxymethyl-imidazol-1-yl)-pyrimidine-5-carbonyl]-amino}-piperidine-1-carboxylic acid tert-butyl ester</p> | 443<br>[M + H] <sup>+</sup> | 0.38 (17)                       |
| 95  |  <p>4-{Cyclopropyl-[2-(4-methyl-pyrazol-1-yl)-pyrimidine-5-carbonyl]-amino}-piperidine-1-carboxylic acid tert-butyl ester</p>        | 427<br>[M + H] <sup>+</sup> | 0.49 (17)                       |
| 96  |  <p>4-{Cyclopropyl-[2-(3-methyl-pyrazol-1-yl)-pyrimidine-5-carbonyl]-amino}-piperidine-1-carboxylic acid tert-butyl ester</p>       | 427<br>[M + H] <sup>+</sup> | 0.48 (17)                       |
| 97  |  <p>4-{Cyclopropyl-[2-(2-ethyl-imidazol-1-yl)-pyrimidine-5-carbonyl]-amino}-piperidine-1-carboxylic acid tert-butyl ester</p>       | 441<br>[M + H] <sup>+</sup> | 0.41 (17)                       |

TABLE 7-continued

| Ex. | Structure   | ESI-MS<br>[m/z]             | HPLC $t_R$<br>[min]<br>(method) |
|-----|---|-----------------------------|---------------------------------|
| 98  |  <p>4-{Cyclopropyl-[2-(2,4-dimethyl-imidazol-1-yl)-pyrimidine-5-carbonyl]-amino}-piperidine-1-carboxylic acid tert-butyl ester</p> | 441<br>[M + H] <sup>+</sup> | 0.41 (17)                       |
| 99  |  <p>4-{Cyclopropyl-[2-(2-methyl-imidazol-1-yl)-pyrimidine-5-carbonyl]-amino}-piperidine-1-carboxylic acid tert-butyl ester</p>    | 427<br>[M + H] <sup>+</sup> | 0.39 (17)                       |
| 100 |  <p>4-[Cyclopropyl-(2-[1,2,4]triazol-4-yl-pyrimidine-5-carbonyl)-amino]-piperidine-1-carboxylic acid tert-butyl ester</p>        | 414<br>[M + H] <sup>+</sup> | 0.44 (17)                       |

## Examples 101-246

General Procedure for the Synthesis of the Amides in Table 8 from (4-{[2-(4-carboxy-phenyl)-pyrimidine-5-carbonyl]-cyclopropyl-amino}-piperidine-1-carboxylic acid tert-butyl ester and Their Respective Amines

**[0601]** To 4-{[2-(4-carboxy-phenyl)-pyrimidine-5-carbonyl]-cyclopropyl-amino}-piperidine-1-carboxylic acid tert-butyl ester (10  $\mu$ mol, 4.7 mg) in N,N-dimethylformamide

(0.1  $\mu$ L) is added ethyldiisopropylamine (5  $\mu$ L) and 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (3.2 mg) and the mixture is stirred for 10 min at room temperature. The corresponding amine (10  $\mu$ mol) is added and the mixture is stirred for 12 h at room temperature. Aqueous K<sub>2</sub>CO<sub>3</sub> solution (3 M, 20  $\mu$ L) is added and stirring is continued for 10 min. Subsequently the mixture is filtered through basic aluminum oxide, washed with N,N-dimethylformamide/methanol (9:1) and concentrated in vacuo to yield the desired amide.

TABLE 8

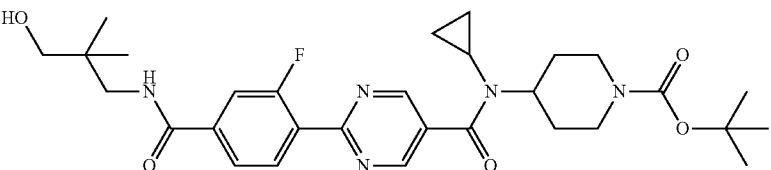
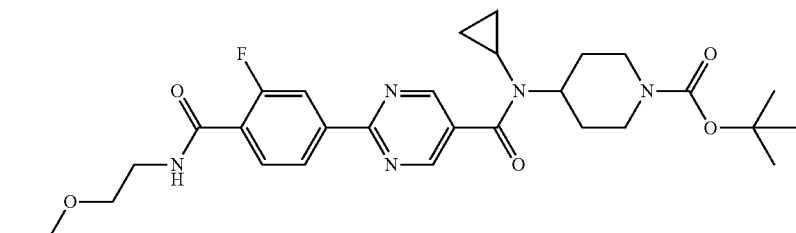
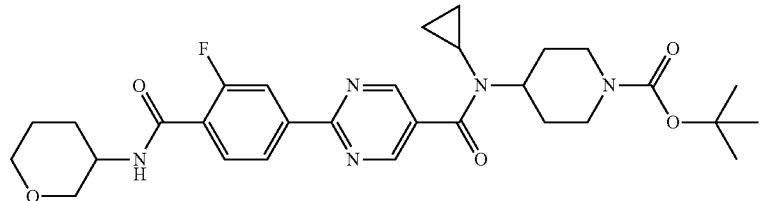
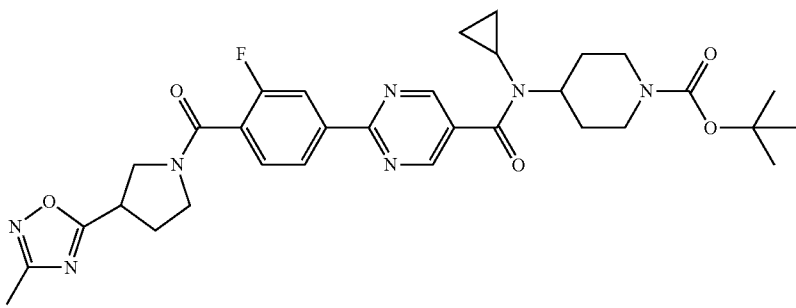
| Ex. | Structure  | ESI-MS<br>[m/z]             | HPLC $t_R$<br>[min]<br>(method) |
|-----|--|-----------------------------|---------------------------------|
| 101 | <br>4-(Cyclopropyl-{2-[2-fluoro-4-(3-hydroxy-2,2-dimethylpropylcarbamoyl)-phenyl]-pyrimidine-5-carbonyl}-amino)-piperidine-1-carboxylic acid tert-butyl ester                      | 570<br>[M + H] <sup>+</sup> | 0.49 (18)                       |
| 102 | <br>4-(Cyclopropyl-{2-[4-(2-ethoxy-ethylcarbamoyl)-3-fluorophenyl]-pyrimidine-5-carbonyl}-amino)-piperidine-1-carboxylic acid tert-butyl ester                                     | 556<br>[M + H] <sup>+</sup> | 0.52 (18)                       |
| 103 | <br>4-(Cyclopropyl-{2-[3-fluoro-4-(tetrahydro-pyran-3-ylcarbamoyl)-phenyl]-pyrimidine-5-carbonyl}-amino)-piperidine-1-carboxylic acid tert-butyl ester                           | 568<br>[M + H] <sup>+</sup> | 0.52 (18)                       |
| 104 | <br>4-[Cyclopropyl-(2-{3-fluoro-4-[3-(3-methyl-1,2,4]oxadiazol-5-yl)-pyrrolidine-1-carbonyl]-phenyl}-pyrimidine-5-carbonyl)-amino]-piperidine-1-carboxylic acid tert-butyl ester | 620<br>[M + H] <sup>+</sup> | 0.51 (18)                       |

TABLE 8-continued

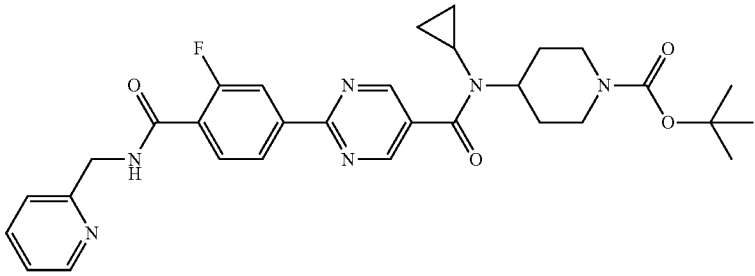
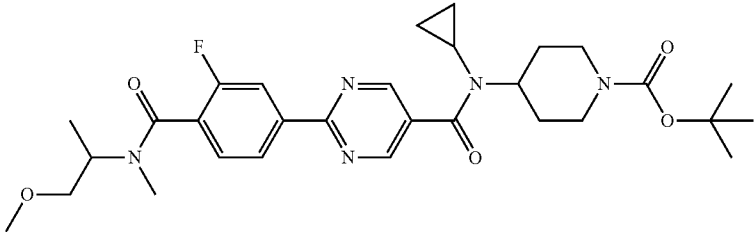
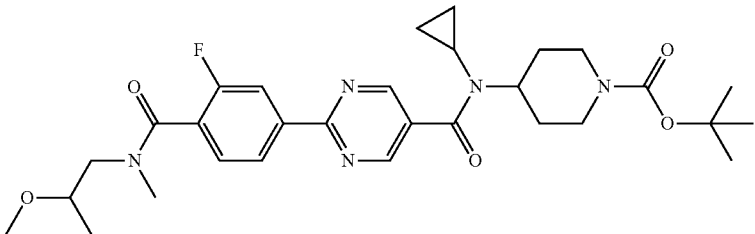
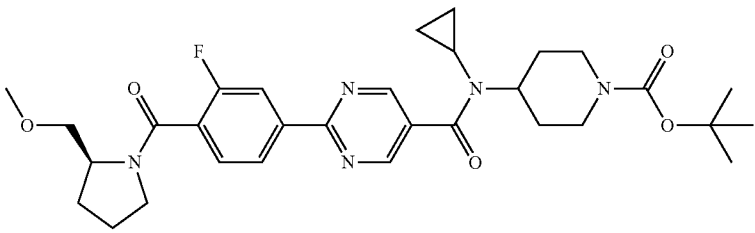
| Ex. | Structure  | ESI-MS<br>[m/z]             | HPLC $t_R$<br>[min]<br>(method) |
|-----|--|-----------------------------|---------------------------------|
| 105 |  <p>4-[Cyclopropyl-(2-{3-fluoro-4-[(pyridin-2-ylmethyl)-carbamoyl]-phenyl}-pyrimidine-5-carbonyl)-amino]-piperidine-1-carboxylic acid tert-butyl ester</p>               | 575<br>[M + H] <sup>+</sup> | 0.5 (18)                        |
| 106 |  <p>4-[Cyclopropyl-(2-{3-fluoro-4-[(2-methoxy-1-methyl-ethyl)-methyl-carbamoyl]-phenyl}-pyrimidine-5-carbonyl)-amino]-piperidine-1-carboxylic acid tert-butyl ester</p> | 570<br>[M + H] <sup>+</sup> | 0.52 (18)                       |
| 107 |  <p>4-[Cyclopropyl-(2-{3-fluoro-4-[(2-methoxy-propyl)-methyl-carbamoyl]-phenyl}-pyrimidine-5-carbonyl)-amino]-piperidine-1-carboxylic acid tert-butyl ester</p>        | 570<br>[M + H] <sup>+</sup> | 0.51 (18)                       |
| 108 |  <p>4-(Cyclopropyl-{2-[3-fluoro-4-(2-methoxymethyl-pyrrolidine-1-carbonyl)-phenyl]-pyrimidine-5-carbonyl)-amino)-piperidine-1-carboxylic acid tert-butyl ester</p>     | 582<br>[M + H] <sup>+</sup> | 0.53 (18)                       |

TABLE 8-continued

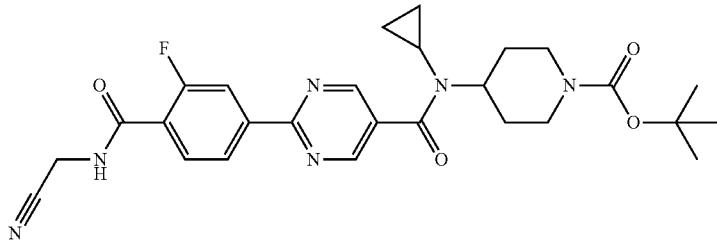
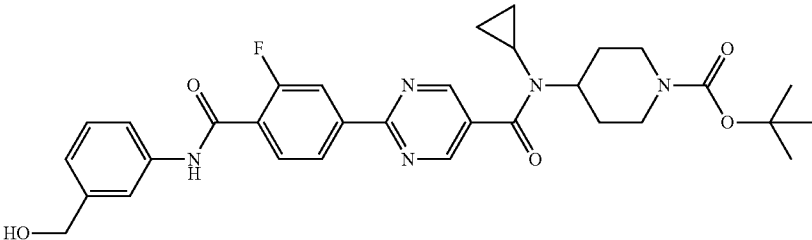
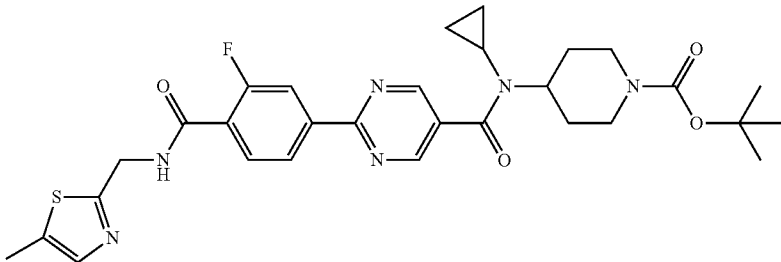
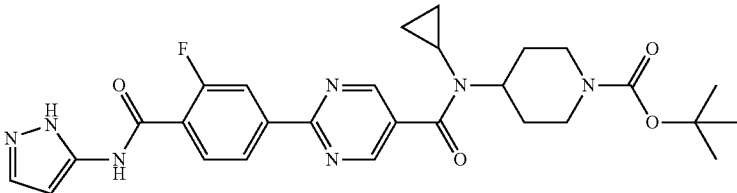
| Ex. | Structure   | ESI-MS<br>[m/z]             | HPLC $t_R$<br>[min]<br>(method) |
|-----|---|-----------------------------|---------------------------------|
| 109 |  <p>4-({2-[4-(Cyanomethyl-carbamoyl)-3-fluoro-phenyl]-pyrimidine-5-carbonyl}-cyclopropyl-amino)-piperidine-1-carboxylic acid tert-butyl ester</p>                     | 523<br>[M + H] <sup>+</sup> | 0.48 (18)                       |
| 110 |  <p>4-(Cyclopropyl-{2-[3-fluoro-4-(3-hydroxymethyl-phenylcarbamoyl)-phenyl]-pyrimidine-5-carbonyl}-amino)-piperidine-1-carboxylic acid tert-butyl ester</p>          | 590<br>[M + H] <sup>+</sup> | 0.5 (18)                        |
| 111 |  <p>4-[Cyclopropyl-(2-{3-fluoro-4-[(5-methyl-thiazol-2-ylmethyl)-carbamoyl]-phenyl}-pyrimidine-5-carbonyl)-amino]-piperidine-1-carboxylic acid tert-butyl ester</p> | 595<br>[M + H] <sup>+</sup> | 0.52 (18)                       |
| 112 |  <p>4-(Cyclopropyl-{2-[3-fluoro-4-(2H-pyrazol-3-ylcarbamoyl)-phenyl]-pyrimidine-5-carbonyl}-amino)-piperidine-1-carboxylic acid tert-butyl ester</p>                | 550<br>[M + H] <sup>+</sup> | 0.5 (18)                        |

TABLE 8-continued

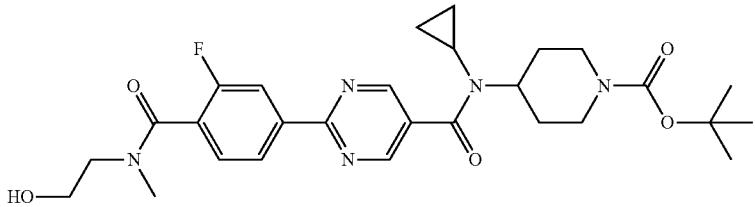
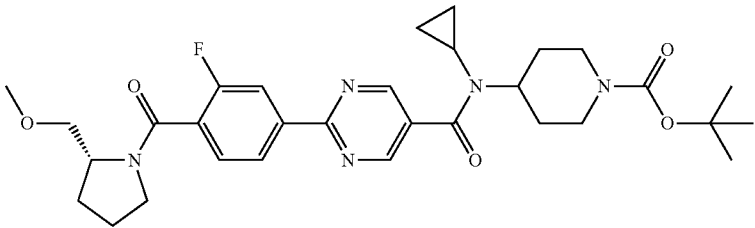
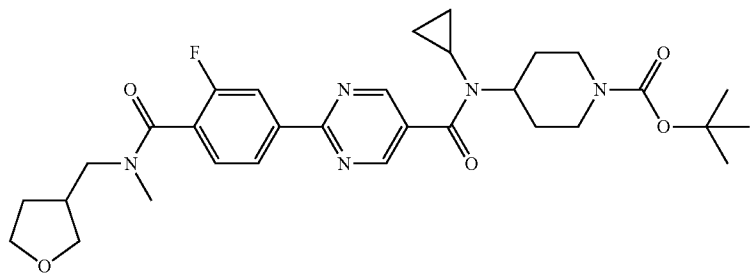
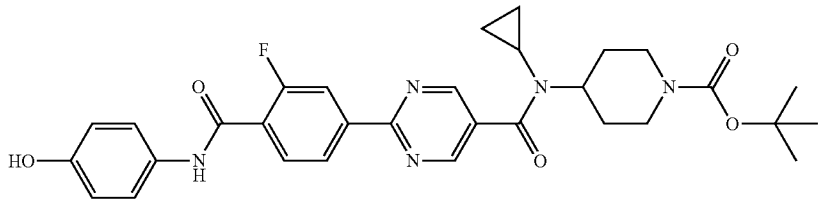
| Ex. | Structure  | ESI-MS<br>[m/z]             | HPLC $t_R$<br>[min]<br>(method) |
|-----|--|-----------------------------|---------------------------------|
| 113 |  <p>4-[Cyclopropyl-(2-{3-fluoro-4-[(2-hydroxy-ethyl)-methyl-carbamoyl]-phenyl}-pyrimidine-5-carbonyl)-amino]-piperidine-1-carboxylic acid tert-butyl ester</p>               | 542<br>[M + H] <sup>+</sup> | 0.46 (18)                       |
| 114 |  <p>4-(Cyclopropyl-{2-[3-fluoro-4-(2-methoxymethyl-pyrrolidine-1-carbonyl)-phenyl]-pyrimidine-5-carbonyl}-amino)-piperidine-1-carboxylic acid tert-butyl ester</p>          | 582<br>[M + H] <sup>+</sup> | 0.53 (18)                       |
| 115 |  <p>4-[Cyclopropyl-(2-{3-fluoro-4-[methyl-(tetrahydro-furan-3-ylmethyl)-carbamoyl]-phenyl}-pyrimidine-5-carbonyl)-amino]-piperidine-1-carboxylic acid tert-butyl ester</p> | 582<br>[M + H] <sup>+</sup> | 0.49 (18)                       |
| 116 |  <p>4-(Cyclopropyl-{2-[3-fluoro-4-(4-hydroxy-phenylcarbamoyl)-phenyl]-pyrimidine-5-carbonyl}-amino)-piperidine-1-carboxylic acid tert-butyl ester</p>                      | 576<br>[M + H] <sup>+</sup> | 0.48 (18)                       |

