(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
02 August 2018 (02.08.2018)

WIPO | PCT

(10) International Publication Number
WO 2018/138030 A1

(51) International Patent Classification:
C07D 403/12 (2006.01) *A61P 9/04* (2006.01)
C07D 401/12 (2006.01) *A61P 9/12* (2006.01)
C07D 405/12 (2006.01) *A61P 3/10* (2006.01)
C07D 413/12 (2006.01) *A61K 31/4965* (2006.01)
C07D 241/18 (2006.01) *A61K 31/497* (2006.01)
A61P 3/04 (2006.01)

(21) International Application Number:
PCT/EP2018/051390

(22) International Filing Date:
22 January 2018 (22.01.2018)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
17153390.4 26 January 2017 (26.01.2017) EP

(71) Applicant: **BOEHRINGER INGELHEIM INTERNATIONAL GMBH** [DE/DE]; Binger Strasse 173, 55216 INGELHEIM AM RHEIN (DE).

(72) Inventors: **ECKHARDT, Matthias**; Boehringer Ingelheim GmbH, Corporate Patents Binger Strasse 173, 55216 INGELHEIM AM RHEIN (DE). **WAGNER, Holger**; Boehringer Ingelheim GmbH, Corporate Patents Binger Strasse 173, 55216 INGELHEIM AM RHEIN (DE).

(74) Agent: **GALLER-SUWA, Eva** et al.; Binger Strasse 173, 55216 INGELHEIM AM RHEIN (DE).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

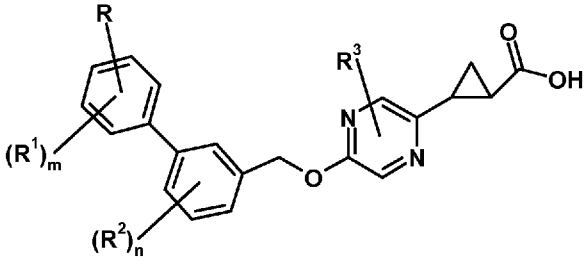
(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

Published:
— *with international search report (Art. 21(3))*

WO 2018/138030 A1

(54) Title: BENZYLOXYPYRAZINYLCYCLOPROPANECARBOXYLIC ACIDS, PHARMACEUTICAL COMPOSITIONS AND USES THEREOF



I

(57) Abstract: The present invention relates to compounds of general formula (I), wherein the groups R, R^1, R^2, R^3, m and n are defined as in claim 1, which have valuable pharmacological properties, in particular bind to the GPR40 receptor and modulate its activity. The compounds are suitable for treatment and prevention of diseases which can be influenced by this receptor, such as metabolic diseases, in particular diabetes type 2.

Benzyloxypyrazinylcyclopropanecarboxylic acids, pharmaceutical compositions and uses thereof

Field of the invention

The present invention relates to novel benzyloxypyrazinylcyclopropanecarboxylic acids, that are agonists of the G-protein coupled receptor 40 (GPR40, also known as free fatty acid receptor FFAR 1), to processes for their preparation, to pharmaceutical compositions containing these compounds and to their medical use for the prophylaxis and/or treatment of diseases which can be influenced by the modulation of the function of GPR40. Particularly, the pharmaceutical compositions of the invention are suitable for the prophylaxis and/or therapy of metabolic diseases, such as diabetes, more specifically type 2 diabetes mellitus, and conditions associated with the disease, including insulin resistance, obesity, cardiovascular disease and dyslipidemia.

Background of the Invention

Metabolic diseases are diseases caused by an abnormal metabolic process and may either be congenital due to an inherited enzyme abnormality or acquired due to a disease of an endocrine organ or failure of a metabolically important organ such as the liver or the pancreas.

Diabetes mellitus is a disease state or process derived from multiple causative factors and is defined as a chronic hyperglycemia associated with resulting damages to organs and dysfunctions of metabolic processes. Depending on its etiology, one differentiates between several forms of diabetes, which are either due to an absolute (lacking or decreased insulin secretion) or to a relative lack of insulin. Diabetes mellitus Type I (IDDM, insulin-dependent diabetes mellitus) generally occurs in adolescents under 20 years of age. It is assumed to be of auto-immune etiology, leading to an insulitis with the subsequent destruction of the beta cells of the islets of Langerhans which are responsible for the insulin synthesis. In addition, in latent autoimmune diabetes in adults (LADA; Diabetes Care. 8: 1460-1467, 2001) beta cells are being destroyed due to autoimmune attack. The amount of insulin produced by the remaining pancreatic islet cells is too low, resulting in elevated blood glucose levels (hyperglycemia). Diabetes mellitus Type II generally occurs at an older age. It

is above all associated with a resistance to insulin in the liver and the skeletal muscles, but also with a defect of the islets of Langerhans. High blood glucose levels (and also high blood lipid levels) in turn lead to an impairment of beta cell function and to an increase in beta cell apoptosis.

Persistent or inadequately controlled hyperglycemia is associated with a wide range of pathologies. Diabetes is a very disabling disease, because today's common anti-diabetic drugs do not control blood sugar levels well enough to completely prevent the occurrence of high and low blood sugar levels. Out of range blood sugar levels are toxic and cause long-term complications for example retinopathy, renopathy, neuropathy and peripheral vascular disease. There is also a host of related conditions, such as obesity, hypertension, stroke, heart disease and hyperlipidemia, for which persons with diabetes are substantially at risk.