TABLE 8-continued

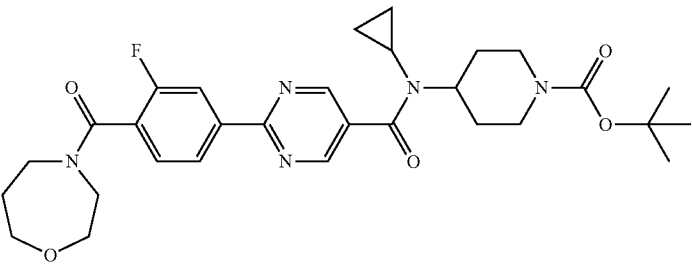
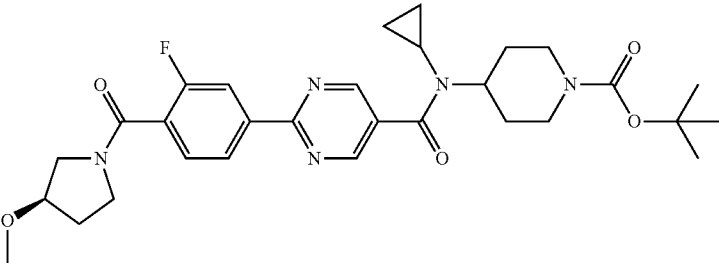
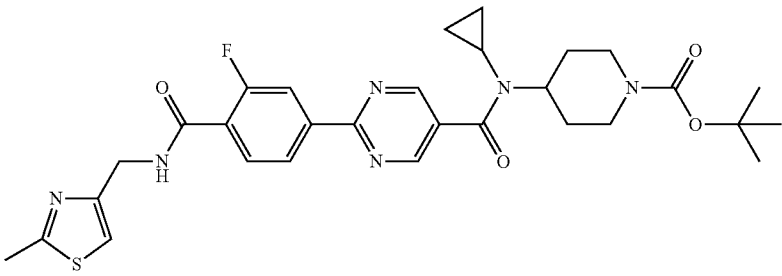
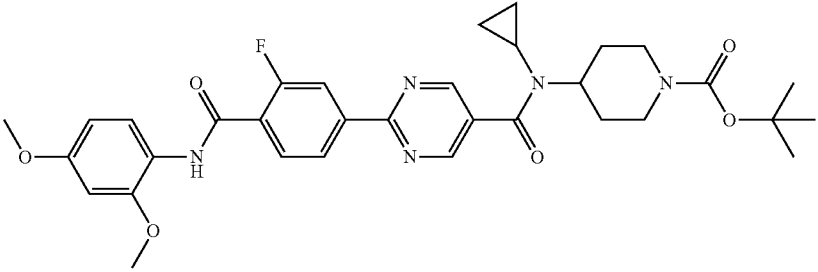
| Ex. | Structure   | ESI-MS<br>[m/z]             | HPLC $t_R$<br>[min]<br>(method) |
|-----|---|-----------------------------|---------------------------------|
| 117 |  <p>4-(Cyclopropyl-{2-[3-fluoro-4-([1,4]oxazepane-4-carbonyl)-phenyl]-pyrimidine-5-carbonyl}-amino)-piperidine-1-carboxylic acid tert-butyl ester</p>                 | 568<br>[M + H] <sup>+</sup> | 0.5 (18)                        |
| 118 |  <p>4-(Cyclopropyl-{2-[3-fluoro-4-(3-methoxy-pyrrolidine-1-carbonyl)-phenyl]-pyrimidine-5-carbonyl}-amino)-piperidine-1-carboxylic acid tert-butyl ester</p>         | 568<br>[M + H] <sup>+</sup> | 0.49 (18)                       |
| 119 |  <p>4-[Cyclopropyl-(2-{3-fluoro-4-[(2-methyl-thiazol-4-ylmethyl)-carbamoyl]-phenyl]-pyrimidine-5-carbonyl)-amino]-piperidine-1-carboxylic acid tert-butyl ester</p> | 595<br>[M + H] <sup>+</sup> | 0.51 (18)                       |
| 120 |  <p>4-(Cyclopropyl-{2-[4-(2,4-dimethoxy-phenylcarbamoyl)-3-fluoro-phenyl]-pyrimidine-5-carbonyl}-amino)-piperidine-1-carboxylic acid tert-butyl ester</p>           | 620<br>[M + H] <sup>+</sup> | 0.57 (18)                       |

TABLE 8-continued

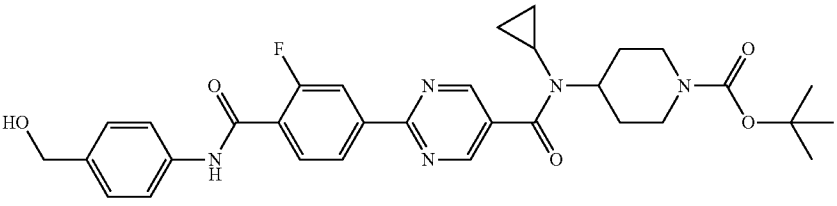
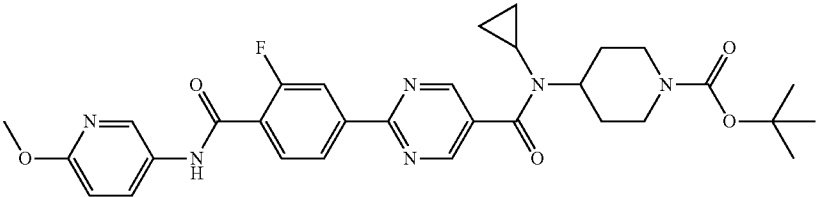
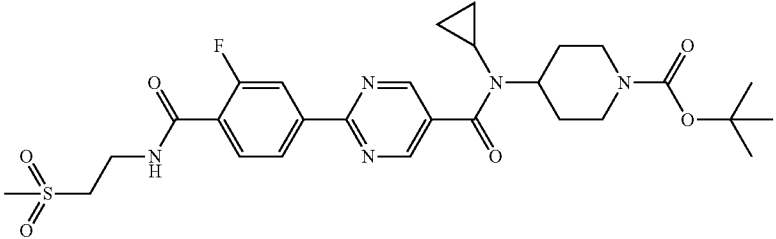
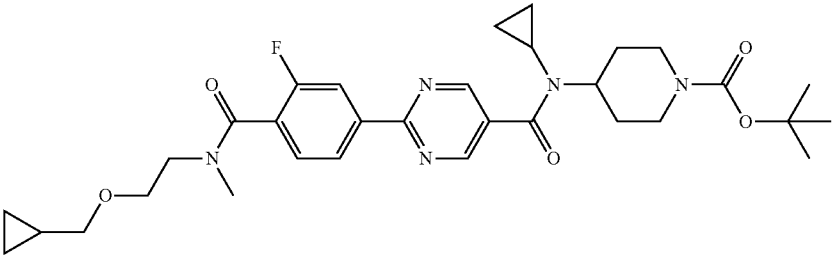
| Ex. | Structure   | ESI-MS<br>[m/z]             | HPLC $t_R$<br>[min]<br>(method) |
|-----|---|-----------------------------|---------------------------------|
| 121 |  <p>4-(Cyclopropyl-{2-[3-fluoro-4-(4-hydroxymethyl-phenylcarbamoyl)-phenyl]-pyrimidine-5-carbonyl}-amino)-piperidine-1-carboxylic acid tert-butyl ester</p>                 | 590<br>[M + H] <sup>+</sup> | 0.49 (18)                       |
| 122 |  <p>4-(Cyclopropyl-{2-[3-fluoro-4-(6-methoxy-pyridin-3-ylcarbamoyl)-phenyl]-pyrimidine-5-carbonyl}-amino)-piperidine-1-carboxylic acid tert-butyl ester</p>                | 591<br>[M + H] <sup>+</sup> | 0.53 (18)                       |
| 123 |  <p>4-(Cyclopropyl-{2-[3-fluoro-4-(2-methanesulfonyl-ethylcarbamoyl)-phenyl]-pyrimidine-5-carbonyl}-amino)-piperidine-1-carboxylic acid tert-butyl ester</p>              | 590<br>[M + H] <sup>+</sup> | 0.46 (18)                       |
| 124 |  <p>4-[Cyclopropyl-(2-{4-[(2-cyclopropylmethoxy-ethyl)-methyl-carbamoyl]-3-fluoro-phenyl}-pyrimidine-5-carbonyl)-amino]-piperidine-1-carboxylic acid tert-butyl ester</p> | 596<br>[M + H] <sup>+</sup> | 0.55 (18)                       |



TABLE 8-continued

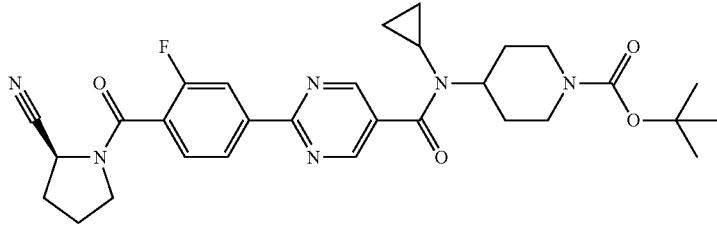
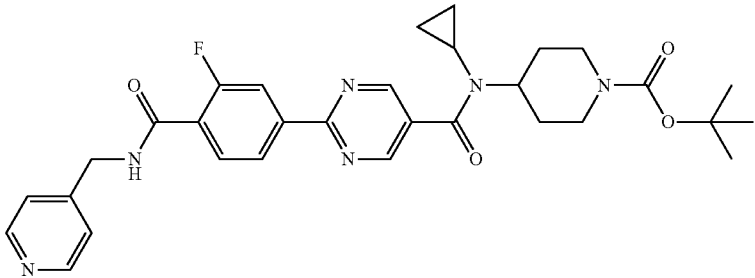
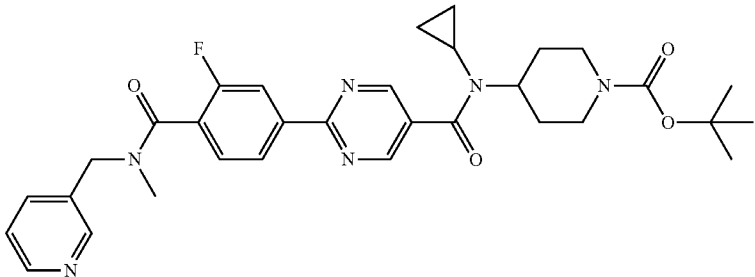
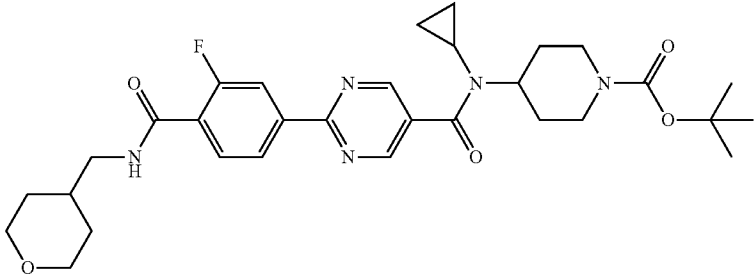
| Ex. | Structure   | ESI-MS<br>[m/z]             | HPLC $t_R$<br>[min]<br>(method) |
|-----|---|-----------------------------|---------------------------------|
| 125 |  <p>4-({2-[4-(2-Cyano-pyrrolidine-1-carbonyl)-3-fluoro-phenyl]-pyrimidine-5-carbonyl}-cyclopropyl-amino)-piperidine-1-carboxylic acid tert-butyl ester</p>            | 563<br>[M + H] <sup>+</sup> | 0.51 (18)                       |
| 126 |  <p>4-[Cyclopropyl-(2-{3-fluoro-4-[(pyridin-4-ylmethyl)-carbamoyl]-phenyl}-pyrimidine-5-carbonyl)-amino]-piperidine-1-carboxylic acid tert-butyl ester</p>           | 575<br>[M + H] <sup>+</sup> | 0.48 (18)                       |
| 127 |  <p>4-(Cyclopropyl-{2-[3-fluoro-4-(methyl-pyridin-3-ylmethyl)-carbamoyl]-phenyl}-pyrimidine-5-carbonyl)-amino)-piperidine-1-carboxylic acid tert-butyl ester</p>    | 589<br>[M + H] <sup>+</sup> | 0.49 (18)                       |
| 128 |  <p>4-[Cyclopropyl-(2-{3-fluoro-4-[(tetrahydro-pyran-4-ylmethyl)-carbamoyl]-phenyl}-pyrimidine-5-carbonyl)-amino]-piperidine-1-carboxylic acid tert-butyl ester</p> | 582<br>[M + H] <sup>+</sup> | 0.5 (18)                        |

TABLE 8-continued

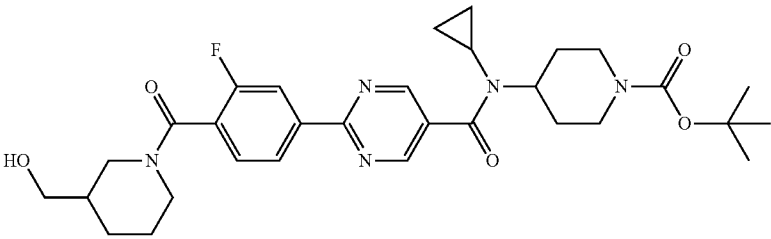
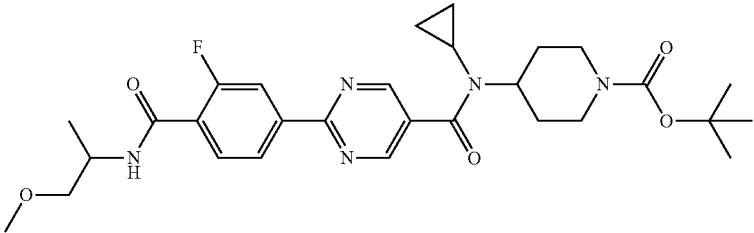
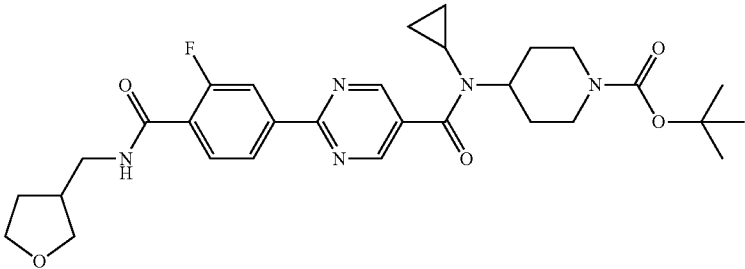
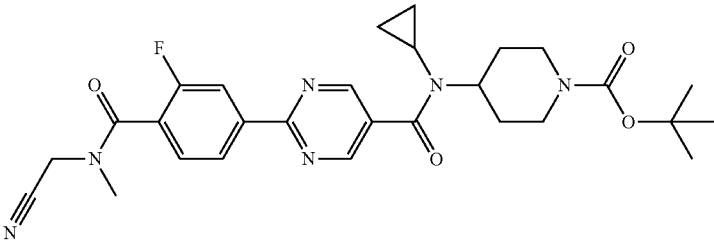
| Ex. | Structure   | ESI-MS<br>[m/z]             | HPLC $t_R$<br>[min]<br>(method) |
|-----|---|-----------------------------|---------------------------------|
| 129 |  <p>4-(Cyclopropyl-{2-[3-fluoro-4-(3-hydroxymethyl)-piperidine-1-carbonyl]-phenyl}-pyrimidine-5-carbonyl}-amino)-piperidine-1-carboxylic acid tert-butyl ester</p>    | 582<br>[M + H] <sup>+</sup> | 0.48 (18)                       |
| 130 |  <p>4-(Cyclopropyl-{2-[3-fluoro-4-(2-methoxy-1-methylethylcarbamoyl)-phenyl]-pyrimidine-5-carbonyl}-amino)-piperidine-1-carboxylic acid tert-butyl ester</p>         | 556<br>[M + H] <sup>+</sup> | 0.52 (18)                       |
| 131 |  <p>4-[Cyclopropyl-(2-{3-fluoro-4-[(tetrahydro-furan-3-ylmethyl)-carbamoyl]-phenyl}-pyrimidine-5-carbonyl)-amino]-piperidine-1-carboxylic acid tert-butyl ester</p> | 568<br>[M + H] <sup>+</sup> | 0.5 (18)                        |
| 132 |  <p>4-({2-[4-(Cyanomethyl-methyl-carbamoyl)-3-fluoro-phenyl]-pyrimidine-5-carbonyl}-cyclopropyl-amino)-piperidine-1-carboxylic acid tert-butyl ester</p>            | 537<br>[M + H] <sup>+</sup> | 0.49 (18)                       |

TABLE 8-continued

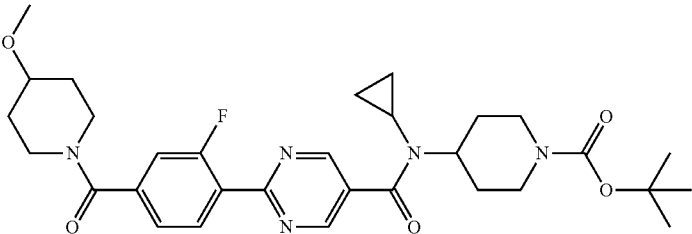
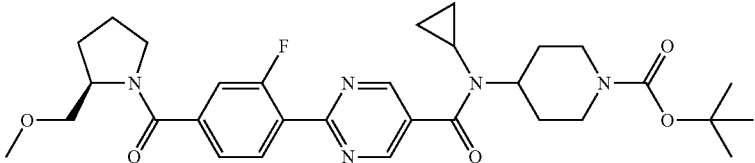
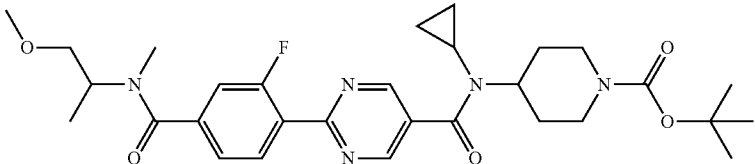
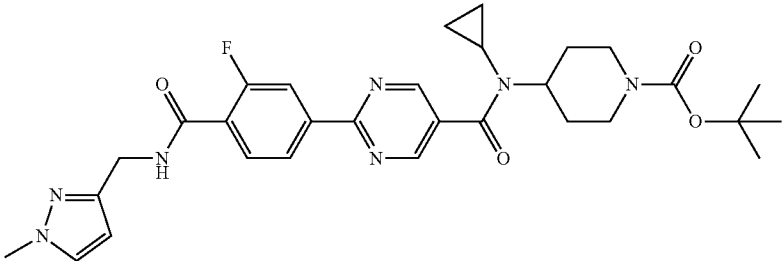
| Ex. | Structure   | ESI-MS<br>[m/z]             | HPLC $t_R$<br>[min]<br>(method) |
|-----|---|-----------------------------|---------------------------------|
| 133 |  <p>4-(Cyclopropyl-{2-[2-fluoro-4-(4-methoxy-piperidine-1-carbonyl)-phenyl]-pyrimidine-5-carbonyl}-amino)-piperidine-1-carboxylic acid tert-butyl ester</p>               | 582<br>[M + H] <sup>+</sup> | 0.49 (18)                       |
| 134 |  <p>4-(Cyclopropyl-{2-[2-fluoro-4-(2-methoxymethyl-pyrrolidine-1-carbonyl)-phenyl]-pyrimidine-5-carbonyl}-amino)-piperidine-1-carboxylic acid tert-butyl ester</p>       | 582<br>[M + H] <sup>+</sup> | 0.5 (18)                        |
| 135 |  <p>4-[Cyclopropyl-(2-{2-fluoro-4-[(2-methoxy-1-methyl-ethyl)-methyl-carbamoyl]-phenyl}-pyrimidine-5-carbonyl)-amino]-piperidine-1-carboxylic acid tert-butyl ester</p> | 570<br>[M + H] <sup>+</sup> | 0.5 (18)                        |
| 136 |  <p>4-[Cyclopropyl-(2-{3-fluoro-4-[(1-methyl-1H-pyrazol-3-ylmethyl)-carbamoyl]-phenyl}-pyrimidine-5-carbonyl)-amino]-piperidine-1-carboxylic acid tert-butyl ester</p>  | 578<br>[M + H] <sup>+</sup> | 0.5 (18)                        |

TABLE 8-continued

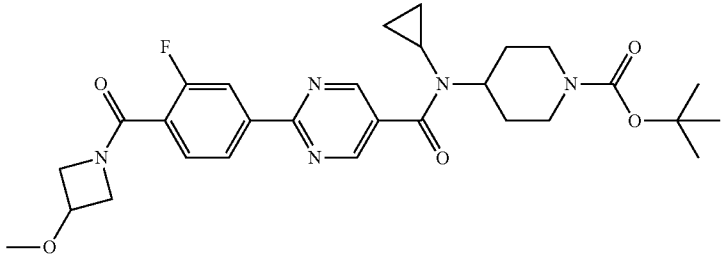
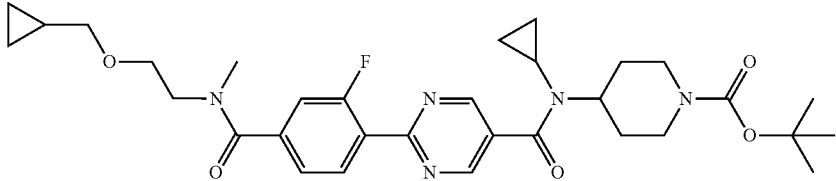
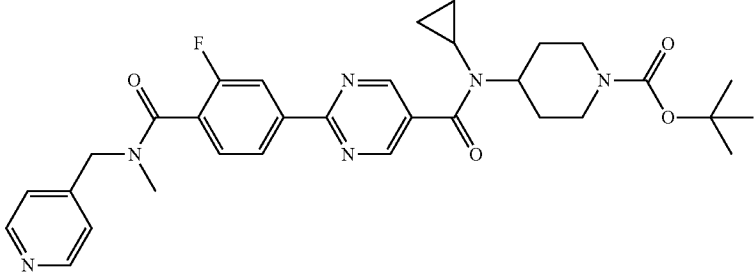
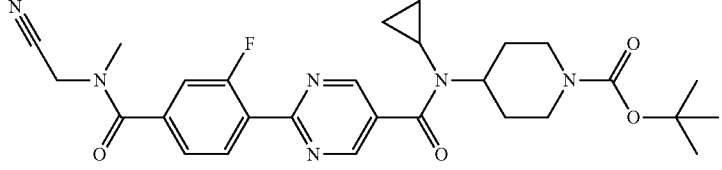
| Ex. | Structure  | ESI-MS<br>[m/z]             | HPLC $t_R$<br>[min]<br>(method) |
|-----|--|-----------------------------|---------------------------------|
| 137 |    | 554<br>[M + H] <sup>+</sup> | 0.5 (18)                        |
| 138 |   | 596<br>[M + H] <sup>+</sup> | 0.53 (18)                       |
| 139 |  | 589<br>[M + H] <sup>+</sup> | 0.51 (18)                       |
| 140 |  | 537<br>[M + H] <sup>+</sup> | 0.48 (18)                       |

TABLE 8-continued

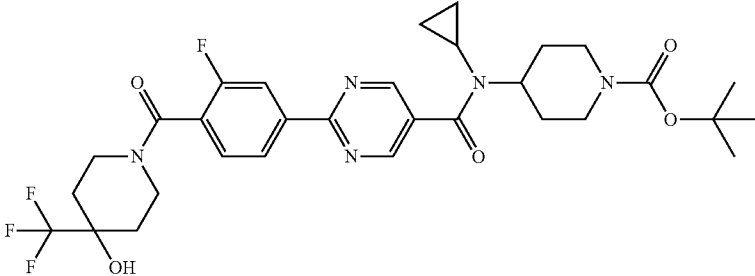
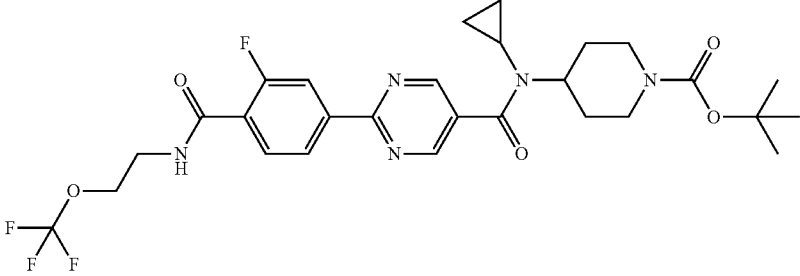
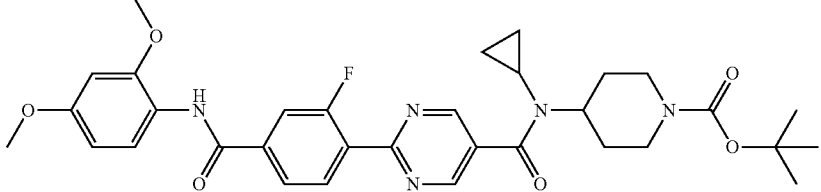
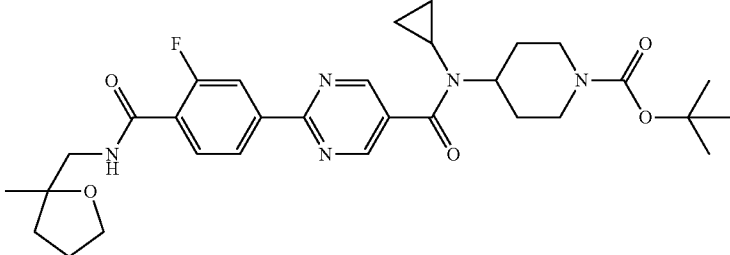
| Ex. | Structure  | ESI-MS<br>[m/z]             | HPLC $t_R$<br>[min]<br>(method) |
|-----|--|-----------------------------|---------------------------------|
| 141 |  <p>4-(Cyclopropyl-{2-[3-fluoro-4-(4-hydroxy-4-trifluoromethyl-piperidine-1-carbonyl)-phenyl]-pyrimidine-5-carbonyl}-amino)-piperidine-1-carboxylic acid tert-butyl ester</p>  | 636<br>[M + H] <sup>+</sup> | 0.51 (18)                       |
| 142 |  <p>4-(Cyclopropyl-{2-[3-fluoro-4-(2-trifluoromethoxy-ethylcarbamoyl)-phenyl]-pyrimidine-5-carbonyl}-amino)-piperidine-1-carboxylic acid tert-butyl ester</p>                 | 596<br>[M + H] <sup>+</sup> | 0.54 (18)                       |
| 143 |  <p>4-(Cyclopropyl-{2-[4-(2,4-dimethoxy-phenylcarbamoyl)-2-fluoro-phenyl]-pyrimidine-5-carbonyl}-amino)-piperidine-1-carboxylic acid tert-butyl ester</p>                    | 620<br>[M + H] <sup>+</sup> | 0.53 (18)                       |
| 144 |  <p>4-[Cyclopropyl-(2-{3-fluoro-4-[(2-methyl-tetrahydro-furan-2-ylmethyl)-carbamoyl]-phenyl}-pyrimidine-5-carbonyl)-amino]-piperidine-1-carboxylic acid tert-butyl ester</p> | 582<br>[M + H] <sup>+</sup> | 0.53 (18)                       |

TABLE 8-continued

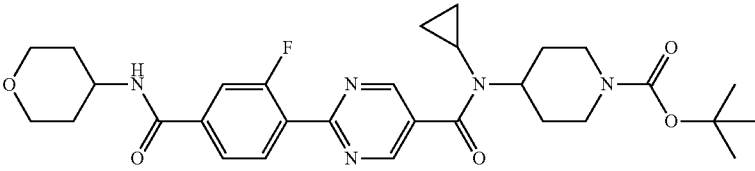
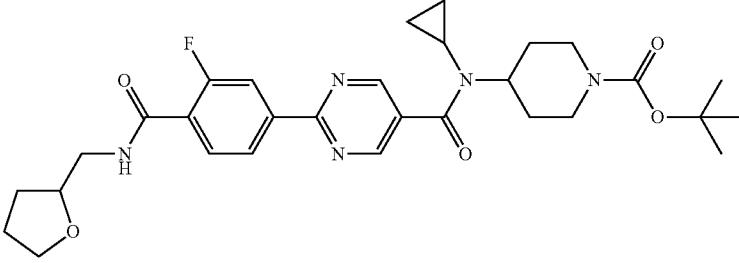
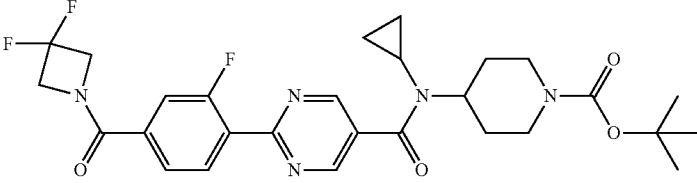
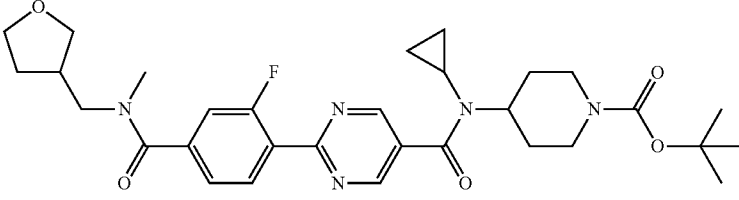
| Ex. | Structure  | ESI-MS<br>[m/z]             | HPLC $t_R$<br>[min]<br>(method) |
|-----|--|-----------------------------|---------------------------------|
| 145 |  <p>4-(Cyclopropyl-{2-[2-fluoro-4-(tetrahydro-pyran-4-ylcarbamoyl)-phenyl]-pyrimidine-5-carbonyl}-amino)-piperidine-1-carboxylic acid tert-butyl ester</p>                   | 568<br>[M + H] <sup>+</sup> | 0.47 (18)                       |
| 146 |  <p>4-[Cyclopropyl-(2-{3-fluoro-4-[(tetrahydro-furan-2-ylmethyl)-carbamoyl]-phenyl}-pyrimidine-5-carbonyl)-amino]-piperidine-1-carboxylic acid tert-butyl ester</p>         | 568<br>[M + H] <sup>+</sup> | 0.51 (18)                       |
| 147 |  <p>4-(Cyclopropyl-{2-[4-(3,3-difluoro-azetidine-1-carbonyl)-2-fluoro-phenyl]-pyrimidine-5-carbonyl}-amino)-piperidine-1-carboxylic acid tert-butyl ester</p>              | 560<br>[M + H] <sup>+</sup> | 0.5 (18)                        |
| 148 |  <p>4-[Cyclopropyl-(2-{2-fluoro-4-[methyl-(tetrahydro-furan-3-ylmethyl)-carbamoyl]-phenyl}-pyrimidine-5-carbonyl)-amino]-piperidine-1-carboxylic acid tert-butyl ester</p> | 582<br>[M + H] <sup>+</sup> | 0.48 (18)                       |

TABLE 8-continued

| Ex. | Structure  | ESI-MS<br>[m/z]             | HPLC $t_R$<br>[min]<br>(method) |
|-----|--|-----------------------------|---------------------------------|
| 149 | <p>4-(Cyclopropyl-(2-[3-fluoro-4-(2-methoxymethyl)-piperidine-1-carbonyl]-phenyl)-pyrimidine-5-carbonyl)-amino]-piperidine-1-carboxylic acid tert-butyl ester</p>  | 596<br>[M + H] <sup>+</sup> | 0.54 (18)                       |
| 150 | <p>4-[Cyclopropyl-(2-[3-fluoro-4-[3-(1-hydroxy-ethyl)-phenylcarbamoyl]-phenyl]-pyrimidine-5-carbonyl)-amino]-piperidine-1-carboxylic acid tert-butyl ester</p>     | 604<br>[M + H] <sup>+</sup> | 0.53 (18)                       |
| 151 | <p>4-[Cyclopropyl-(2-[3-fluoro-4-[(oxazol-4-ylmethyl)-carbamoyl]-phenyl]-pyrimidine-5-carbonyl)-amino]-piperidine-1-carboxylic acid tert-butyl ester</p>           | 565<br>[M + H] <sup>+</sup> | 0.49 (18)                       |
| 152 | <p>4-[Cyclopropyl-(2-[3-fluoro-4-[(tetrahydro-pyran-2-ylmethyl)-carbamoyl]-phenyl]-pyrimidine-5-carbonyl)-amino]-piperidine-1-carboxylic acid tert-butyl ester</p> | 582<br>[M + H] <sup>+</sup> | 0.54 (18)                       |

TABLE 8-continued

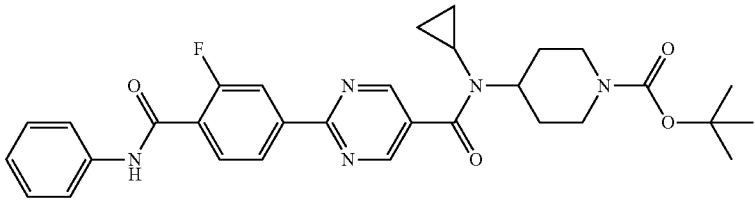
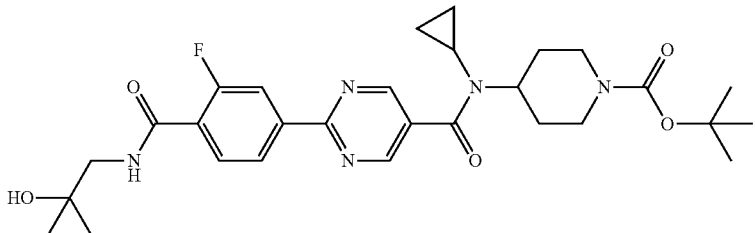
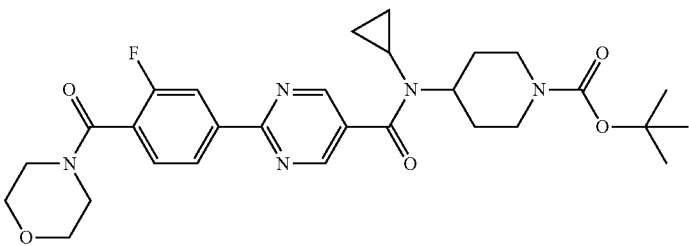
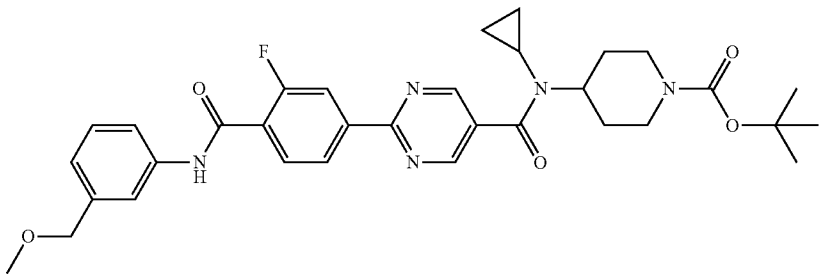
| Ex. | Structure  | ESI-MS<br>[m/z]             | HPLC $t_R$<br>[min]<br>(method) |
|-----|--|-----------------------------|---------------------------------|
| 153 | <br>4-((Cyclopropyl-2-((3-fluoro-4-phenylcarbamoyl-phenyl)-pyrimidine-5-carbonyl)-amino)-piperidine-1-carboxylic acid tert-butyl ester                       | 560<br>[M + H] <sup>+</sup> | 0.55 (18)                       |
| 154 | <br>4-((Cyclopropyl-2-((3-fluoro-4-((2-hydroxy-2-methylpropylcarbamoyl)-phenyl)-pyrimidine-5-carbonyl)-amino)-piperidine-1-carboxylic acid tert-butyl ester | 556<br>[M + H] <sup>+</sup> | 0.48 (18)                       |
| 155 | <br>4-((Cyclopropyl-2-((3-fluoro-4-(morpholine-4-carbonyl)-phenyl)-pyrimidine-5-carbonyl)-amino)-piperidine-1-carboxylic acid tert-butyl ester             | 554<br>[M + H] <sup>+</sup> | 0.49 (18)                       |
| 156 | <br>4-((Cyclopropyl-2-((3-fluoro-4-(3-methoxymethyl-phenylcarbamoyl)-phenyl)-pyrimidine-5-carbonyl)-amino)-piperidine-1-carboxylic acid tert-butyl ester   | 604<br>[M + H] <sup>+</sup> | 0.55 (18)                       |



TABLE 8-continued

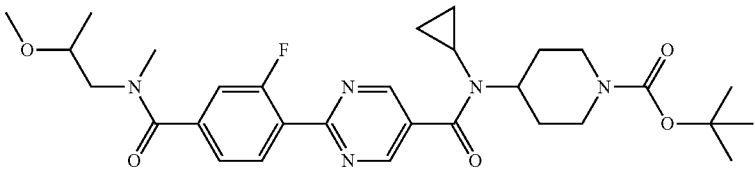
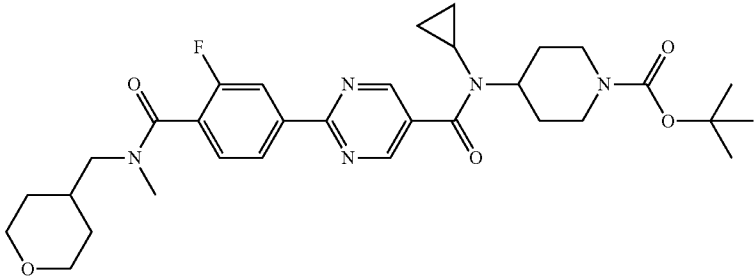
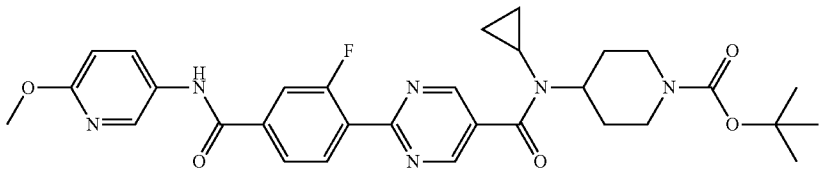
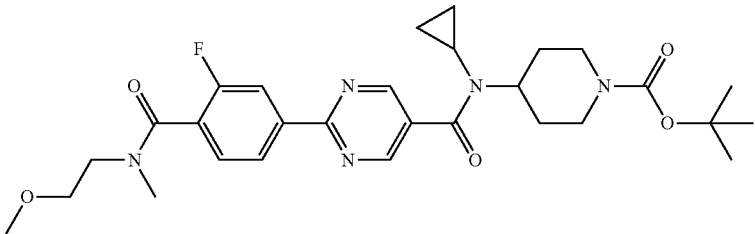
| Ex. | Structure   | ESI-MS<br>[m/z]             | HPLC $t_R$<br>[min]<br>(method) |
|-----|---|-----------------------------|---------------------------------|
| 157 |  <p>4-[Cyclopropyl-(2-{2-fluoro-4-[(2-methoxy-propyl)-methyl-carbamoyl]-phenyl}-pyrimidine-5-carbonyl)-amino]-piperidine-1-carboxylic acid tert-butyl ester</p>             | 570<br>[M + H] <sup>+</sup> | 0.5 (18)                        |
| 158 |  <p>4-[Cyclopropyl-(2-{3-fluoro-4-[methyl-(tetrahydro-pyran-4-ylmethyl)-carbamoyl]-phenyl}-pyrimidine-5-carbonyl)-amino]-piperidine-1-carboxylic acid tert-butyl ester</p> | 596<br>[M + H] <sup>+</sup> | 0.51 (18)                       |
| 159 |  <p>4-(Cyclopropyl-{2-[2-fluoro-4-(6-methoxy-pyridin-3-ylcarbamoyl)-phenyl]-pyrimidine-5-carbonyl}-amino)-piperidine-1-carboxylic acid tert-butyl ester</p>               | 591<br>[M + H] <sup>+</sup> | 0.5 (18)                        |
| 160 |  <p>4-[Cyclopropyl-(2-{3-fluoro-4-[(2-methoxy-ethyl)-methyl-carbamoyl]-phenyl}-pyrimidine-5-carbonyl)-amino]-piperidine-1-carboxylic acid tert-butyl ester</p>            | 556<br>[M + H] <sup>+</sup> | 0.53 (18)                       |

TABLE 8-continued

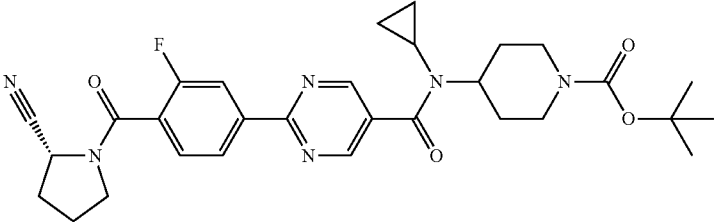
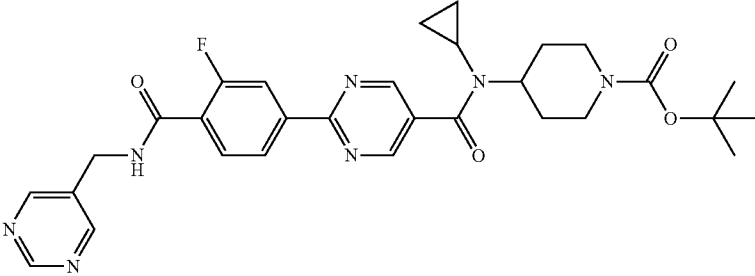
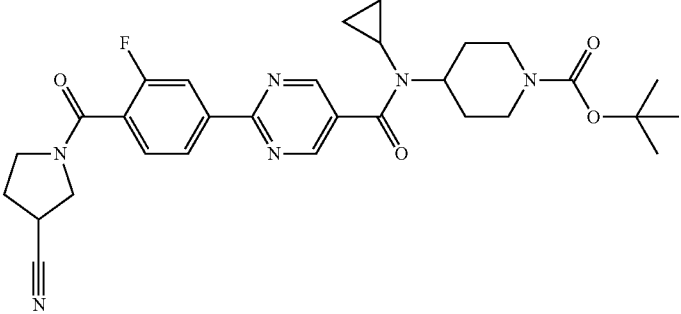
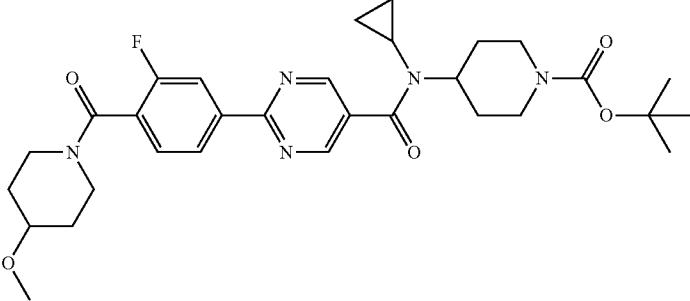
| Ex. | Structure   | ESI-MS<br>[m/z]             | HPLC $t_R$<br>[min]<br>(method) |
|-----|---|-----------------------------|---------------------------------|
| 161 |  <p>4-({2-[4-(2-Cyano-pyrrolidine-1-carbonyl)-3-fluoro-phenyl]-pyrimidine-5-carbonyl}-cyclopropyl-amino)-piperidine-1-carboxylic acid tert-butyl ester</p>    | 563<br>[M + H] <sup>+</sup> | 0.51 (18)                       |
| 162 |  <p>4-[Cyclopropyl-(2-{3-fluoro-4-[(pyrimidin-5-ylmethyl)-carbamoyl]-phenyl}-pyrimidine-5-carbonyl)-amino]-piperidine-1-carboxylic acid tert-butyl ester</p> | 576<br>[M + H] <sup>+</sup> | 0.48 (18)                       |
| 163 |  <p>4-({2-[4-(3-Cyano-pyrrolidine-1-carbonyl)-3-fluoro-phenyl]-pyrimidine-5-carbonyl}-cyclopropyl-amino)-piperidine-1-carboxylic acid tert-butyl ester</p>  | 563<br>[M + H] <sup>+</sup> | 0.5 (18)                        |
| 164 |  <p>4-(Cyclopropyl-{2-[3-fluoro-4-(4-methoxy-piperidine-1-carbonyl)-phenyl]-pyrimidine-5-carbonyl}-amino)-piperidine-1-carboxylic acid tert-butyl ester</p> | 582<br>[M + H] <sup>+</sup> | 0.52 (18)                       |