Obesity is associated with an increased risk of follow-up diseases such as cardiovascular diseases, hypertension, diabetes, hyperlipidemia and an increased mortality. Diabetes (insulin resistance) and obesity are part of the "metabolic syndrome" which is defined as the linkage between several diseases (also referred to as syndrome X, insulin-resistance syndrome, or deadly quartet). These often occur in the same patients and are major risk factors for development of diabetes type II and cardiovascular disease. It has been suggested that the control of lipid levels and glucose levels is required to treat diabetes type II, heart disease, and other occurrences of metabolic syndrome (see e.g., Diabetes 48: 1836-1841, 1999; JAMA 288: 2209-2716, 2002).

The free fatty acid receptor GPR40 (also referred to as either FFAR, FFAR1, or FFA1) is a cell-surface receptor and a member of the gene superfamily of G-protein coupled receptors, which was first identified as a so-called orphan receptor, i.e. a receptor without a known ligand, based on the predicted presence of seven putative transmembrane regions in the corresponding protein (Sawzdargo et al. (1997) Biochem. Biophys. Res. Commun. 239: 543-547). GPR40 is found to be highly expressed in several particular cell types: the pancreatic β cells and insulin-secreting cell lines, as well as in enteroendocrine cells, taste cells, and is reported to be expressed in immune cells, splenocytes, and in the human and monkey brain.

Meanwhile, fatty acids of varying chain lengths are thought to represent the endogenous ligands for GPR40, activation of which is linked primarily to the modulation of the Gq family of intra-cellular signaling G proteins and concomitant induction of elevated calcium levels, although activation of Gs- and Gi-proteins to modulate intracellular levels of cAMP have also been reported. GPR40 is activated especially by long-chain FFA, particularly oleate, as well as the PPAR-gamma agonist rosiglitazone.

It has been recognized that the fatty acids that serve as activators for GPR40 augment the elevated plasma glucose-induced secretion of insulin through GPR40 receptors that are expressed in the insulin secreting cells (Itoh et al. (2003) Nature 422: 173-176; Briscoe et al. (2003) J. Biol. Chem. 278: 11303-11311; Kotarsky et al. (2003) Biochem. Biophys. Res. Commun. 301: 406-410). Despite initial controversy, the use of GPR40 agonist appears to be the appropriate for increasing insulin release for the treatment of diabetes (see e.g. Diabetes 2008, 57, 2211; J. Med. Chem. 2007, 50, 2807). Typically, long term diabetes therapy leads to the gradual diminution of islet activity, so that after extended periods of treatment Type 2 diabetic patients need treatment with daily insulin injections instead. GPR40 agonists may have the potential to restore or preserve islet function, therefore, GPR40 agonists may be beneficial also in that that they may delay or prevent the diminution and loss of islet function in a Type 2 diabetic patient.

It is well established that the incretins GLP-1 (glucagon-like peptide- 1) and GIP (glucose-dependent insulinotropic peptide; also known as gastric inhibitory peptide) stimulate insulin secretion and are rapidly inactivated in vivo by DPP-4. These peptidyl hormones are secreted by endocrine cells that are located in the epithelium of the small intestine. When these endocrine cells sense an increase in the concentration of glucose in the lumen of the digestive tract, they act as the trigger for incretin release. Incretins are carried through the circulation to beta cells in the pancreas and cause the beta cells to secrete more insulin in anticipation of an increase of blood glucose resulting from the digesting meal. Further studies indicating that the GPR40 modulatory role on the release of incretins from the enteroendocrine cells, including CCK, GLP-1, GIP, PYY, and possibly others, suggest that GPR40 modulators may contribute to enhanced insulin release from the

pancreatic beta cells also indirectly by e.g. a synergistic effect of GLP-1 and possibly GIP on the insulin release, and the other release incretins may also contribute to an overall beneficial contribution of GPR40 modulation on metabolic diseases. The indirect contributions of GPR40 modulation on insulin release through the elevation of plasma levels of incretins may be further augmented by the coadministration of inhibitors of the enzymes responsible for the incretin degradation, such as inhibitors of DPP-4.

Insulin imbalances lead to conditions such as type II diabetes mellitus, a serious metabolic disease. The modulation of the function of GPR40 in modulating insulin secretion indicates the therapeutic agents capable of modulating GPR40 function could be useful for the treatment of disorders such as diabetes and conditions associated with the disease, including insulin resistance, obesity, cardiovascular disease and dyslipidemia.

Object of the present invention

The object of the present invention is to provide new compounds, hereinafter described as compounds of formula **I**, in particular new benzyloxypyrazinyl-cyclopropanecarboxylic acids, which are active with regard to the G-protein-coupled receptor GPR40, notably are agonists of the G-protein-coupled receptor GPR40.

A further object of the present invention is to provide new compounds, in particular new benzyloxypyrazinylcyclopropanecarboxylic acids, which have an activating effect on the G-protein-coupled receptor GPR40 *in vitro* and/or *in vivo* and possess suitable pharmacological and pharmacokinetic properties to use them as medicaments.

A further object of the present invention is to provide effective GPR40 agonists, in particular for the treatment of metabolic disorders, for example diabetes, dyslipidemia and/or obesity.

A further object of the present invention is to provide methods for treating a disease or condition mediated by the activation the G-protein-coupled receptor GPR40 in a patient.

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

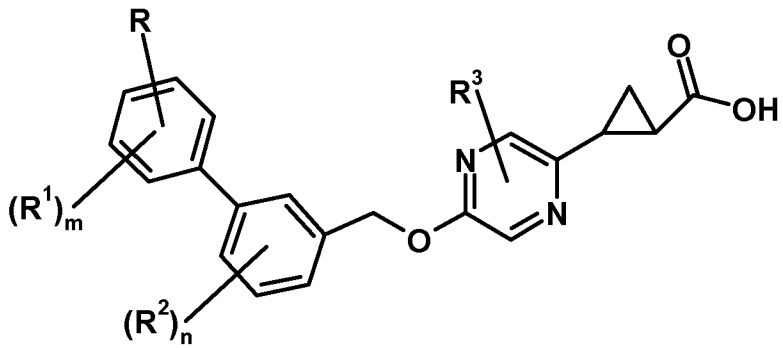
A further object of the present invention is to provide a combination of at least one compound according to the invention with one or more additional therapeutic agents.

Further objects 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.

GPR40 modulators are known in the art, for example, the compounds disclosed in WO 2004/041266 (EP 1 559 422), WO 2007/033002, WO 2009/157418, and WO 2013/178575. The benzyloxypyrazinylcyclopropanecarboxylic acids of the present invention may provide several advantages, such as enhanced potency, high metabolic and/or chemical stability, high selectivity and tolerability, enhanced solubility, and the possibility to form stable salts.

Summary of the Invention

In a first aspect, the invention relates to a compound of formula



I,

wherein

R is selected from the group R-G1 consisting of

H, F, Cl, Br, I, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{3-6}-cycloalkyl, NC-, HNR^N-C(=O)-, C_{1-4}-alkyl-NR^N-C(=O)-, C_{3-6}-cycloalkyl-NR^N-C(=O)-, heterocyclyl-NR^N-C(=O)-, heteroaryl-NR^N-C(=O)-, HOOC-, C_{1-4}-alkyl-O-C(=O)-, O_2N-, HR^NN-, C_{1-4}-alkyl-R^NN-, C_{1-4}-alkyl-C(=O)NR^N-, C_{3-6}-cycloalkyl-C(=O)NR^N-, heterocyclyl-

$C(=O)NR^N$-, heteroaryl-$C(=O)NR^N$-, C_{1-4}-alkyl-$S(=O)_2NR^N$-, C_{3-6}-cycloalkyl-$S(=O)_2NR^N$-, heterocyclyl-$S(=O)_2NR^N$-, heteroaryl-$S(=O)_2NR^N$-, HO-, C_{1-6}-alkyl-O-, HOOC-C_{1-3}-alkyl-O-, C_{3-6}-cycloalkyl-C_{1-3}-alkyl-O-, heterocyclyl-C_{1-3}-alkyl-O-, phenyl-C_{1-3}-alkyl-O-, C_{3-6}-cycloalkyl-O-, heterocyclyl-O-, heteroaryl-O-, C_{1-4}-alkyl-S-, C_{3-6}-cycloalkyl-S-, heterocyclyl-S-, C_{1-4}-alkyl-S(=O)-, C_{3-6}-cycloalkyl-S(=O)-, heterocyclyl-S(=O)-, C_{1-4}-alkyl-$S(=O)_2$-, C_{3-6}-cycloalkyl-$S(=O)_2$-, heterocyclyl-$S(=O)_2$-, phenyl-$S(=O)_2$-, heteroaryl-$S(=O)_2$-, HNR^N-$S(=O)_2$-, C_{1-4}-alkyl-NR^N-$S(=O)_2$-, heterocyclyl, phenyl, and heteroaryl,

wherein each alkyl, cycloalkyl, and heterocyclyl group or sub-group within the groups forming R is optionally substituted with 1 or more F atoms and optionally substituted with 1 to 3 groups independently selected from Cl, C_{1-3}-alkyl, NC-, $(R^N)_2N$-, HO-, C_{1-3}-alkyl-O-, and C_{1-3}-alkyl-$S(=O)_2$-; and

wherein each phenyl and heteroaryl group or sub-group within the groups forming R is optionally substituted with 1 to 5 substituents independently selected from F, Cl, C_{1-3}-alkyl, HF_2C-, F_3C-, NC-, $(R^N)_2N$-, HO-, C_{1-3}-alkyl-O-, F_3C-O-, and C_{1-3}-alkyl-$S(=O)_2$-;

wherein each heterocyclyl group or sub-group within the groups forming R is selected from

a cyclobutyl group wherein 1 CH_2 group is replaced by $-NR^N$- or -O-;

a C_{5-6}-cycloalkyl group wherein 1 CH_2 group is replaced by -C(=O)-, $-NR^N$-, -O-, -S- or $-S(=O)_2$- and/or 1 CH group is replaced by N;

a C_{5-6}-cycloalkyl group wherein 1 CH_2 group is replaced by $-NR^N$- or -O-, a second CH_2 group is replaced by $-NR^N$-, -C(=O)- or $-S(=O)_2$- and/or 1 CH group is replaced by N; and

a C_{5-6}-cycloalkyl group wherein 2 CH_2 groups are replaced by $-NR^N$- or 1 CH_2 group by $-NR^N$- and the other by -O- and a third CH_2 group is replaced by -C(=O)- or $-S(=O)_2$- and/or 1 CH group is replaced by N;

wherein each heteroaryl group or sub-group within the groups forming R is selected from

tetrazolyl 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-, wherein in heteroaromatic groups containing a -HC=N- unit this group is optionally replaced by $-NR^N$-C(=O)-;

wherein in heteroaryl and heterocyclyl rings with one or more NH groups, each of said NH groups is replaced by NR^N;

R^1 is selected from the group R^1-G1 consisting of H, F, Cl, C_{1-4}-alkyl, C_{3-6}-cycloalkyl-, HO-C_{1-4}-alkyl, C_{1-4}-alkyl-O-C_{1-4}-alkyl, NC-, HO-, C_{1-4}-alkyl-O-, C_{3-6}-cycloalkyl-O-, C_{1-4}-alkyl-S-, C_{1-4}-alkyl-S(O)-, and C_{1-4}-alkyl-$S(O)_2$-,

wherein any alkyl and cycloalkyl group or sub-group within the groups forming R^1 is optionally substituted with 1 or more F atoms, and wherein multiple R^1 may be identical or different if m is 2, 3 or 4;

m is an integer selected from 1, 2, 3, and 4;