TABLE 8-continued

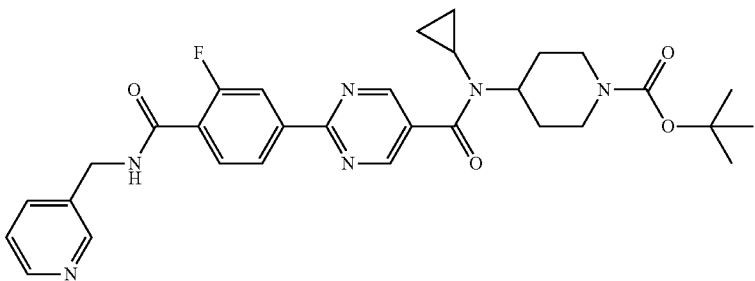
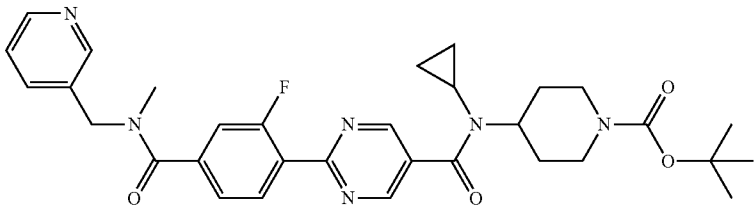
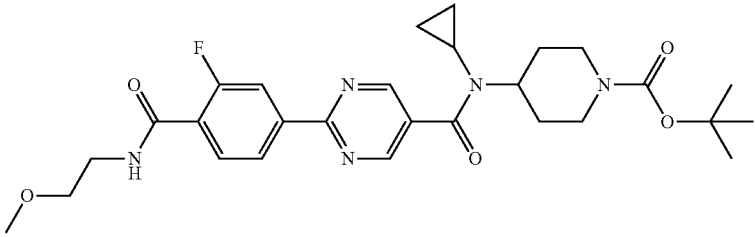
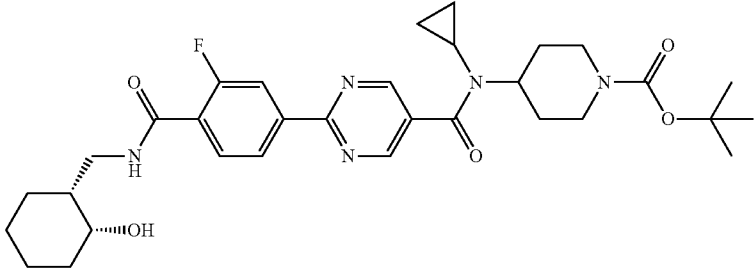
| Ex. | Structure  | ESI-MS<br>[m/z]             | HPLC $t_R$<br>[min]<br>(method) |
|-----|--|-----------------------------|---------------------------------|
| 165 |  <p>4-[Cyclopropyl-(2-{3-fluoro-4-[(pyridin-3-ylmethyl)-carbamoyl]-phenyl}-pyrimidine-5-carbonyl)-amino]-piperidine-1-carboxylic acid tert-butyl ester</p>           | 575<br>[M + H] <sup>+</sup> | 0.49 (18)                       |
| 166 |  <p>4-(Cyclopropyl-{2-[2-fluoro-4-(methyl-pyridin-3-ylmethyl)-carbamoyl]-phenyl}-pyrimidine-5-carbonyl)-amino)-piperidine-1-carboxylic acid tert-butyl ester</p>    | 589<br>[M + H] <sup>+</sup> | 0.47 (18)                       |
| 167 |  <p>4-(Cyclopropyl-{2-[3-fluoro-4-(2-methoxy-ethylcarbamoyl)-phenyl]-pyrimidine-5-carbonyl)-amino)-piperidine-1-carboxylic acid tert-butyl ester</p>               | 542<br>[M + H] <sup>+</sup> | 0.49 (18)                       |
| 168 |  <p>4-[Cyclopropyl-(2-{3-fluoro-4-[(2-hydroxy-cyclohexylmethyl)-carbamoyl]-phenyl}-pyrimidine-5-carbonyl)-amino]-piperidine-1-carboxylic acid tert-butyl ester</p> | 596<br>[M + H] <sup>+</sup> | 0.53 (18)                       |

TABLE 8-continued

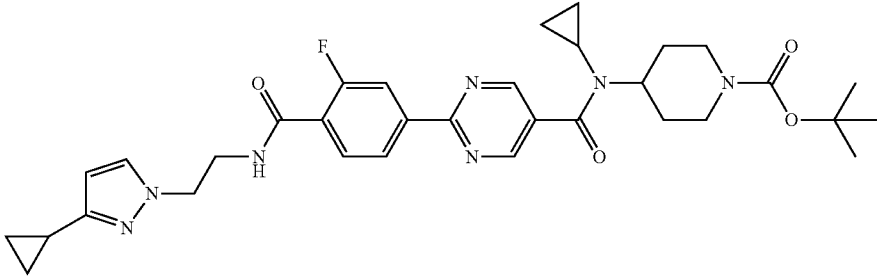
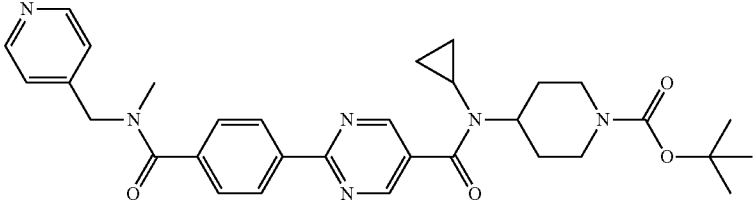
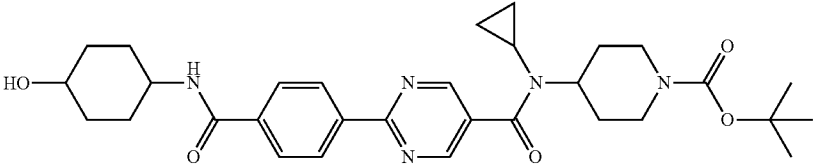
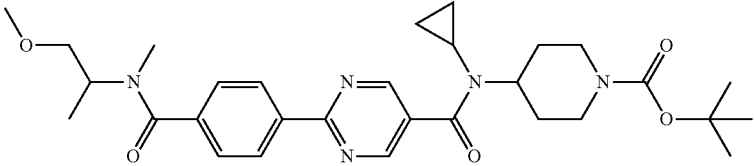
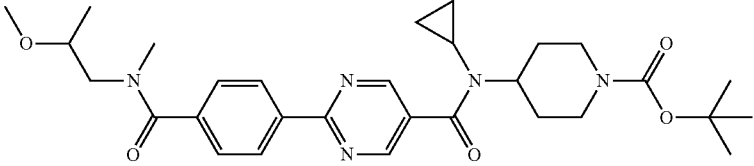
| Ex. | Structure   | ESI-MS<br>[m/z]             | HPLC $t_R$<br>[min]<br>(method) |
|-----|---|-----------------------------|---------------------------------|
| 169 |  <p>4-[Cyclopropyl-(2-{4-[2-(3-cyclopropyl-pyrazol-1-yl)-ethylcarbamoyl]-3-fluoro-phenyl}-pyrimidine-5-carbonyl)-amino]-piperidine-1-carboxylic acid tert-butyl ester</p> | 618<br>[M + H] <sup>+</sup> | 0.53 (18)                       |
| 170 |  <p>4-(Cyclopropyl-{2-[4-(methyl-pyridin-4-ylmethyl-carbamoyl)-phenyl]-pyrimidine-5-carbonyl}-amino)-piperidine-1-carboxylic acid tert-butyl ester</p>                   | 571<br>[M + H] <sup>+</sup> | 0.47 (18)                       |
| 171 |  <p>4-(Cyclopropyl-{2-[4-(4-hydroxy-cyclohexylcarbamoyl)-phenyl]-pyrimidine-5-carbonyl}-amino)-piperidine-1-carboxylic acid tert-butyl ester</p>                        | 564<br>[M + H] <sup>+</sup> | 0.47 (18)                       |
| 172 |  <p>4-[Cyclopropyl-(2-{4-[(2-methoxy-1-methyl-ethyl)-methyl-carbamoyl]-phenyl}-pyrimidine-5-carbonyl)-amino]-piperidine-1-carboxylic acid tert-butyl ester</p>          | 552<br>[M + H] <sup>+</sup> | 0.5 (18)                        |
| 173 |  <p>4-[Cyclopropyl-(2-{4-[(2-methoxy-propyl)-methyl-carbamoyl]-phenyl}-pyrimidine-5-carbonyl)-amino]-piperidine-1-carboxylic acid tert-butyl ester</p>                  | 552<br>[M + H] <sup>+</sup> | 0.51 (18)                       |

TABLE 8-continued

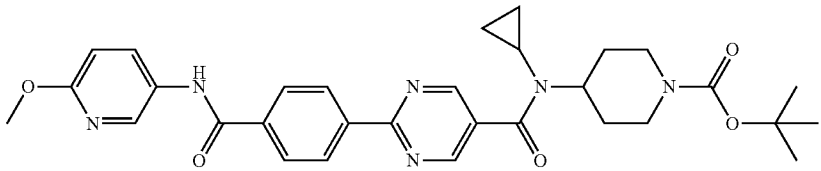
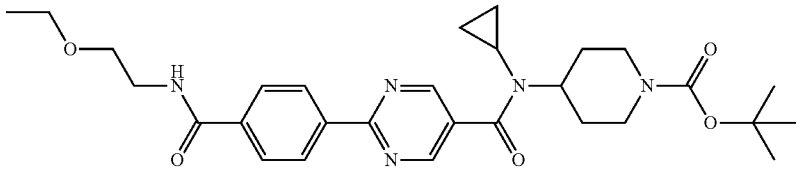
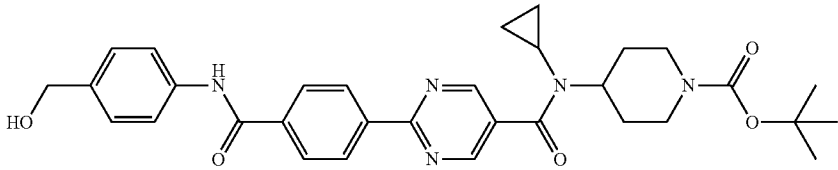
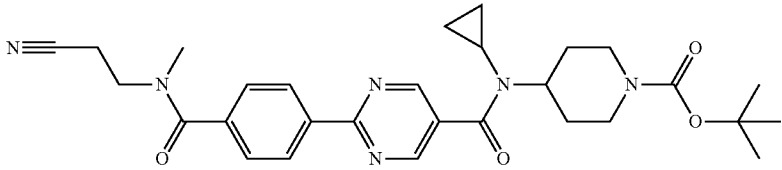
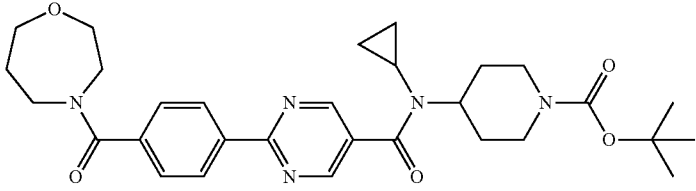
| Ex. | Structure   | ESI-MS<br>[m/z]             | HPLC $t_R$<br>[min]<br>(method) |
|-----|---|-----------------------------|---------------------------------|
| 174 |  <p>4-(Cyclopropyl-{2-[4-(6-methoxy-pyridin-3-ylcarbamoyl)-phenyl]-pyrimidine-5-carbonyl}-amino)-piperidine-1-carboxylic acid tert-butyl ester</p>    | 573<br>[M + H] <sup>+</sup> | 0.5 (18)                        |
| 175 |  <p>4-(Cyclopropyl-{2-[4-(2-ethoxy-ethylcarbamoyl)-phenyl]-pyrimidine-5-carbonyl}-amino)-piperidine-1-carboxylic acid tert-butyl ester</p>            | 537<br>[M + H] <sup>+</sup> | 0.49 (18)                       |
| 176 |  <p>4-(Cyclopropyl-{2-[4-(4-hydroxymethyl-phenylcarbamoyl)-phenyl]-pyrimidine-5-carbonyl}-amino)-piperidine-1-carboxylic acid tert-butyl ester</p>  | 572<br>[M + H] <sup>+</sup> | 0.48 (18)                       |
| 177 |  <p>4-[(2-{4-[(2-Cyano-ethyl)-methyl-carbamoyl]-phenyl}-pyrimidine-5-carbonyl)-cyclopropyl-amino]-piperidine-1-carboxylic acid tert-butyl ester</p> | 533<br>[M + H] <sup>+</sup> | 0.48 (18)                       |
| 178 |  <p>4-(Cyclopropyl-{2-[4-([1,4]oxazepane-4-carbonyl)-phenyl]-pyrimidine-5-carbonyl}-amino)-piperidine-1-carboxylic acid tert-butyl ester</p>        | 550<br>[M + H] <sup>+</sup> | 0.48 (18)                       |

TABLE 8-continued

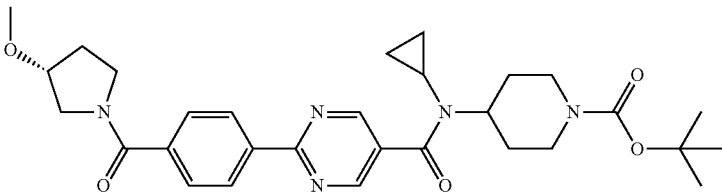
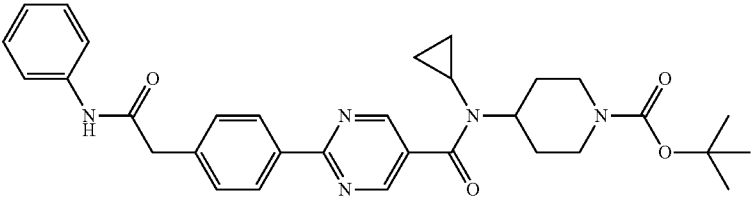
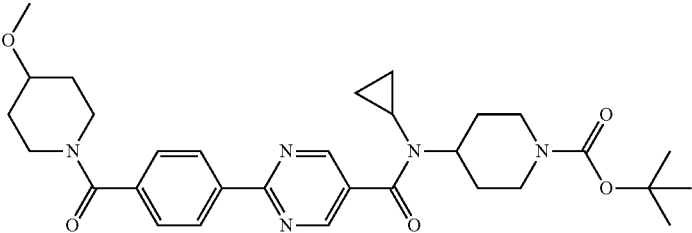
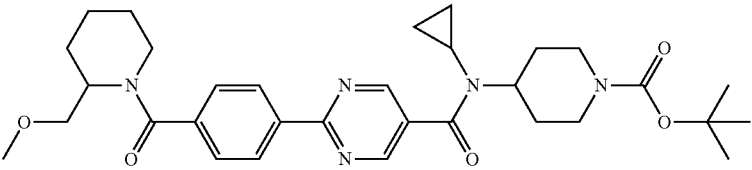
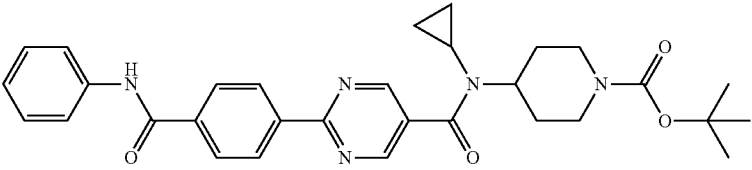
| Ex. | Structure  | ESI-MS<br>[m/z]             | HPLC $t_R$<br>[min]<br>(method) |
|-----|--|-----------------------------|---------------------------------|
| 179 |  <p>4-(Cyclopropyl-{2-[4-(3-methoxy-pyrrolidine-1-carbonyl)-phenyl]-pyrimidine-5-carbonyl}-amino)-piperidine-1-carboxylic acid tert-butyl ester</p>        | 550<br>[M + H] <sup>+</sup> | 0.5 (18)                        |
| 180 |  <p>4-{Cyclopropyl-[2-(4-phenylcarbamoylmethyl-phenyl)-pyrimidine-5-carbonyl]-amino}-piperidine-1-carboxylic acid tert-butyl ester</p>                     | 556<br>[M + H] <sup>+</sup> | 0.52 (18)                       |
| 181 |  <p>4-(Cyclopropyl-{2-[4-(4-methoxy-piperidine-1-carbonyl)-phenyl]-pyrimidine-5-carbonyl}-amino)-piperidine-1-carboxylic acid tert-butyl ester</p>       | 564<br>[M + H] <sup>+</sup> | 0.5 (18)                        |
| 182 |  <p>4-(Cyclopropyl-{2-[4-(2-methoxymethyl-piperidine-1-carbonyl)-phenyl]-pyrimidine-5-carbonyl}-amino)-piperidine-1-carboxylic acid tert-butyl ester</p> | 578<br>[M + H] <sup>+</sup> | 0.53 (18)                       |
| 183 |  <p>4-{Cyclopropyl-[2-(4-phenylcarbamoyl-phenyl)-pyrimidine-5-carbonyl]-amino}-piperidine-1-carboxylic acid tert-butyl ester</p>                         | 542<br>[M + H] <sup>+</sup> | 0.54 (18)                       |