R^2 is selected from the group R^2-G1 consisting of H, F, Cl, C_{1-4}-alkyl, NC-, and C_{1-4}-alkyloxy,

wherein any alkyl group or sub-group within the groups forming R^2 is optionally substituted with 1 or more F atoms, and wherein multiple R^2 may be identical or different if n is 2 or 3;

R^3 is selected from the group R^3-G1 consisting of H, F, Cl, C_{1-4}-alkyl, NC-, and C_{1-4}-alkyl-O-,

wherein each alkyl group or sub-group within the groups forming R^3 is optionally substituted with 1 or more F atoms;

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

R^N is independently of each other selected from the group R^N-G1 consisting of H, C_{1-4}-alkyl, HO-C_{1-4}-alkyl-(H_2C)-, C_{1-3}-alkyl-O-C_{1-4}-alkyl-, C_{1-4}-alkyl-C(=O)-, C_{1-4}-alkyl-NH-C(=O)-, C_{1-4}-alkyl-N(C_{1-4}-alkyl)-C(=O)-, C_{1-4}-alkyl-O-C(=O)-, and C_{1-4}-alkyl-$S(=O)_2$-,

wherein each alkyl group or sub-group within the groups forming R^N is optionally substituted with 1 or more F atoms;

wherein in any definition mentioned hereinbefore and if not specified otherwise, any alkyl group or sub-group may be straight-chained or branched,

the isoforms, tautomers, stereoisomers, metabolites, prodrugs, solvates, hydrates, and the salts thereof, particularly the physiologically acceptable salts thereof with inorganic or organic acids or bases, or the combinations thereof.

The extension -Gn used within the definitions is meant to identify genus n of the respective substituent. For example, R-G1 defines genus 1 of the substituent R.

The expression "optionally substituted with 1 or more F atoms" means that none or one up to successively all H atoms bound to carbon atoms of the respective group or submoiety may be replaced by F atoms, preferably 1 to 5 H atoms or, more preferred, 1 to 3 H atoms may be replaced by F atoms.

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.

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 GPR40 in a patient in need thereof characterized in that a compound of general formula **I** or a pharmaceutically acceptable salt thereof is administered to the patient.

According to another aspect of the invention, there is provided a method for treating a metabolic disease or disorder, such as diabetes, dyslipidemia and/or obesity, in a patient in need thereof characterized in that a therapeutically effective amount of a compound of general formula **I** or a pharmaceutically acceptable salt thereof is administered to the patient.

According to another aspect of the invention, there is provided the use of a compound of the general formula **I** or a pharmaceutically acceptable salt thereof for

the manufacture of a medicament for a therapeutic method as described hereinbefore and hereinafter.

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

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 GPR40 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.

In a further aspect this invention relates to the use of a compound of the general formula **I** or a pharmaceutically acceptable salt thereof in combination with one or more additional therapeutic agents for the treatment of diseases or conditions which are mediated by the activation of the G-protein-coupled receptor GPR40.

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.

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

Unless otherwise stated, the groups, residues, and substituents, particularly R, R^1, R^2, R^3, m and n are defined as above and hereinafter. If residues, substituents, or groups occur several times in a compound, 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:

R-G1:

The group R is preferably selected from the group R-G1 as defined hereinbefore.

R-G2:

In another embodiment the group R is selected from the group R-G2 consisting of

H, F, Cl, C_{1-6}-alkyl, C_{3-6}-cycloalkyl, NC-, HNR^N-C(=O)-, C_{1-4}-alkyl-NR^N-C(=O)-, C_{3-6}-cycloalkyl-NR^N-C(=O)-, heterocyclyl-NR^N-C(=O)-, HOOC-, HR^NN-, C_{1-4}-alkyl-R^NN-, C_{1-4}-alkyl-C(=O)NR^N-, C_{3-6}-cycloalkyl-C(=O)NR^N-, heterocyclyl-C(=O)NR^N-, C_{1-4}-alkyl-S(=O)$_2NR^N$-, HO-, C_{1-6}-alkyl-O-, HOOC-(C_{1-2}-alkyl)-O-, C_3-cycloalkyl-H_2C-O-, heterocyclyl-C_{1-2}-alkyl-O-, phenyl-C_{1-2}-alkyl-O-, C_{3-6}-cycloalkyl-O-, heterocyclyl-O-, heteroaryl-O-, C_{1-4}-alkyl-S(=O)$_2$-, C_{3-6}-cycloalkyl-S(=O)$_2$-, heterocyclyl-S(=O)$_2$-, HNR^N-S(=O)$_2$-, C_{1-4}-alkyl-NR^N-S(=O)$_2$-, heterocyclyl, and heteroaryl,

wherein each alkyl, cycloalkyl, and heterocyclyl group or sub-group within the groups forming R is optionally substituted with 1 or more F atoms and optionally substituted with 1 to 2 groups independently selected from Cl, H_3C-, NC-, R^NHN-, HO-, H_3C-O-, and H_3C-S(=O)$_2$-;

wherein each heteroaryl group or sub-group within the groups forming R is optionally substituted with 1 to 3 substituents independently selected from F, Cl, H_3C-, F_3C-, NC-, $(R^N)_2N$-, HO-, H_3C-O-, F_3C-O-, and H_3C-S(=O)$_2$-;

wherein each heterocyclyl group or sub-group within the groups forming R is selected from

a cyclobutyl group wherein 1 CH_2 group is replaced by -NR^N- or -O-;

a C_{5-6}-cycloalkyl group wherein 1 CH_2 group is replaced by -C(=O)-, -NR^N-, -O-, -S- or -S(=O)$_2$- and/or 1 CH group is replaced by N;

a C_{5-6}-cycloalkyl group wherein 1 CH_2 group is replaced by -NR^N- or -O-, a second CH_2 group is replaced by -NR^N-, -C(=O)- or -S(=O)$_2$- and/or 1 CH group is replaced by N;

wherein each heteroaryl group or sub-group within the groups forming R is selected from

tetrazolyl, a 5-membered heteroaromatic ring which contains 1, 2 or 3 heteroatoms independently of each other selected from =N-, -NH-, O and S,

and a 6-membered heteroaromatic ring which contains 1 or 2 =N- atoms, wherein a -HC=N- unit is optionally replaced by -NH-C(=O)-;

and wherein in each of the above heteroaryl and heterocyclyl group or sub-group containing one or more NH, said NH group(s) is/are replaced by NR^N.