TABLE 8-continued

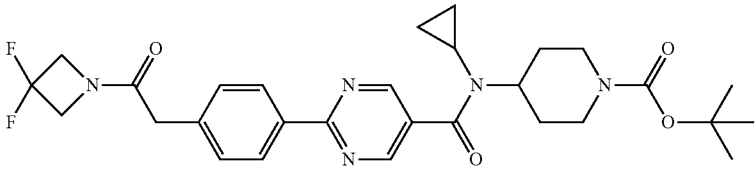
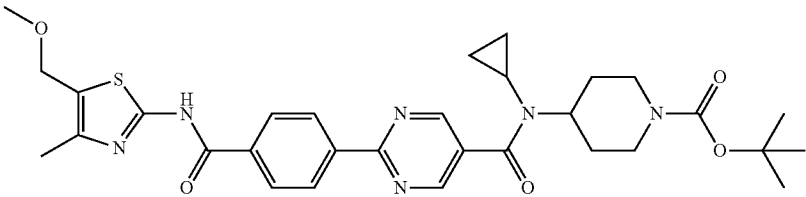
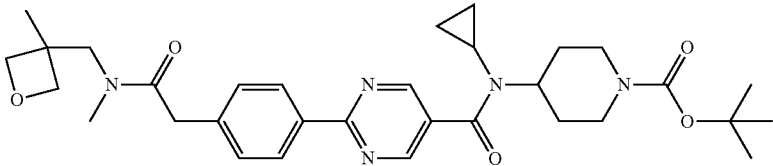
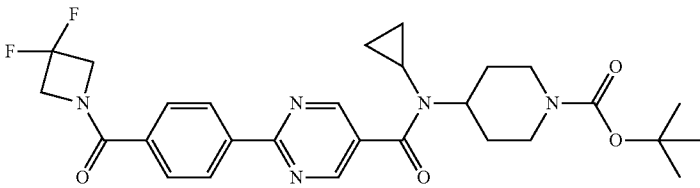
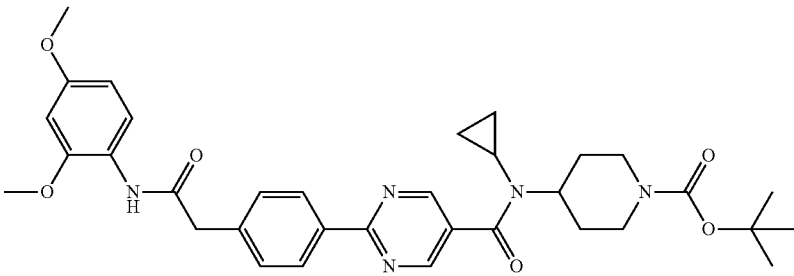
| Ex. | Structure   | ESI-MS<br>[m/z]             | HPLC $t_R$<br>[min]<br>(method) |
|-----|---|-----------------------------|---------------------------------|
| 184 |  <p>4-[(Cyclopropyl-{2-[4-(3,3-difluoro-azetidin-1-yl)-2-oxoethyl]-phenyl}-pyrimidine-5-carbonyl)-amino]-piperidine-1-carboxylic acid tert-butyl ester</p>                  | 556<br>[M + H] <sup>+</sup> | 0.5 (18)                        |
| 185 |  <p>4-[(Cyclopropyl-{2-[4-(5-methoxymethyl-4-methyl-thiazol-2-ylcarbamoyl)-phenyl]-pyrimidine-5-carbonyl}-amino)-piperidine-1-carboxylic acid tert-butyl ester</p>          | 607<br>[M + H] <sup>+</sup> | 0.45 (18)                       |
| 186 |  <p>4-[(Cyclopropyl-{2-[4-([methyl-(3-methyl-oxetan-3-ylmethyl)-carbamoyl]-methyl)-phenyl]-pyrimidine-5-carbonyl}-amino)-piperidine-1-carboxylic acid tert-butyl ester</p> | 578<br>[M + H] <sup>+</sup> | 0.46 (18)                       |
| 187 |  <p>4-[(Cyclopropyl-{2-[4-(3,3-difluoro-azetidine-1-carbonyl)-phenyl]-pyrimidine-5-carbonyl}-amino)-piperidine-1-carboxylic acid tert-butyl ester</p>                     | 541<br>[M + H] <sup>+</sup> | 0.51 (18)                       |
| 188 |  <p>4-[(Cyclopropyl-{2-[4-[(2,4-dimethoxy-phenyl)carbamoyl]-methyl]-phenyl]-pyrimidine-5-carbonyl)-amino]-piperidine-1-carboxylic acid tert-butyl ester</p>               | 616<br>[M + H] <sup>+</sup> | 0.5 (18)                        |

TABLE 8-continued

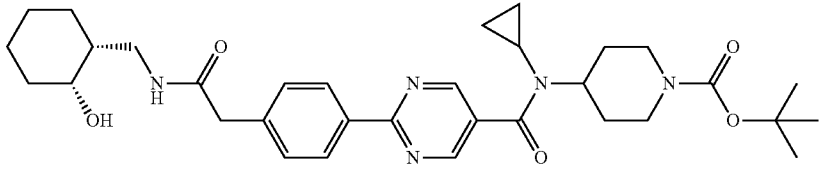
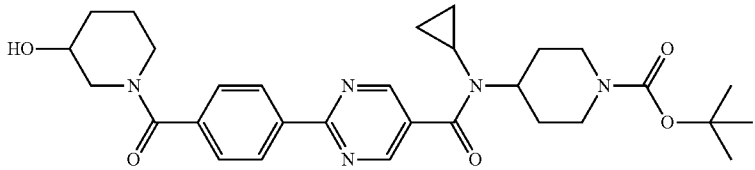
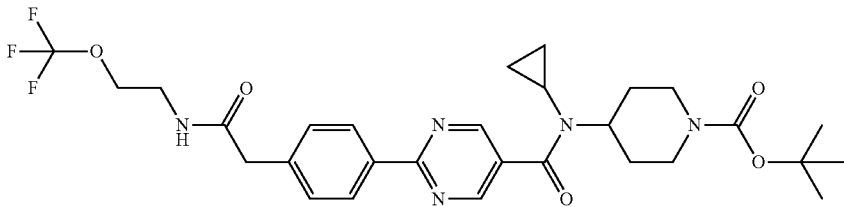
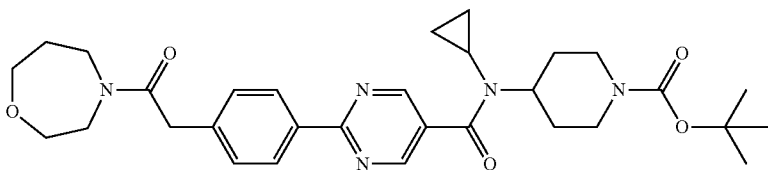
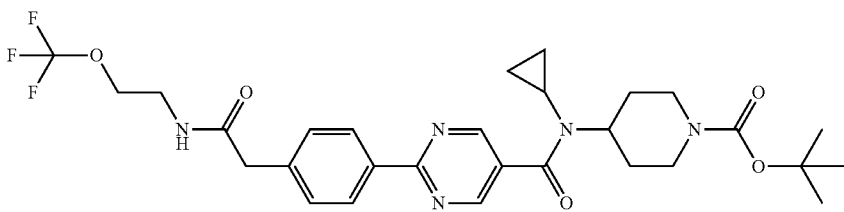
| Ex. | Structure  | ESI-MS<br>[m/z]             | HPLC $t_R$<br>[min]<br>(method) |
|-----|--|-----------------------------|---------------------------------|
| 189 |  <p>4-{Cyclopropyl-[2-([(2-hydroxy-cyclohexyl)methyl]-carbamoyl)-methyl]-phenyl}-pyrimidine-5-carbonyl]-amino}-piperidine-1-carboxylic acid tert-butyl ester</p>     | 592<br>[M + H] <sup>+</sup> | 0.47 (18)                       |
| 190 |  <p>4-(Cyclopropyl-[2-[4-(3-hydroxy-piperidine-1-carbonyl)-phenyl]-pyrimidine-5-carbonyl]-amino)-piperidine-1-carboxylic acid tert-butyl ester</p>                   | 550<br>[M + H] <sup>+</sup> | 0.46 (18)                       |
| 191 |  <p>4-[Cyclopropyl-(2-{4-[(2-trifluoromethoxy-ethyl)carbamoyl]-methyl]-phenyl}-pyrimidine-5-carbonyl)-amino]-piperidine-1-carboxylic acid tert-butyl ester</p>     | 591<br>[M + H] <sup>+</sup> | 0.48 (18)                       |
| 192 |  <p>4-(Cyclopropyl-[2-[4-(2-[1,4]oxazepan-4-yl-2-oxo-ethyl)-phenyl]-pyrimidine-5-carbonyl]-amino)-piperidine-1-carboxylic acid tert-butyl ester</p>                | 564<br>[M + H] <sup>+</sup> | 0.48 (18)                       |
| 193 |  <p>4-[Cyclopropyl-(2-{4-[methyl-(tetrahydro-pyran-4-yl)methyl]-carbamoyl]-phenyl}-pyrimidine-5-carbonyl)-amino]-piperidine-1-carboxylic acid tert-butyl ester</p> | 578<br>[M + H] <sup>+</sup> | 0.5 (18)                        |



TABLE 8-continued

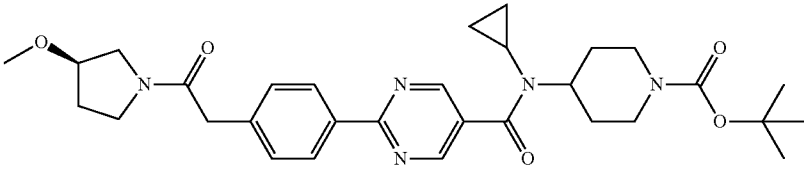
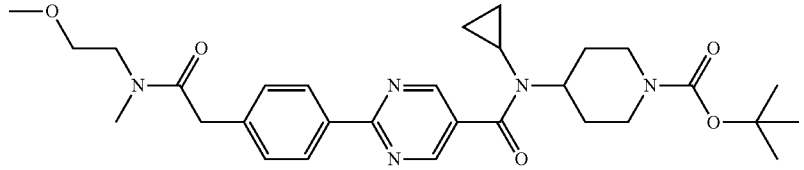
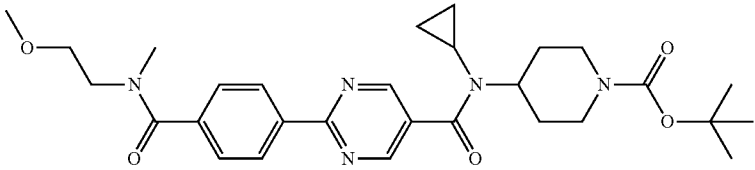
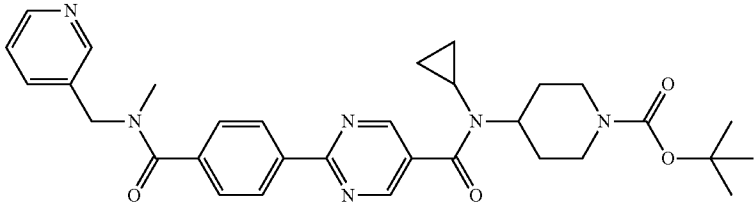
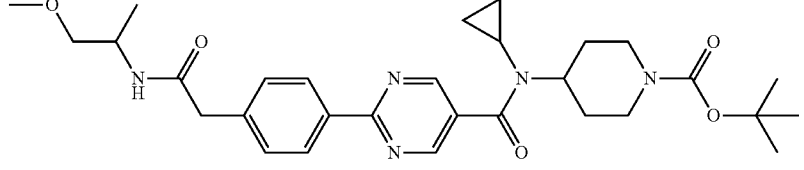
| Ex. | Structure   | ESI-MS<br>[m/z]             | HPLC $t_R$<br>[min]<br>(method) |
|-----|---|-----------------------------|---------------------------------|
| 194 | <br>4-[Cyclopropyl-(2-{4-[2-(3-methoxy-pyrrolidin-1-yl)-2-oxo-ethyl]-phenyl}-pyrimidine-5-carbonyl)-amino]-piperidine-1-carboxylic acid tert-butyl ester    | 564<br>[M + H] <sup>+</sup> | 0.49 (18)                       |
| 195 | <br>4-{Cyclopropyl-[2-(4-{[(2-methoxy-ethyl)-methyl-carbamoyl]-methyl]-phenyl}-pyrimidine-5-carbonyl)-amino]-piperidine-1-carboxylic acid tert-butyl ester  | 552<br>[M + H] <sup>+</sup> | 0.49 (18)                       |
| 196 | <br>4-[Cyclopropyl-(2-{4-[(2-methoxy-ethyl)-methyl-carbamoyl]-phenyl}-pyrimidine-5-carbonyl)-amino]-piperidine-1-carboxylic acid tert-butyl ester         | 538<br>[M + H] <sup>+</sup> | 0.49 (18)                       |
| 197 | <br>4-(Cyclopropyl-{2-[4-(methyl-pyridin-3-ylmethyl-carbamoyl)-phenyl]-pyrimidine-5-carbonyl}-amino)-piperidine-1-carboxylic acid tert-butyl ester        | 571<br>[M + H] <sup>+</sup> | 0.48 (18)                       |
| 198 | <br>4-[Cyclopropyl-(2-{4-[(2-methoxy-1-methyl-ethylcarbamoyl)-methyl]-phenyl}-pyrimidine-5-carbonyl)-amino]-piperidine-1-carboxylic acid tert-butyl ester | 552<br>[M + H] <sup>+</sup> | 0.48 (18)                       |

TABLE 8-continued

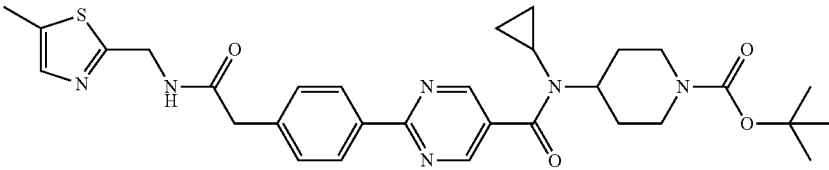
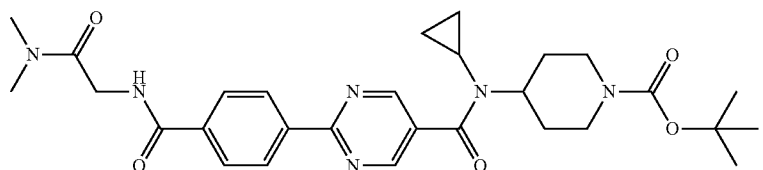
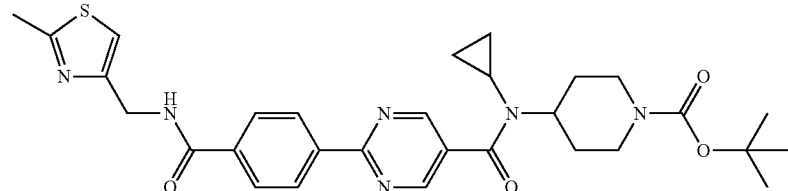
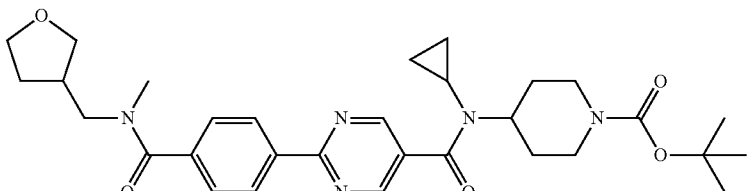
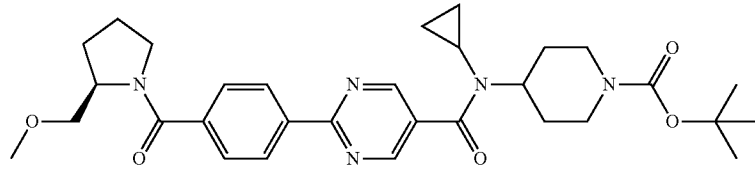
| Ex. | Structure   | ESI-MS<br>[m/z]             | HPLC $t_R$<br>[min]<br>(method) |
|-----|---|-----------------------------|---------------------------------|
| 199 |  <p>4-{Cyclopropyl-[2-(4-[(5-methyl-thiazol-2-ylmethyl)-carbamoyl]-methyl)-phenyl]-pyrimidine-5-carbonyl]-amino}-piperidine-1-carboxylic acid tert-butyl ester</p>  | 591<br>[M + H] <sup>+</sup> | 0.46 (18)                       |
| 200 |  <p>4-(Cyclopropyl-{2-[4-(dimethylcarbamoylmethyl)-carbamoyl]-phenyl}-pyrimidine-5-carbonyl)-amino)-piperidine-1-carboxylic acid tert-butyl ester</p>               | 551<br>[M + H] <sup>+</sup> | 0.46 (18)                       |
| 201 |  <p>4-[Cyclopropyl-(2-{4-[(2-methyl-thiazol-4-ylmethyl)-carbamoyl]-phenyl}-pyrimidine-5-carbonyl)-amino]-piperidine-1-carboxylic acid tert-butyl ester</p>        | 577<br>[M + H] <sup>+</sup> | 0.5 (18)                        |
| 202 |  <p>4-[Cyclopropyl-(2-{4-[methyl-(tetrahydro-furan-3-ylmethyl)-carbamoyl]-phenyl}-pyrimidine-5-carbonyl)-amino]-piperidine-1-carboxylic acid tert-butyl ester</p> | 564<br>[M + H] <sup>+</sup> | 0.49 (18)                       |
| 203 |  <p>4-(Cyclopropyl-{2-[4-(2-methoxymethyl-pyrrolidine-1-carbonyl)-phenyl]-pyrimidine-5-carbonyl)-amino)-piperidine-1-carboxylic acid tert-butyl ester</p>         | 564<br>[M + H] <sup>+</sup> | 0.51 (18)                       |

TABLE 8-continued

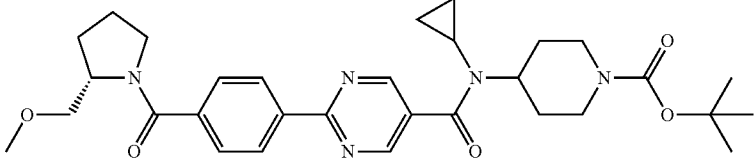
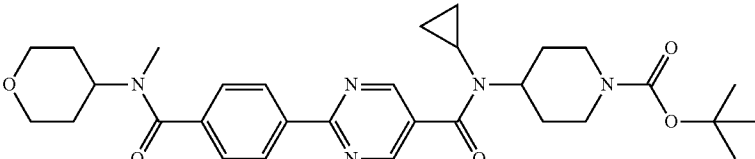
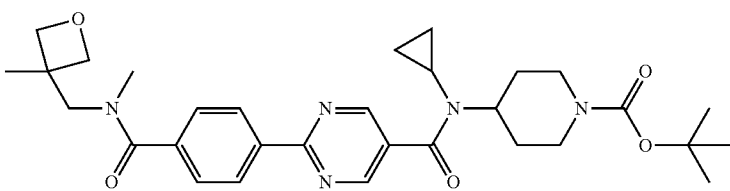
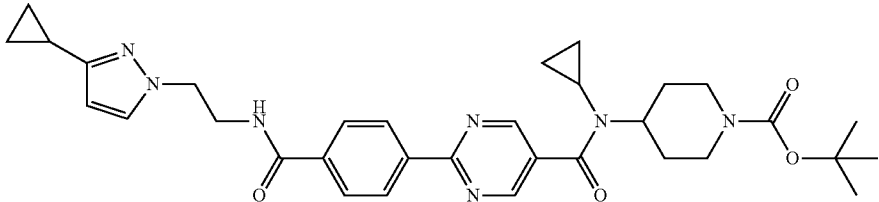
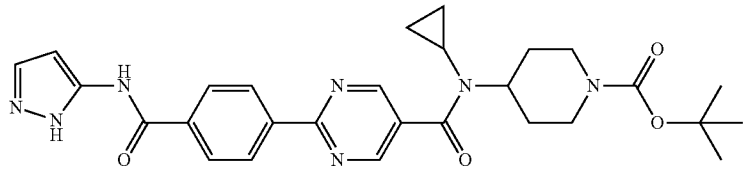
| Ex. | Structure  | ESI-MS<br>[m/z]             | HPLC $t_R$<br>[min]<br>(method) |
|-----|--|-----------------------------|---------------------------------|
| 204 |  <p>4-(Cyclopropyl-{2-[4-(2-methoxymethyl-pyrrolidine-1-carbonyl)-phenyl]-pyrimidine-5-carbonyl}-amino)-piperidine-1-carboxylic acid tert-butyl ester</p>          | 564<br>[M + H] <sup>+</sup> | 0.51 (18)                       |
| 205 |  <p>4-[Cyclopropyl-(2-{4-[methyl-(tetrahydro-pyran-4-yl)-carbamoyl]-phenyl}-pyrimidine-5-carbonyl)-amino]-piperidine-1-carboxylic acid tert-butyl ester</p>        | 564<br>[M + H] <sup>+</sup> | 0.49 (18)                       |
| 206 |  <p>4-[Cyclopropyl-(2-{4-[methyl-(3-methyl-oxetan-3-ylmethyl)-carbamoyl]-phenyl}-pyrimidine-5-carbonyl)-amino]-piperidine-1-carboxylic acid tert-butyl ester</p> | 564<br>[M + H] <sup>+</sup> | 0.5 (18)                        |
| 207 |  <p>4-[Cyclopropyl-(2-{4-[2-(3-cyclopropyl-pyrazol-1-yl)-ethylcarbamoyl]-phenyl}-pyrimidine-5-carbonyl)-amino]-piperidine-1-carboxylic acid tert-butyl ester</p> | 600<br>[M + H] <sup>+</sup> | 0.52 (18)                       |
| 208 |  <p>4-(Cyclopropyl-{2-[4-(2H-pyrazol-3-ylcarbamoyl)-phenyl]-pyrimidine-5-carbonyl}-amino)-piperidine-1-carboxylic acid tert-butyl ester</p>                      | 532<br>[M + H] <sup>+</sup> | 0.49 (18)                       |