R-G3:

In another embodiment the group R is selected from the group R-G3 consisting of H, F, Cl, C_{1-4}-alkyl, NC-, H_2N-C(=O)-, C_{1-3}-alkyl-NR^N-C(=O)-, HOOC-, H_2N-, C_{1-3}-alkyl-C(=O)NR^N-, C_{1-4}-alkyl-S(=O)$_2NR^N$-, HO-, C_{1-5}-alkyl-O-, HOOC-CH_2-O-, C_3-cycloalkyl-H_2C-O-, heterocyclyl-CH_2-O-, phenyl-CH_2-O-, C_{3-6}-cycloalkyl-O-, heterocyclyl-O-, heteroaryl-O-, heterocyclyl-S(=O)$_2$-, heterocyclyl, and heteroaryl,

wherein each alkyl, cycloalkyl, and heterocyclyl group or sub-group within the groups forming R is optionally substituted with 1 or more F atoms and optionally substituted with 1 group selected from Cl, H_3C-, NC-, R^NHN-, HO-, H_3C-O-, and H_3C-S(=O)$_2$-;

wherein each heteroaryl group or sub-group within the groups forming R is optionally substituted with 1 to 2 substituents independently selected from F, Cl, H_3C-, F_3C-, NC-, $(R^N)_2N$-, HO-, H_3C-O-, F_3C-O-, and H_3C-S(=O)$_2$-;

wherein each heterocyclyl or sub-group within the groups forming R is selected from

a cyclobutyl group wherein 1 CH_2 group is replaced by -NR^N- or -O-;

a C_{5-6}-cycloalkyl group wherein 1 CH_2 group is replaced by -C(=O)-, -NR^N-, -O-, -S- or -S(=O)$_2$- and/or 1 CH group is replaced by N;

wherein each heteroaryl group or sub-group within the groups forming R is selected from tetrazolyl, a 5-membered heteroaromatic ring which contains 1, 2 or 3 heteroatoms independently of each other selected from =N-, -NH-, O and S, and a 6-membered heteroaromatic ring which contains 1 or 2 =N- atoms, wherein a -HC=N- unit is optionally replaced by -NH-C(=O)-;

and wherein in each heteroaryl and heterocyclyl group or sub-group mentioned for R-G3 containing one or more NH, said NH group(s) is/are replaced by NR^N.

R-G4:

According to another embodiment the group R is selected from the group R-G4 consisting of

H, Cl, C_{1-3}-alkyl optionally substituted with 1 or more F;

H_3C-O- optionally monosubstituted with C_{1-4}-alkyl, tetrahydrofuranyl, or tetrahydropyranyl,

wherein the C_{1-4}-alkyl group optionally attached to H_3C-O- is optionally monosubstituted with HO- or H_3C-S(=O)$_2$-;

tetrahydrofuranyl-O- and tetrahydropyranyl-O-; and

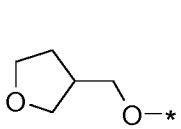
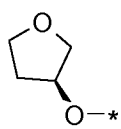
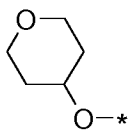
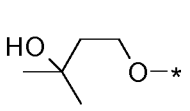
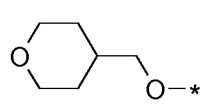
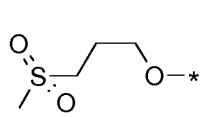
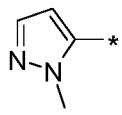
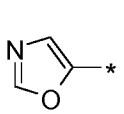
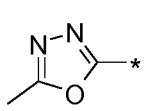
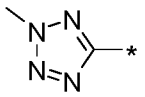
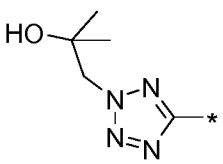
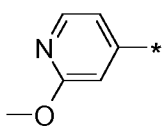
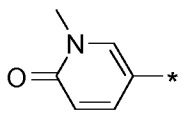
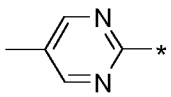
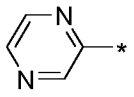
a heteroaryl group selected from pyrazolyl, oxazolyl, oxadiazolyl, tetrazolyl, pyridyl, pyridin-2-onyl, pyrazinyl, and pyrimidinyl,

wherein each of said heteroaryl groups is optionally monosubstituted with H_3C- or H_3C-O-, and

wherein each H-N group in said heteroaryl groups is optionally replaced with H_3C-N or $(H_3C)_2C(OH)$-H_2C-N.

R-G5:

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

H, Cl, H_3C-H_2C-, $(H_3C)_2CH$-, F_3C-, H_3C-O-,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , and  ,

wherein the asterisk (-*) indicates the site/point of attachment.

R^1:

R^1-G1:

The group R^1 is preferably selected from the group R^1-G1 as defined hereinbefore.