TABLE 8-continued

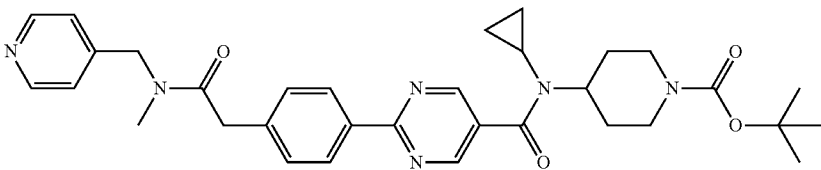
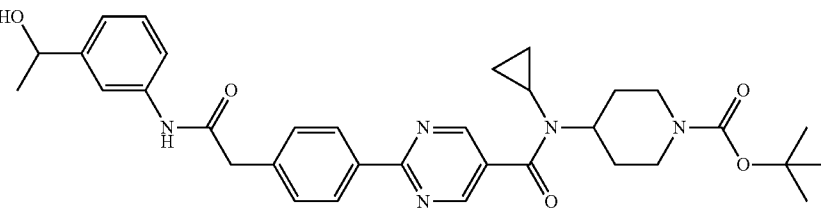
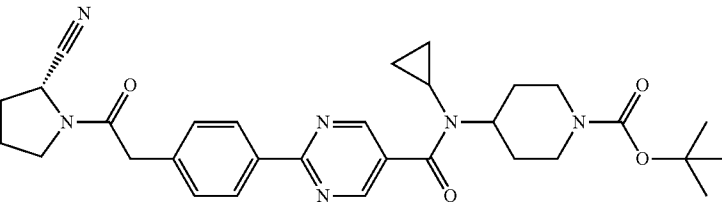
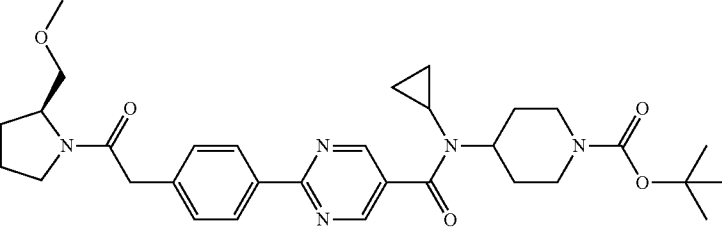
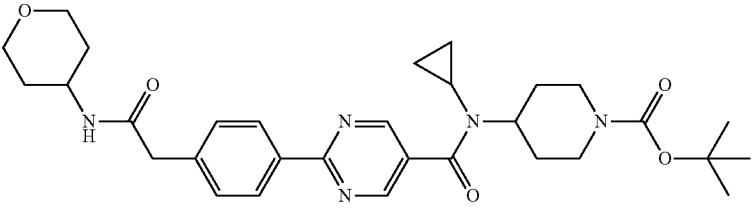
| Ex. | Structure  | ESI-MS<br>[m/z]             | HPLC $t_R$<br>[min]<br>(method) |
|-----|--|-----------------------------|---------------------------------|
| 209 |  <p>4-[Cyclopropyl-(2-{4-[(methyl-pyridin-4-ylmethyl-carbamoyl)-methyl]-phenyl}-pyrimidine-5-carbonyl)-amino]-piperidine-1-carboxylic acid tert-butyl ester</p>      | 585<br>[M + H] <sup>+</sup> | 0.48 (18)                       |
| 210 |  <p>4-{Cyclopropyl-[2-(4-{[3-(1-hydroxy-ethyl)-phenylcarbamoyl]-methyl}-phenyl)-pyrimidine-5-carbonyl]-amino}-piperidine-1-carboxylic acid tert-butyl ester</p>      | 600<br>[M + H] <sup>+</sup> | 0.47 (18)                       |
| 211 |  <p>4-[(2-{4-[2-(2-Cyano-pyrrolidin-1-yl)-2-oxo-ethyl]-phenyl}-pyrimidine-5-carbonyl)-cyclopropyl-amino]-piperidine-1-carboxylic acid tert-butyl ester</p>         | 559<br>[M + H] <sup>+</sup> | 0.46 (18)                       |
| 212 |  <p>4-[Cyclopropyl-(2-{4-[2-(2-methoxymethyl-pyrrolidin-1-yl)-2-oxo-ethyl]-phenyl}-pyrimidine-5-carbonyl)-amino]-piperidine-1-carboxylic acid tert-butyl ester</p> | 578<br>[M + H] <sup>+</sup> | 0.51 (18)                       |
| 213 |  <p>4-[Cyclopropyl-(2-{4-[(tetrahydro-pyran-4-ylcarbamoyl)-methyl]-phenyl}-pyrimidine-5-carbonyl)-amino]-piperidine-1-carboxylic acid tert-butyl ester</p>         | 564<br>[M + H] <sup>+</sup> | 0.48 (18)                       |

TABLE 8-continued

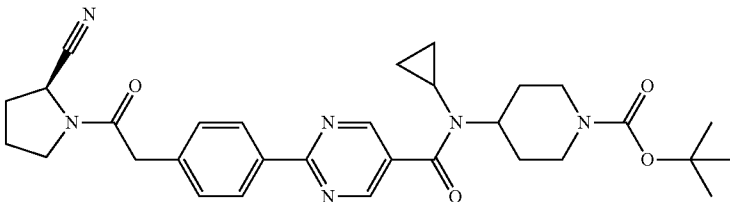
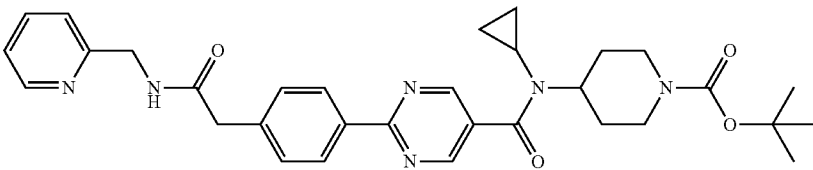
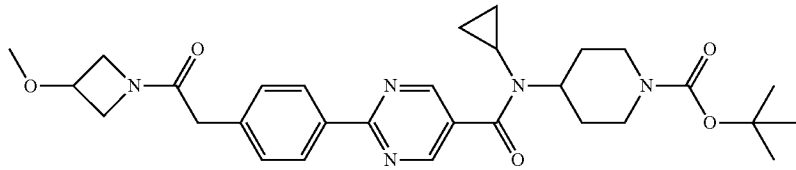
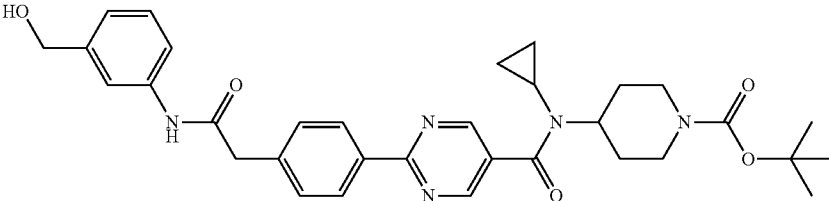
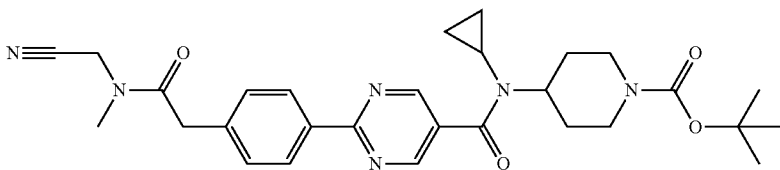
| Ex. | Structure   | ESI-MS<br>[m/z]             | HPLC $t_R$<br>[min]<br>(method) |
|-----|---|-----------------------------|---------------------------------|
| 214 |  <p>4-[(2-{4-[2-(2-Cyano-pyrrolidin-1-yl)-2-oxo-ethyl]-phenyl}-pyrimidine-5-carbonyl)-cyclopropyl-amino]-piperidine-1-carboxylic acid tert-butyl ester</p>      | 559<br>[M + H] <sup>+</sup> | 0.47 (18)                       |
| 215 |  <p>4-{Cyclopropyl-[2-(4-{[(pyridin-2-ylmethyl)-carbamoyl]-methyl}-phenyl)-pyrimidine-5-carbonyl]-amino}-piperidine-1-carboxylic acid tert-butyl ester</p>      | 571<br>[M + H] <sup>+</sup> | 0.45 (18)                       |
| 216 |  <p>4-[Cyclopropyl-(2-{4-[2-(3-methoxy-azetidin-1-yl)-2-oxo-ethyl]-phenyl}-pyrimidine-5-carbonyl)-amino]-piperidine-1-carboxylic acid tert-butyl ester</p>    | 550<br>[M + H] <sup>+</sup> | 0.45 (18)                       |
| 217 |  <p>4-[Cyclopropyl-(2-{4-[2-(3-hydroxymethyl-phenylcarbamoyl)-methyl]-phenyl}-pyrimidine-5-carbonyl)-amino]-piperidine-1-carboxylic acid tert-butyl ester</p> | 586<br>[M + H] <sup>+</sup> | 0.48 (18)                       |
| 218 |  <p>4-[(2-{4-[(Cyanomethyl-methyl)-carbamoyl]-methyl}-phenyl)-pyrimidine-5-carbonyl]-cyclopropyl-amino]-piperidine-1-carboxylic acid tert-butyl ester</p>     | 533<br>[M + H] <sup>+</sup> | 0.45 (18)                       |

TABLE 8-continued

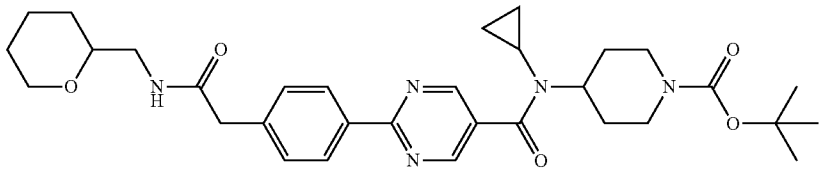
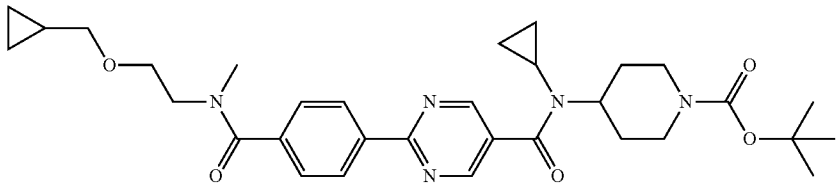
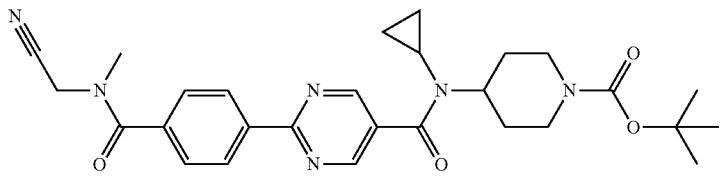
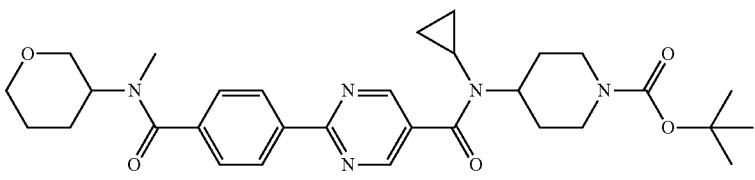
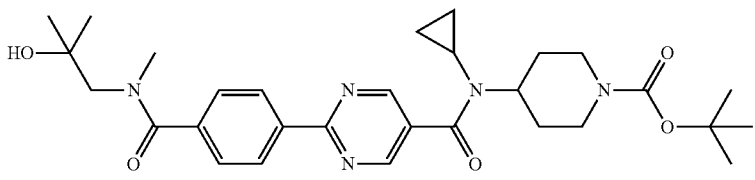
| Ex. | Structure  | ESI-MS<br>[m/z]             | HPLC $t_R$<br>[min]<br>(method) |
|-----|--|-----------------------------|---------------------------------|
| 219 |    | 578<br>[M + H] <sup>+</sup> | 0.47 (18)                       |
| 220 |    | 578<br>[M + H] <sup>+</sup> | 0.54 (18)                       |
| 221 |  | 519<br>[M + H] <sup>+</sup> | 0.51 (18)                       |
| 222 |  | 564<br>[M + H] <sup>+</sup> | 0.51 (18)                       |
| 223 |  | 552<br>[M + H] <sup>+</sup> | 0.5 (18)                        |

TABLE 8-continued

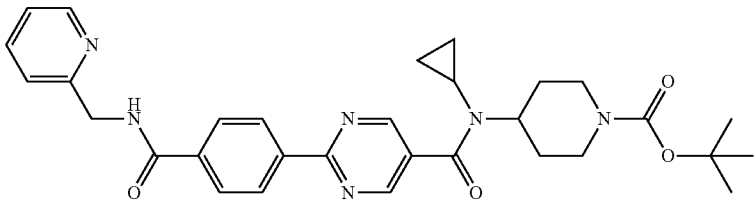
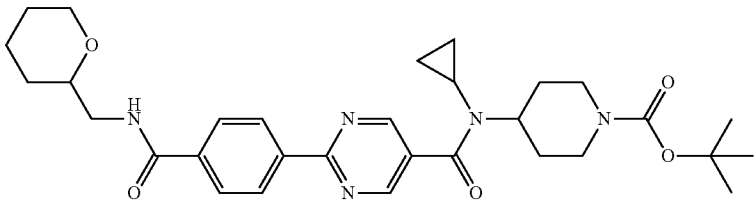
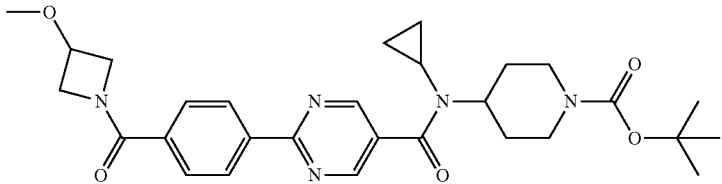
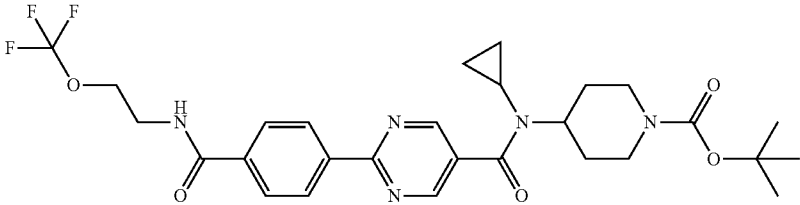
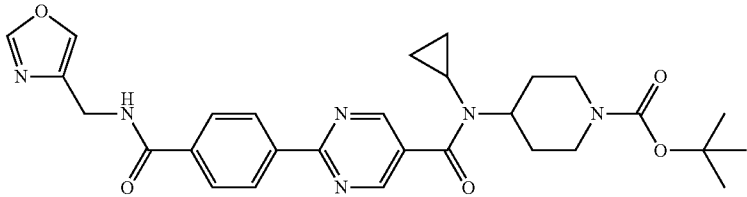
| Ex. | Structure  | ESI-MS<br>[m/z]             | HPLC $t_R$<br>[min]<br>(method) |
|-----|--|-----------------------------|---------------------------------|
| 224 |  <p>4-[Cyclopropyl-(2-{4-[(pyridin-2-ylmethyl)-carbamoyl]-phenyl}-pyrimidine-5-carbonyl)-amino]-piperidine-1-carboxylic acid tert-butyl ester</p>          | 557<br>[M + H] <sup>+</sup> | 0.52 (18)                       |
| 225 |  <p>4-[Cyclopropyl-(2-{4-[(tetrahydro-pyran-2-ylmethyl)-carbamoyl]-phenyl}-pyrimidine-5-carbonyl)-amino]-piperidine-1-carboxylic acid tert-butyl ester</p> | 564<br>[M + H] <sup>+</sup> | 0.52 (18)                       |
| 226 |  <p>4-(Cyclopropyl-{2-[4-(3-methoxy-azetidine-1-carbonyl)-phenyl]-pyrimidine-5-carbonyl}-amino)-piperidine-1-carboxylic acid tert-butyl ester</p>        | 536<br>[M + H] <sup>+</sup> | 0.51 (18)                       |
| 227 |  <p>4-(Cyclopropyl-{2-[4-(2-trifluoromethoxy-ethylcarbamoyl)-phenyl]-pyrimidine-5-carbonyl}-amino)-piperidine-1-carboxylic acid tert-butyl ester</p>     | 578<br>[M + H] <sup>+</sup> | 0.55 (18)                       |
| 228 |  <p>4-[Cyclopropyl-(2-{4-[(oxazol-4-ylmethyl)-carbamoyl]-phenyl}-pyrimidine-5-carbonyl)-amino]-piperidine-1-carboxylic acid tert-butyl ester</p>         | 547<br>[M + H] <sup>+</sup> | 0.48 (18)                       |

TABLE 8-continued

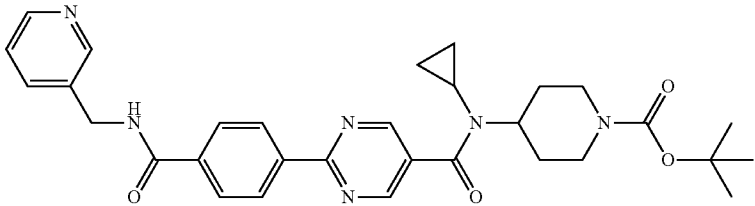
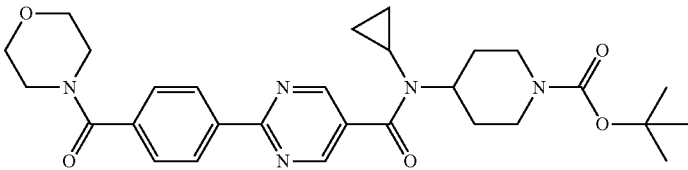
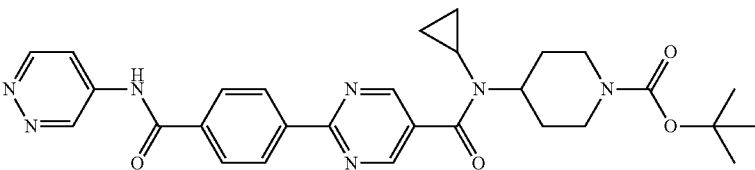
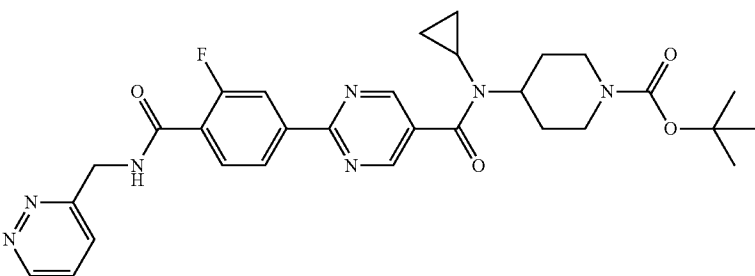
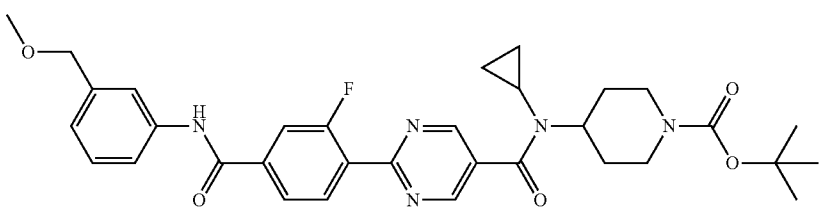
| Ex. | Structure  | ESI-MS<br>[m/z]             | HPLC $t_R$<br>[min]<br>(method) |
|-----|--|-----------------------------|---------------------------------|
| 229 |  <p>4-[Cyclopropyl-(2-{4-[(pyridin-3-ylmethyl)-carbamoyl]-phenyl}-pyrimidine-5-carbonyl)-amino]-piperidine-1-carboxylic acid tert-butyl ester</p>              | 557<br>[M + H] <sup>+</sup> | 0.49 (18)                       |
| 230 |  <p>4-(Cyclopropyl-{2-[4-(morpholine-4-carbonyl)-phenyl]-pyrimidine-5-carbonyl}-amino)-piperidine-1-carboxylic acid tert-butyl ester</p>                       | 536<br>[M + H] <sup>+</sup> | 0.5 (18)                        |
| 231 |  <p>4-(Cyclopropyl-{2-[4-(pyridazin-4-ylcarbamoyl)-phenyl]-pyrimidine-5-carbonyl}-amino)-piperidine-1-carboxylic acid tert-butyl ester</p>                    | 544<br>[M + H] <sup>+</sup> | 0.48 (18)                       |
| 232 |  <p>4-[Cyclopropyl-(2-{3-fluoro-4-[(pyridazin-3-ylmethyl)-carbamoyl]-phenyl}-pyrimidine-5-carbonyl)-amino]-piperidine-1-carboxylic acid tert-butyl ester</p> | 576<br>[M + H] <sup>+</sup> | 0.47 (18)                       |
| 233 |  <p>4-(Cyclopropyl-{2-[2-fluoro-4-(3-methoxymethyl-phenylcarbamoyl)-phenyl]-pyrimidine-5-carbonyl}-amino)-piperidine-1-carboxylic acid tert-butyl ester</p>  | 604<br>[M + H] <sup>+</sup> | 0.54 (18)                       |