R^1-G2:

According to one embodiment the group R^1 is selected from the group R^1-G2 consisting of H, F, Cl, C_{1-3}-alkyl, cyclopropyl, NC-, HO-, and C_{1-3}-alkyl-O-,

wherein each alkyl group or sub-group within the groups mentioned under R^1-G2 is optionally substituted with 1 or more F atoms.

R^1-G3:

According to one embodiment the group R^1 is selected from the group R^1-G3 consisting of H, F, Cl, H_3C-, H_3C-H_2C-, $(H_3C)_2HC$-, F_3C-, NC-, and H_3C-O-.

R^1-G4:

According to one embodiment the group R^1 is selected from the group R^1-G4 consisting of H and H_3C-.

R^2:

R^2-G1:

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

R^2-G2:

In another embodiment the group R^2 is selected from the group R^2-G2 consisting of H, F, Cl, H_3C-, F_3C-, NC-, and H_3CO-.

R^2-G3:

In another embodiment the group R^2 is selected from the group R^2-G3 consisting of H, F, and F_3C-.

R^2-G4:

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

R^2-G5:

In another embodiment the group R^2 is selected from the group R^2-G5 consisting of F.

R^2-G6:

In another embodiment the group R^2 is selected from the group R^2-G5 consisting of F_3C-.

R^3:

R^3-G1:

The group R^3 is preferably selected from the group R^3-G1 as defined hereinbefore.

R^3-G2:

In another embodiment the group R^3 is selected from the group R^3-G2 consisting of of H, H_3C-, and H_3CO-.

R^3-G3:

In another embodiment the group R^3 is selected from the group R^3-G3 consisting of H.

R^N:

R^N-G1:

The group R^N is preferably selected from the group R^N-G1 as defined hereinbefore.

R^N-G2:

In another embodiment the group R^N is selected from the group R^N-G2 consisting of H, C_{1-3}-alkyl, HO-C_{1-4}-alkyl-H_2C-, H_3C-O-C_{1-4}-alkyl-, C_{1-3}-alkyl-C(=O)-, and C_{1-3}-alkyl-$S(=O)_2$-.

R^N-G3:

In another embodiment the group R^N is selected from the group R^N-G3 consisting of H, H_3C-, HO-C_3-alkyl-H_2C-, H_3C-C(=O)-, and H_3C-S(=O)$_2$-.

m:

m is an integer selected from 1, 2, 3 and 4.

Preferably, m is an integer selected from 1 and 2.

More preferably, m is 2.

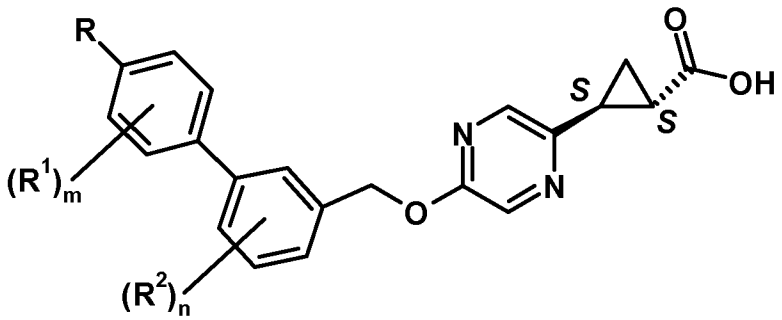
n:

n is an integer selected from 1, 2 and 3.

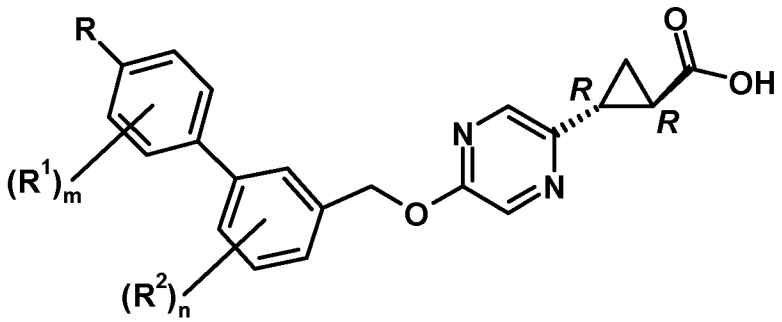
Preferably, n is an integer selected from 1 and 2.

More preferably, n is 2.

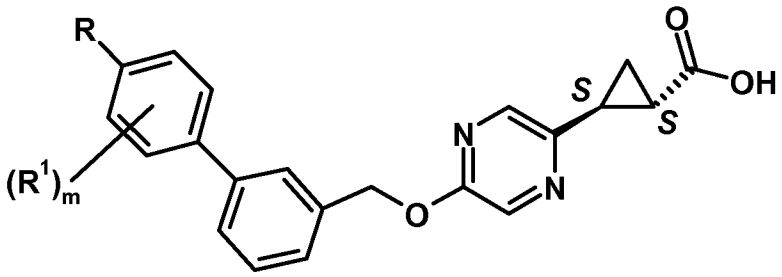
The following preferred embodiments of compounds of the formula **I** are described using generic formulae I.1, I.2, I.3, I.4, I.5, and I.6, wherein any tautomers, solvates, hydrates and salts thereof, in particular the pharmaceutically acceptable salts thereof, are encompassed.