TABLE 8-continued

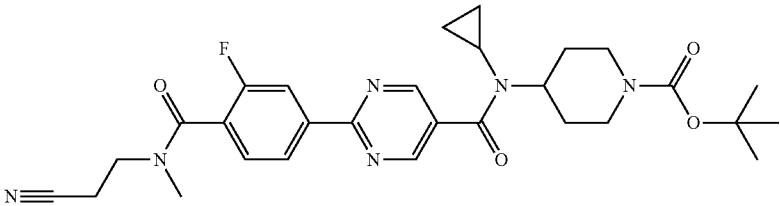
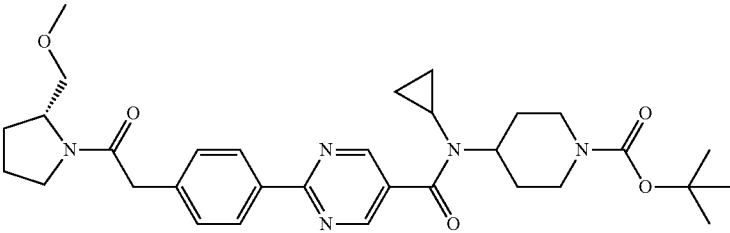
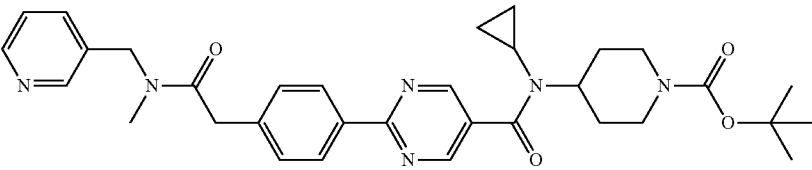
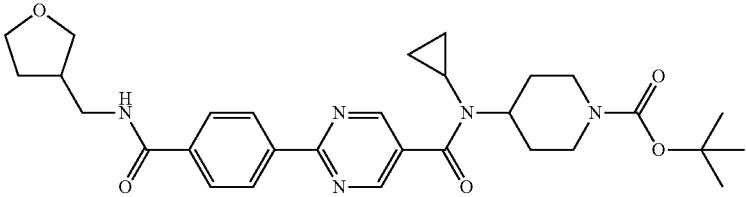
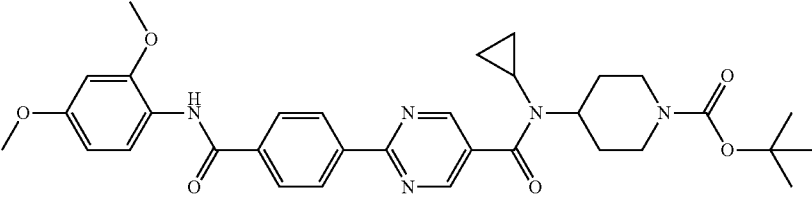
| Ex. | Structure  | ESI-MS<br>[m/z]             | HPLC $t_R$<br>[min]<br>(method) |
|-----|--|-----------------------------|---------------------------------|
| 234 |  <p>4-[(2-{4-[(2-Cyano-ethyl)-methyl-carbamoyl]-3-fluoro-phenyl}-pyrimidine-5-carbonyl)-cyclopropyl-amino]-piperidine-1-carboxylic acid tert-butyl ester</p>       | 551<br>[M + H] <sup>+</sup> | 0.49 (18)                       |
| 235 |  <p>4-[Cyclopropyl-(2-{4-[2-(2-methoxymethyl-pyrrolidin-1-yl)-2-oxo-ethyl]-phenyl}-pyrimidine-5-carbonyl)-amino]-piperidine-1-carboxylic acid tert-butyl ester</p> | 578<br>[M + H] <sup>+</sup> | 0.51 (18)                       |
| 236 |  <p>4-[Cyclopropyl-(2-{4-[(methyl-pyridin-3-ylmethyl)-carbamoyl]-methyl]-phenyl}-pyrimidine-5-carbonyl)-amino]-piperidine-1-carboxylic acid tert-butyl ester</p> | 585<br>[M + H] <sup>+</sup> | 0.48 (18)                       |
| 237 |  <p>4-[Cyclopropyl-(2-{4-[(tetrahydro-furan-3-ylmethyl)-carbamoyl]-phenyl}-pyrimidine-5-carbonyl)-amino]-piperidine-1-carboxylic acid tert-butyl ester</p>       | 550<br>[M + H] <sup>+</sup> | 0.48 (18)                       |
| 238 |  <p>4-(Cyclopropyl-{2-[4-(2,4-dimethoxy-phenyl)-carbamoyl]-phenyl}-pyrimidine-5-carbonyl)-amino)-piperidine-1-carboxylic acid tert-butyl ester</p>               | 602<br>[M + H] <sup>+</sup> | 0.56 (18)                       |

TABLE 8-continued

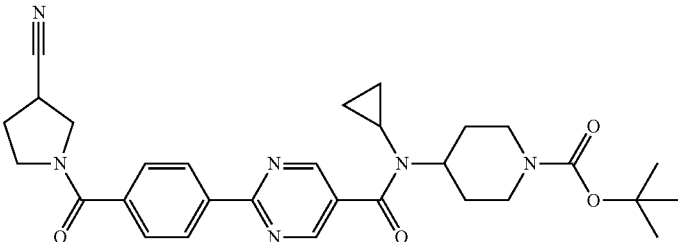
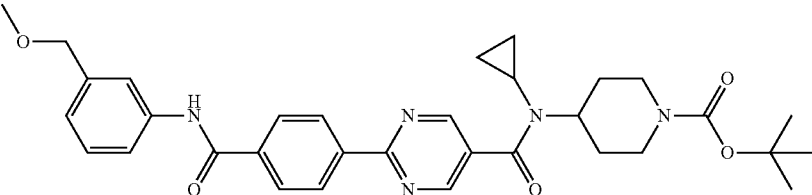
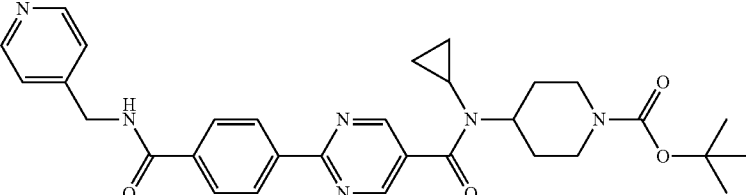
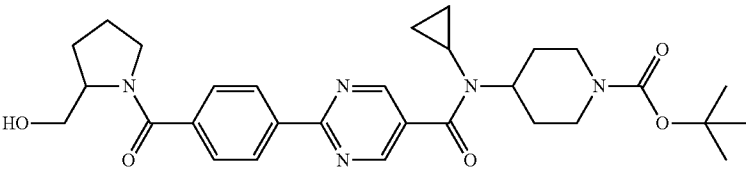
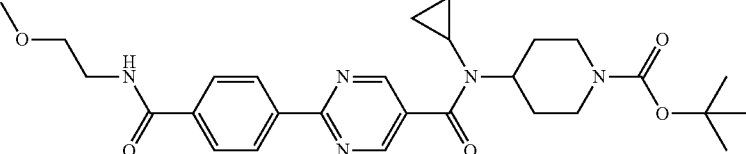
| Ex. | Structure  | ESI-MS<br>[m/z]             | HPLC $t_R$<br>[min]<br>(method) |
|-----|--|-----------------------------|---------------------------------|
| 239 |    | 545<br>[M + H] <sup>+</sup> | 0.48 (18)                       |
| 240 |    | 586<br>[M + H] <sup>+</sup> | 0.55 (18)                       |
| 241 |  | 557<br>[M + H] <sup>+</sup> | 0.5 (18)                        |
| 242 |  | 550<br>[M + H] <sup>+</sup> | 0.51 (18)                       |
| 243 |  | 524<br>[M + H] <sup>+</sup> | 0.51 (18)                       |

TABLE 8-continued

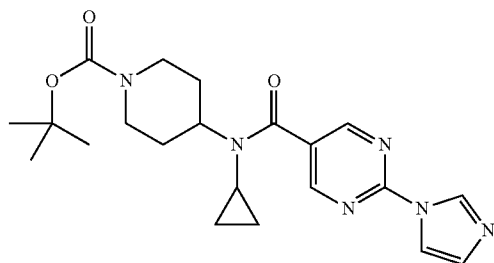
| Ex. | Structure   | ESI-MS<br>[m/z]             | HPLC $t_R$<br>[min]<br>(method) |
|-----|---|-----------------------------|---------------------------------|
| 244 | <p>4-[Cyclopropyl-(2-{4-[(tetrahydro-furan-2-ylmethyl)-carbamoyl]-phenyl}-pyrimidine-5-carbonyl)-amino]-piperidine-1-carboxylic acid tert-butyl ester</p> | 550<br>[M + H] <sup>+</sup> | 0.53 (18)                       |
| 245 | <p>4-[(2-{4-(2-Cyano-pyrrolidine-1-carbonyl)-phenyl}-pyrimidine-5-carbonyl)-cyclopropyl-amino]-piperidine-1-carboxylic acid tert-butyl ester</p>          | 545<br>[M + H] <sup>+</sup> | 0.52 (18)                       |
| 246 | <p>4-[Cyclopropyl-(2-{4-[(5-methyl-thiazol-2-ylmethyl)-carbamoyl]-phenyl}-pyrimidine-5-carbonyl)-amino]-piperidine-1-carboxylic acid tert-butyl ester</p> | 577<br>[M + H] <sup>+</sup> | 0.52 (18)                       |

## Example 247

4-[Cyclopropyl-(2-imidazol-1-yl-pyrimidine-5-carbonyl)-amino]-piperidine-1-carboxylic acid tert-butyl ester

[0602]

ester (3.0 g), imidazole (0.52 g) and ethyldiisopropylamine (2.0 mL) in N-methyl-2-pyrrolidinone (10 mL) is stirred for 12 h at 100° C. After cooling, water is added, the precipitate is filtered off and washed with water to yield the desired product. LC (19):  $t_R$ =1.29 min; Mass spectrum (ESI<sup>+</sup>): m/z=413 [M+H]<sup>+</sup>.



[0603] A mixture of 4-[(2-chloro-pyrimidine-5-carbonyl)-cyclopropyl-amino]-piperidine-1-carboxylic acid tert-butyl

## Examples 248-257

General Procedure for the Synthesis of the Amides in Table 9 from their Respective Amines and Carboxylic Acids

[0604] Amines (~5 mg) and carboxylic acids (~6-10 mg) are combined with triethylamine (0.015 mL) and N-hydroxy-benzotriazole (3 mg) in N,N-dimethylformamide (0.2 mL) and 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (20 mg) is added in N,N-dimethylformamide (0.2 mL) and stirred at room temperature for 18 h. The product amides are purified by preparative HPLC.

TABLE 9

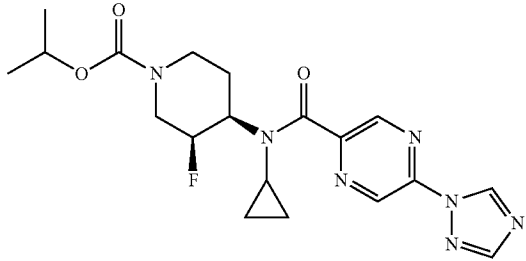
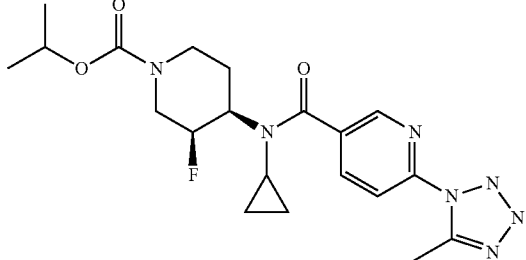
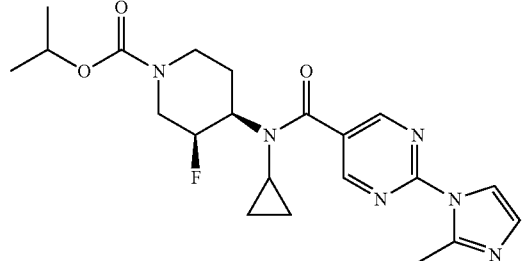
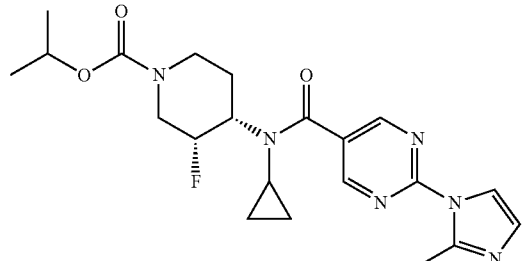
| Ex. | Structure  | MS (APCI)<br>m/z<br>[M + H] <sup>+</sup> | HPLC t <sub>R</sub><br>(method 22)<br>[min] |
|-----|--|--|---|
| 248 |  <p>(3S,4R)-4-[(Cyclopropyl-(5-[1,2,4]triazol-1-yl)-pyrazine-2-carbonyl)-amino]-3-fluoro-piperidine-1-carboxylic acid isopropyl ester (absolute stereochemistry arbitrarily assigned)</p>         | 418                                      | 2.70  |
| 249 |  <p>(3S,4R)-4-[(Cyclopropyl-[6-(5-methyl-tetrazol-1-yl)-pyridine-3-carbonyl]-amino]-3-fluoro-piperidine-1-carboxylic acid isopropyl ester (absolute stereochemistry arbitrarily assigned)</p>    | 432                                      | 2.98  |
| 250 |  <p>(3S,4R)-4-[(Cyclopropyl-[2-(2-methyl-imidazol-1-yl)-pyrimidine-5-carbonyl]-amino]-3-fluoro-piperidine-1-carboxylic acid isopropyl ester (absolute stereochemistry arbitrarily assigned)</p> | 431                                      | 3.77  |
| 251 |  <p>(3R,4S)-4-[(Cyclopropyl-[2-(2-methyl-imidazol-1-yl)-pyrimidine-5-carbonyl]-amino]-3-fluoro-piperidine-1-carboxylic acid isopropyl ester (absolute stereochemistry arbitrarily assigned)</p> | 431                                      | 3.62  |

TABLE 9-continued

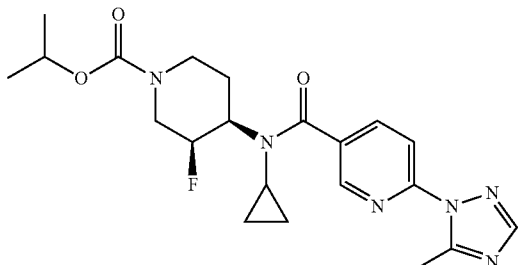
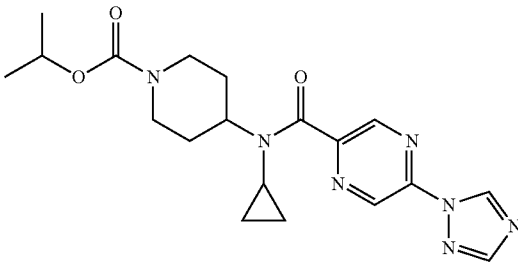
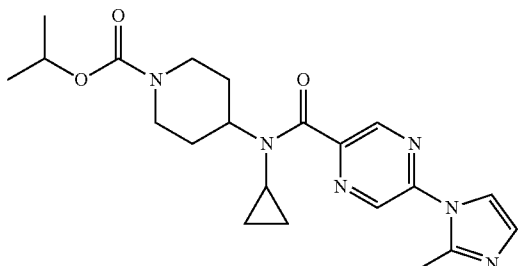
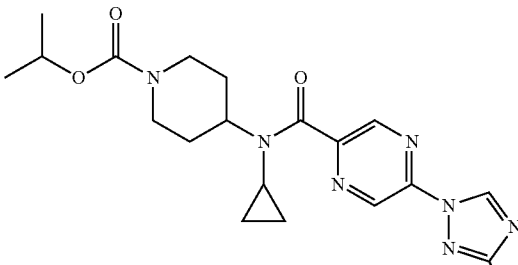
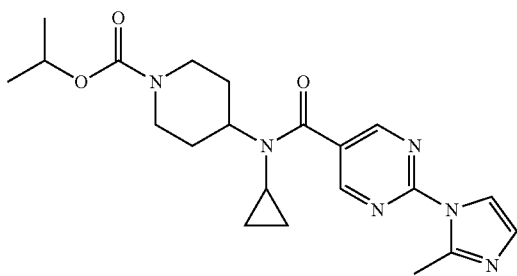
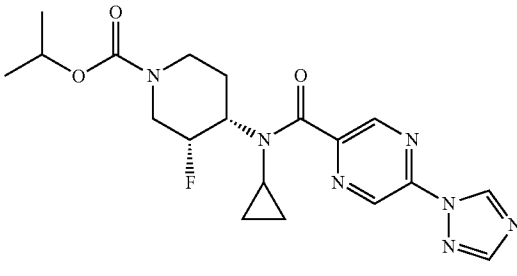
| Ex. | Structure  | MS (APCI)<br>m/z<br>[M + H] <sup>+</sup> | HPLC t <sub>R</sub><br>(method 22)<br>[min] |
|-----|--|--|---|
| 252 |  <p>(3S,4R)-4-((Cyclopropyl-[6-(5-methyl-[1,2,4]triazol-1-yl)-pyridine-3-carbonyl]-amino)-3-fluoro-piperidine-1-carboxylic acid isopropyl ester (absolute stereochemistry arbitrarily assigned)</p> | 431                                      | 3.70  |
| 253 |  <p>4-((Cyclopropyl-(5-[1,2,4]triazol-1-yl-pyrazine-2-carbonyl)-amino)-piperidine-1-carboxylic acid isopropyl ester</p>  | 400                                      | 4.65  |
| 254 |  <p>4-((Cyclopropyl-[5-(2-methyl-imidazol-1-yl)-pyrazine-2-carbonyl]-amino)-piperidine-1-carboxylic acid isopropyl ester</p>  | 413                                      | 4.17  |
| 255 |  <p>4-((Cyclopropyl-[5-(3-methyl-[1,2,4]triazol-1-yl)-pyrazine-2-carbonyl]-amino)-piperidine-1-carboxylic acid isopropyl ester</p>  | 414                                      | 4.28  |

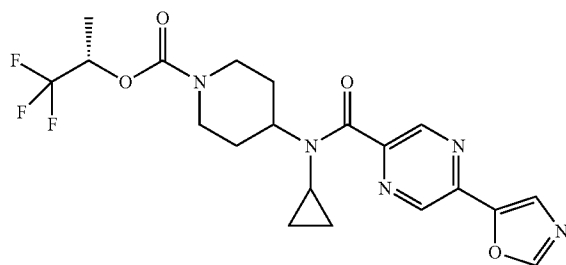
TABLE 9-continued

| Ex. | Structure  | MS (APCI)<br>m/z<br>[M + H] <sup>+</sup> | HPLC t <sub>R</sub><br>(method 22)<br>[min] |
|-----|--|--|---|
| 256 |   | 413                                      | 3.97  |
| 257 |  | 418                                      | 3.56  |

## Example 258

4-[Cyclopropyl-(5-oxazol-5-yl-pyrazine-2-carbonyl)-amino]-piperidine-1-carboxylic acid (S)-2,2,2-trifluoro-1-methyl-ethyl ester

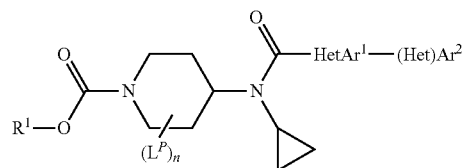
[0605]



[0606] Carbonic acid 4-nitro-phenyl ester (S)-2,2,2-trifluoro-1-methyl-ethyl ester (83 mg) is added to a solution of 5-oxazol-5-yl-pyrazine-2-carboxylic acid cyclopropyl-piperidin-4-yl-amide trifluoroacetic acid salt (obtained from Example 12 upon treatment with trifluoroacetic acid in dichloromethane and concentration of the reaction mixture; 110 mg) and N,N-diisopropyl-ethylamine (110  $\mu$ L) in tetrahydrofuran (2 mL) at room temperature. The solution is stirred at room temperature overnight. Ethyl acetate is added, and the solution is washed with 1 M aqueous NaOH solution, water, and brine. The organic solution is dried (MgSO<sub>4</sub>) and

concentrated. The residue is chromatographed on silica gel (cyclohexane/ethyl acetate 1:1 $\rightarrow$ 0:1) to give the title compound. LC (method 23): t<sub>R</sub>=0.98 min; Mass spectrum (ESI<sup>+</sup>): m/z=454 [M+H]<sup>+</sup>.

1. A compound of formula I



wherein:

R<sup>1</sup> is a linear or branched C<sub>1-6</sub>-alkyl or C<sub>3-7</sub>-cycloalkyl, each optionally substituted with one or more F and optionally substituted with 1 or 2 groups independently selected from H<sub>3</sub>C—, FH<sub>2</sub>C—, F<sub>2</sub>HC—, and F<sub>3</sub>C—;

L<sup>p</sup> is F or C<sub>1-3</sub>-alkyl, wherein the alkyl group is optionally substituted with one or more F atoms;

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

HetAr<sup>1</sup> is a 5- or 6-membered heteroaromatic ring containing 1, 2, or 3 heteroatoms independently selected from N, NR<sup>N</sup>, O, and S, wherein each heteroaromatic ring is optionally substituted with 1 or more substituents L<sup>Q</sup>;

L<sup>Q</sup> is 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—, or C<sub>3-7</sub>-cycloalkyl-O—; and

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

(Het)Ar<sup>2</sup> is:

- a) phenyl, tetrazolyl, pyridinonyl, or a 5- or 6-membered heteroaromatic ring containing 1, 2, or 3 heteroatoms independently selected from N,  $NR^N$ , O, and S, wherein each phenyl, pyridinonyl, and heteroaromatic ring thereof is optionally substituted with one or more substituents independently selected from  $L^{Ar}$  and each phenyl, tetrazolyl, pyridinonyl, and heteroaromatic ring thereof is optionally substituted with one group T, or
- b) 1,2,3,6-tetrahydropyridin-4-yl substituted at the N atom with a  $-S(=O)_2-C_{1-6}$ -alkyl or  $-S(=O)_2-C_{3-6}$ -cycloalkyl group, wherein the alkyl and cycloalkyl substituents of the sulfonyl groups are optionally substituted with one or more substituents independently selected from F, Cl, CN, OH, and  $C_{1-3}$ -alkyl-O-;

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

T is F, Cl, Br, I, CN, OH,  $NO_2$ ,  $C_{3-6}$ -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- $S(=O)_2-$ ,  $C_{1-4}$ -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, or heteroaryl-O-;

wherein: each alkyl, alkenyl, alkynyl and cycloalkyl group is optionally substituted with one or more substituents independently selected from F, Cl, CN, OH,  $C_{1-3}$ -alkyl,  $C_{3-6}$ -cycloalkyl,  $R^{NT1}R^{NT2}N-$ ,  $R^{NT1}R^{NT2}N-C(=O)-$ ,  $C_{1-4}$ -alkyl- $S(=O)_2-$ ,  $C_{1-4}$ -alkyl- $S(=O)_2-$ ,  $R^{NT1}R^{NT2}N-S(=O)_2-$ , aryl, heteroaryl, and heterocyclyl,

aryl is phenyl or naphthyl,

heteroaryl is a 5- or 6-membered aromatic ring containing 1, 2, 3, or 4 heteroatoms independently selected from N,  $NR^N$ , O, and S,

heterocyclyl is a 4- to 7-membered unsaturated or saturated carbocyclic ring in which 1, 2, or 3  $-CH_2-$  groups are 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

each aryl, heteroaryl, and heterocyclyl group is optionally substituted with one or more substituents independently selected from  $L^{Ar}$ ; and

$R^{NT1}$  is H,  $C_{1-6}$ -alkyl,  $C_{3-6}$ -cycloalkyl,  $C_{1-6}$ -alkyl- $C(=O)-$ ,  $C_{1-6}$ -alkyl- $S(=O)_2-$ , heterocyclyl, aryl, or heteroaryl,

wherein: each alkyl and cycloalkyl group is optionally substituted with 1 or more substituents independently selected from F,  $C_{1-4}$ -alkyl,  $NC-$ ,  $(H_3C)_2N-C(=O)-$ ,  $HO-$ ,  $C_{1-4}$ -alkyl-O-, cyclopropyl- $H_2C-O-$ ,  $F_3C-O-$ ,  $(R^N)_2N-$ ,  $C_{1-4}$ -alkyl- $S(=O)_2-$ , and  $C_{3-6}$ -cycloalkyl optionally substituted with 1 or 2

groups independently selected from F,  $H_3C-$ ,  $HO-$  and  $H_3CO-$ , heterocyclyl, phenyl, and heteroaryl, heterocyclyl is a  $C_{4-7}$ -cycloalkyl ring in which 1 or 2  $-CH_2-$  groups are independently replaced by  $NR^N$ , O,  $C(=O)-$ , S,  $S(=O)-$  or  $S(=O)_2-$ ,

heterocyclyl is optionally substituted with one or more substituents independently selected from F,  $C_{1-4}$ -alkyl,  $(R^N)_2N-$ ,  $HO-$ , and  $C_{1-4}$ -alkyl-O,

aryl is phenyl or naphthyl,

heteroaryl is a 5- or 6-membered aromatic ring which contains 1, 2, or 3 heteroatoms independently selected from N,  $NR^N$ , O, and S; and

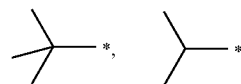
aryl, phenyl, and heteroaryl are optionally substituted with one or more substituents  $L^{Ar}$ ; and

$R^{NT2}$  is H or  $C_{1-6}$ -alkyl; or

$R^{NT1}$  and  $R^{NT2}$  are linked to form one group selected from a group consisting of a  $C_{3-6}$ -alkylene group, wherein 1 or 2  $-CH_2-$  groups are independently replaced by  $NR^N$ , O,  $C(=O)-$ , S,  $S(=O)-$ , or  $S(=O)_2-$ , and which is optionally substituted with 1 or more substituents independently selected from F,  $C_{1-4}$ -alkyl,  $HO-(C_{1-3}$ -alkyl-,  $H_3C-O-(C_{1-3}$ -alkyl)-,  $F_3C-$ ,  $NC-$ ,  $(R^N)_2N-$ ,  $HO-$ ,  $C_{1-4}$ -alkyl-O-, and 3-methyl-[1,2,4]oxadiazol-5-yl,

or a salt thereof.

2. The compound according to claim 1, wherein  $R^1$  is

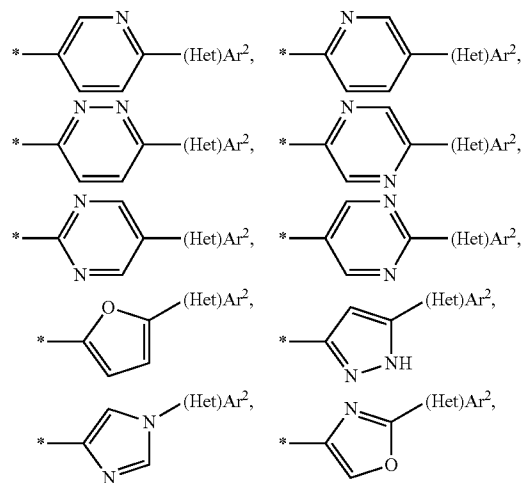


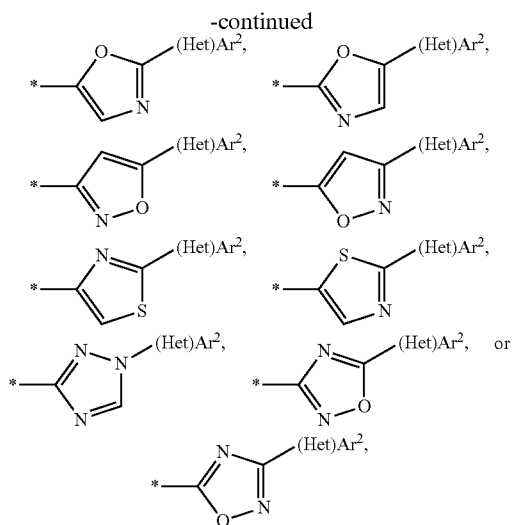
or



each optionally substituted with 1 to 3 F atoms.

3. The compound according to claim 1, wherein HetAr<sup>1</sup> is:

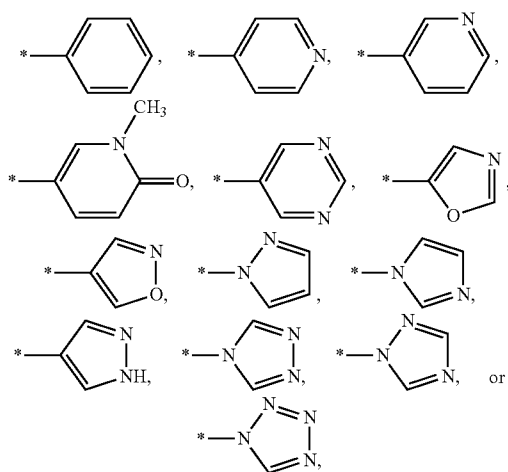




wherein each group is optionally additionally substituted with one  $\text{H}_3\text{C}$ — group, and (Het)Ar<sup>2</sup>-group shows the position of the HetAr<sup>2</sup>-moiety within the compound of formula I.

4. The compound according to claim 1, wherein (Het)Ar<sup>2</sup> is phenyl, tetrazolyl, pyridinonyl, or a heteroaromatic ring selected from pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, isoxazolyl, oxazolyl, oxadiazolyl, imidazolyl, pyrazolyl, triazolyl, thienyl, or thiazolyl, and each phenyl and heteroaromatic ring is optionally substituted with one or more substituents independently selected from  $\text{L}^{\text{Ar}}$ , each phenyl, tetrazolyl, and heteroaromatic ring is optionally substituted with one group T, and in the heteroaromatic ring, the H-atom in one NH group is optionally replaced by  $\text{R}^{\text{N}}$ .

5. The compound according to claim 1, wherein (Het)Ar<sup>2</sup> is:

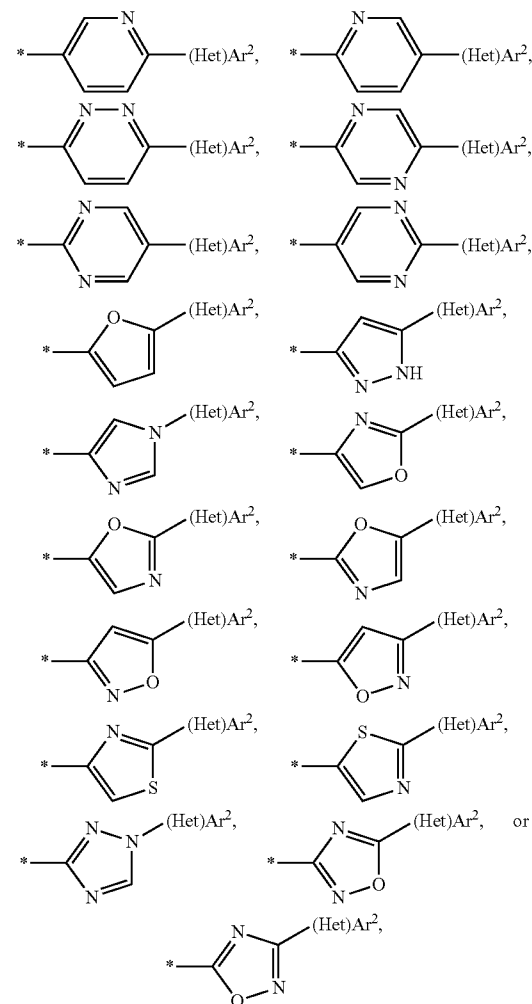


and each group is optionally substituted with one group T and 1 or 2 substituents independently selected from  $\text{L}^{\text{Ar}}$ .

6. The compound according to claim 1, wherein n is 1 and  $\text{L}^{\text{P}}$  is  $\text{H}_3\text{C}$ — or F.

7. The compound according to claim 1, wherein n is 0 or 1 and  $\text{L}^{\text{P}}$  is F.

8. The compound according to claim 2, wherein HetAr<sup>1</sup> is:



wherein each group is optionally additionally substituted with one  $\text{H}_3\text{C}$ — group, and the (Het)Ar<sup>2</sup>-group shows the position of the HetAr<sup>2</sup>-moiety within the compound of formula I;

(Het)Ar<sup>2</sup> is phenyl, tetrazolyl, pyridinonyl, or a heteroaromatic ring selected from pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, isoxazolyl, oxazolyl, oxadiazolyl, imidazolyl, pyrazolyl, triazolyl, thienyl, or thiazolyl, wherein the phenyl and heteroaromatic ring are optionally substituted with one or more substituents independently selected from  $\text{L}^{\text{Ar}}$  and the phenyl, tetrazolyl, and heteroaromatic ring are optionally substituted with one group T, and in the heteroaromatic ring, the H-atom in one NH group is optionally replaced by  $\text{R}^{\text{N}}$ ;

$\text{R}^{\text{N}}$  is H,  $\text{H}_3\text{C}$ —,  $\text{H}_3\text{C}$ — $\text{C}(=\text{O})$ —, or  $\text{H}_3\text{C}$ — $\text{S}(=\text{O})_2$ —;

T is F, Br,  $-\text{CH}_3$ ,  $-\text{CH}_2\text{CH}_3$ ,  $-\text{CH}_2\text{CN}$ ,  $-\text{CH}_2\text{C}(=\text{O})\text{NR}^{\text{NT1}}\text{R}^{\text{NT2}}$ ,  $-\text{CH}_2\text{NHC}(=\text{O})\text{CH}_3$ ,  $-\text{CH}_2\text{OH}$ ,  $-\text{CH}_2\text{CH}_2\text{OH}$ ,  $-\text{CN}$ ,  $-\text{C}(=\text{O})\text{NR}^{\text{NT1}}\text{R}^{\text{NT2}}$ ,  $-\text{CO}_2\text{CH}_3$ ,  $-\text{NO}_2$ ,  $-\text{N}(\text{CH}_3)_2$ , morpholin-4-yl,  $-\text{NH}-\text{S}(=\text{O})_2-\text{CH}_3$ ,  $-\text{O}-\text{CH}_3$ ,



—O—CH<sub>2</sub>CH<sub>3</sub>, —O—CF<sub>3</sub>, —S(=O)<sub>2</sub>—CH<sub>3</sub>,  
—S(=O)<sub>2</sub>—NH<sub>2</sub>—, or —S(=O)<sub>2</sub>—NHCH<sub>3</sub>;

R<sup>NT1</sup> is H, C<sub>1-5</sub>-alkyl, C<sub>3-6</sub>-cycloalkyl, heterocyclyl, phenyl, or heteroaryl,

wherein each alkyl and cycloalkyl group is optionally substituted with 1 or 2 substituents independently selected from F, NC—, HO—, C<sub>1-3</sub>-alkyl-O—, F<sub>3</sub>C—O—, H<sub>3</sub>C—S(=O)<sub>2</sub>—, heterocyclyl, and heteroaryl,

phenyl is optionally substituted with 1 or 2 groups independently selected from F, H<sub>3</sub>C—, HO—(C<sub>1-2</sub>-alkyl)—, H<sub>3</sub>C—O—CH<sub>2</sub>—, HO—, and H<sub>3</sub>C—O—,

each heteroaryl is pyrazolyl, oxazolyl, thiazolyl, pyridyl, or pyridazinyl, optionally substituted with 1 or 2 substituents independently selected from H<sub>3</sub>C—, H<sub>3</sub>C—O—CH<sub>2</sub>—, cyclopropyl, HO—, and H<sub>3</sub>C—O—,

each heterocyclyl is oxetanyl, tetrahydrofuranyl, or tetrahydropyranyl, optionally substituted with one H<sub>3</sub>C— group, and

R<sup>NT1</sup>-G3 comprises the residues (H<sub>3</sub>C)<sub>2</sub>N—C(=O)—CH<sub>2</sub>—, cyclopropyl-CH<sub>2</sub>—O—CH<sub>2</sub>CH<sub>2</sub>—, 2-hydroxycyclohexyl-CH<sub>2</sub>—, and tetrahydropyranyl;

R<sup>NT2</sup> is H or —CH<sub>3</sub>; or

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 consisting of: azetidiny, pyrrolidiny, piperidiny, morpholiny, or 1,4-oxazepany, each optionally substituted with 1 or 2 substituents independently of each other selected from F, F<sub>3</sub>C—, HO—CH<sub>2</sub>—, H<sub>3</sub>CO—CH<sub>2</sub>—, NC—, HO—, CH<sub>3</sub>—O—, and 3-methyl-[1,2,4]oxadiazol-5-yl;

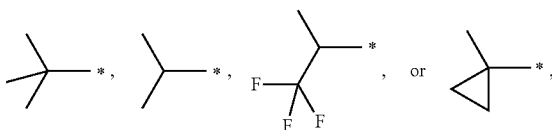
L<sup>Ar</sup> is F or H<sub>3</sub>C—;

L<sup>P</sup> is H<sub>3</sub>C— or F; and

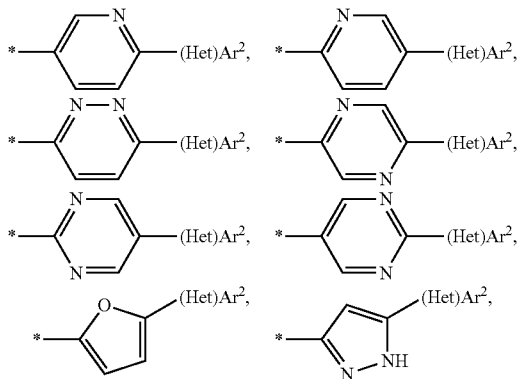
n is 0 or 1.

9. The compound according to claim 1, wherein:

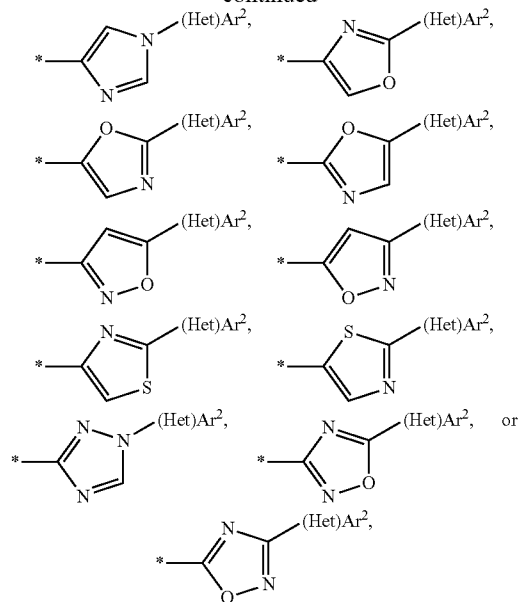
R<sup>1</sup> is



HetAr<sup>1</sup> is:

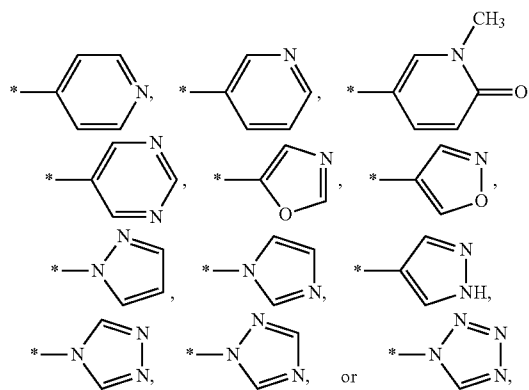


-continued



wherein each group is optionally additionally substituted with one H<sub>3</sub>C— group, and the (Het)Ar<sup>2</sup>-group shows the position of the HetAr<sup>2</sup>-moiety within the compound of formula I;

(Het)Ar<sup>2</sup> is:



wherein each group is optionally substituted with one group C<sub>1-3</sub>-alkyl, HO—(C<sub>1-3</sub>-alkyl)—, CN, (H<sub>3</sub>C)<sub>2</sub>N—, or C<sub>1-3</sub>-alkyl-O— and is optionally additionally substituted with one H<sub>3</sub>C— group;

L<sup>P</sup> is F; and

n is 0 or 1.

10. A pharmaceutically acceptable salt of the compound according to claim 1.

11. A pharmaceutical composition comprising a compound according to claim 1 or a pharmaceutically acceptable salt thereof, and an inert carrier or diluent.

12. A method for treating diseases or conditions which are mediated by activating the G-protein-coupled receptor GPR119, comprising administering to a patient in need thereof the compound according to claim 1 or a pharmaceutically acceptable salt thereof.

**13.** A method according to claim **12**, wherein the diseases or conditions mediated by activating the G-protein-coupled receptor GPR119 is diabetes, dislipidemia, or obesity.

**14.-15.** (canceled)

**16.** A pharmaceutical composition comprising a compound according claim **1** or a pharmaceutically acceptable salt thereof, an additional therapeutic agents, and an inert carrier or diluents.

**17.** (canceled)

\* \* \* \* \*