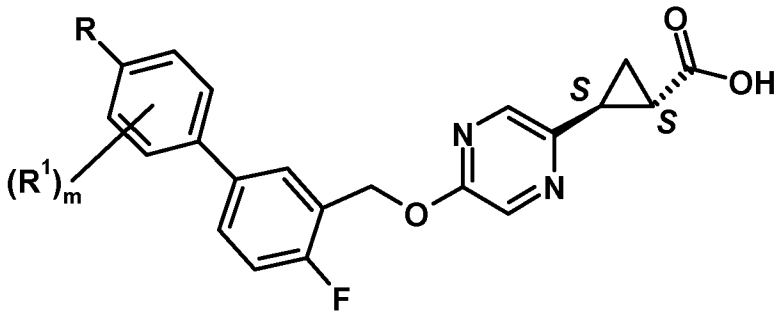
I.1



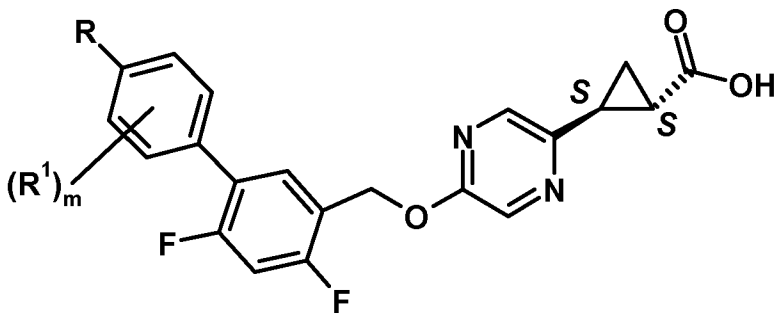
I.2



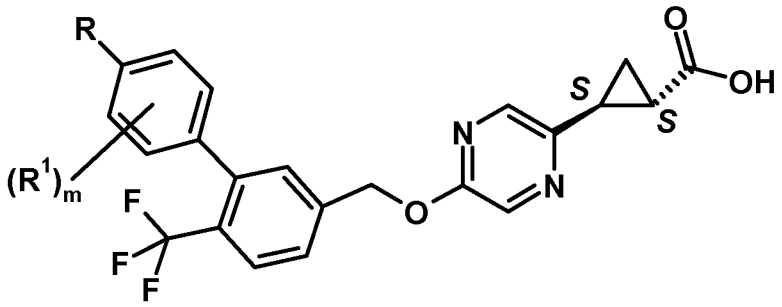
I.3



I.4



I.5



I.6

Examples of preferred subgeneric embodiments (E) according to the present invention are set forth in the following Table 1, wherein each substituent group of each embodiment is defined according to the definitions set forth hereinbefore and wherein all other substituents of the formulae **I**, I.1, I.2, I.3, I.4, I.5, and I.6 are defined according to the definitions set forth hereinbefore. For example, the entry –G1 in the column under R- and in the line of E1 means that in embodiment E1 substituent R is

selected from the definition designated R-G1. The same applies analogously to the other variables incorporated in the general formulae.

Table 1:

E	R-	R^1-	R^2-	R^3-	R^N-	m	n
E1	-G1	-G1	-G1	-G1	-G1	1,2,3,4	1,2,3
E2	-G1	-G1	-G1	-G2	-G2	1,2	1,2
E3	-G1	-G1	-G1	-G3	-G3	1,2	1,2
E4	-G1	-G1	-G2	-G3	-G3	1,2	1,2
E5	-G1	-G2	-G2	-G3	-G1	1,2	1,2
E6	-G1	-G2	-G2	-G2	-G2	1,2	1,2
E7	-G1	-G2	-G2	-G3	-G3	1,2	1,2
E8	-G2	-G1	-G1	-G1	-G1	1,2	1,2
E9	-G3	-G1	-G1	-G1	-G1	1,2	1,2
E10	-G3	-G1	-G2	-G2	-G2	1,2	1,2
E11	-G3	-G2	-G2	-G2	-G2	1,2	1,2
E12	-G2	-G2	-G2	-G3	-G3	1,2	1,2
E13	-G3	-G2	-G2	-G3	-G3	1,2	1,2
E14	-G1	-G3	-G2	-G3	-G3	1,2	1,2
E15	-G1	-G2	-G3	-G3	-G3	1,2	1,2
E16	-G1	-G3	-G3	-G3	-G3	1,2	1,2
E17	-G1	-G4	-G3	-G3	-G3	1,2	1,2
E18	-G2	-G3	-G2	-G3	-G3	1,2	1,2
E19	-G2	-G2	-G3	-G3	-G3	1,2	1,2
E20	-G2	-G3	-G3	-G3	-G3	1,2	1,2
E21	-G2	-G4	-G3	-G3	-G3	1,2	1,2
E22	-G3	-G3	-G2	-G3	-G3	1,2	1,2
E23	-G3	-G2	-G3	-G3	-G3	1,2	1,2
E24	-G3	-G3	-G3	-G3	-G3	1,2	1,2
E25	-G3	-G4	-G3	-G3	-G3	1,2	1,2
E26	-G4	-G3	-G2	-G3	-	2	1,2
E27	-G4	-G2	-G3	-G3	-	2	1,2
E28	-G4	-G3	-G3	-G3	-	2	1,2
E29	-G4	-G4	-G3	-G3	-	2	1,2
E30	-G5	-G3	-G2	-G3	-	2	1,2
E31	-G5	-G2	-G3	-G3	-	2	1,2

E	R-	R^1-	R^2-	R^3-	R^N-	m	n
E32	-G5	-G3	-G3	-G3	-	2	1,2
E33	-G5	-G4	-G3	-G3	-	2	1,2

Another embodiment concerns those compounds of formula I, wherein

R is selected from the group consisting of

H, Cl, C_{1-3}-alkyl optionally substituted with 1 or more F;

H_3C-O- optionally monosubstituted with C_{1-4}-alkyl, tetrahydrofuranyl, or tetrahydropyranyl,

wherein the C_{1-4}-alkyl group optionally attached to H_3C-O- is optionally monosubstituted with HO- or H_3C-S(=O)$_2$-;

tetrahydrofuranyl-O- and tetrahydropyranyl-O-; and

a heteroaryl group selected from pyrazolyl, oxazolyl, oxadiazolyl, tetrazolyl, pyridyl, pyridin-2-onyl, pyrazinyl, and pyrimidinyl,

wherein each of said heteroaryl groups is optionally monosubstituted with H_3C- or H_3C-O-, and

wherein each H-N group in said heteroaryl groups is optionally replaced with H_3C-N or $(H_3C)_2C(OH)$-H_2C-N;

R^1 is selected from the group consisting of H, F, Cl, H_3C-, H_3C-H_2C-, $(H_3C)_2HC$-, F_3C-, NC-, and H_3C-O-;

m is 2;

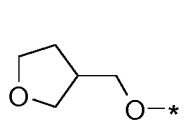
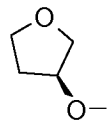
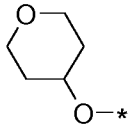
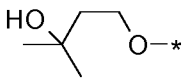
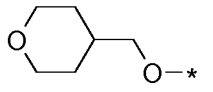
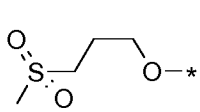
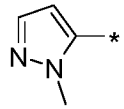
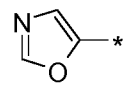
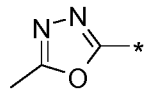
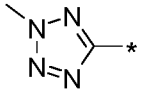
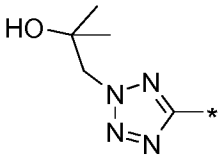
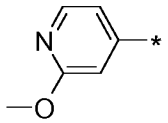
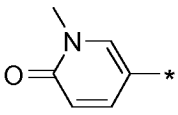
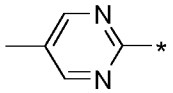
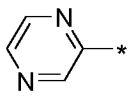
R^2 is H, F, or F_3C-;

n is 2; and

R^3 is H.

Another embodiment concerns those compounds of formula I, wherein

R is selected from the group consisting of

H, Cl, H_3C-H_2C-, $(H_3C)_2CH$-, F_3C-, H_3C-O-,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , and  ,

wherein the asterisk (-*) indicates the site/point of attachment;

R^1 is H or H_3C-;

m is 2;

R^2 is H, F, or F_3C-;

n is 2; and

R^3 is H.

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

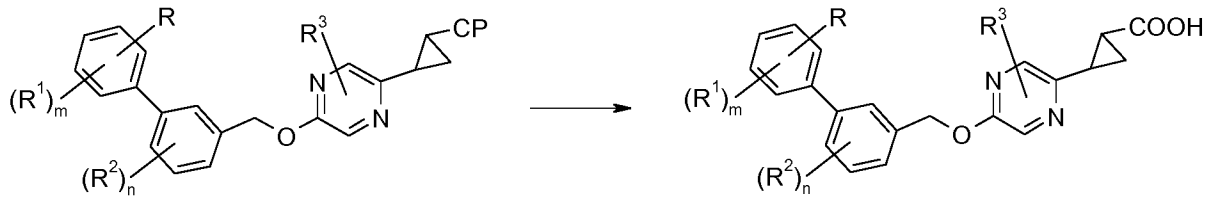
The compounds according to the invention and their intermediates may be obtained using methods of synthesis which are known to the one skilled in the art and described in the literature of organic synthesis for example using methods described in “Comprehensive Organic Transformations”, 2nd Edition, Richard C. Larock, John Wiley & Sons, 2010, and “March’s Advanced Organic Chemistry”, 7th Edition, Michael

B. Smith, John Wiley & Sons, 2013. Preferably, the compounds are obtained analogously to the methods of preparation explained more fully hereinafter, in particular as described in the experimental section. In some cases the sequence adopted in carrying out the reaction schemes may be varied. Variants of these reactions that are known to the skilled man but are not described in detail here may also be used. The general processes for preparing the compounds according to the invention will become apparent to the skilled man on studying the schemes that follow. Starting compounds are commercially available or may be prepared by methods that are described in the literature or herein, or may be prepared in an analogous or similar manner. Before the reaction is carried out any corresponding functional groups in the compounds may be protected using conventional protecting groups. These protecting groups may be cleaved again at a suitable stage within the reaction sequence using methods familiar to the skilled man and described in the literature for example in "Protecting Groups", 3rd Edition, Philip J. Kocienski, Thieme, 2005, and "Protective Groups in Organic Synthesis", 4th Edition, Peter G. M. Wuts, Theodora W. Greene, John Wiley & Sons, 2006.

The compounds of the invention **I** are preferably accessed from a precursor **II** that bears the carboxylic acid function in a protected or masked form as sketched in Scheme 1; R, R^1, R^2, R^3, m and n have the meanings as defined hereinbefore and hereinafter. Suited precursor groups for the carboxylic acid may be, e.g., a carboxylic ester, a carboxylic amide, cyano, an olefin, an oxazole, or a thiazole. All these groups have been transformed into the carboxylic acid function by different means which are described in the organic chemistry literature and are known to the one skilled in the art. The preferred precursor group is a C_{1-4}-alkyl or benzyl carboxylate, each of which may be additionally mono- or polysubstituted with fluorine, methyl, and/or methoxy. These ester groups may be hydrolyzed with an acid, such as hydrochloric acid or sulfuric acid, or an alkali metal hydroxide, such as lithium hydroxide, sodium hydroxide, or potassium hydroxide, to yield the carboxylic acid function; the hydrolysis is preferably conducted in aqueous solvents, such as water and tetrahydrofuran, 1,4-dioxane, alcohol, e.g., methanol, ethanol, and isopropanol, or dimethyl sulfoxide, at 0 to 120 °C. A *tert*-butyl ester is preferably cleaved under acidic conditions with, e.g., trifluoroacetic acid or hydrochloric acid, in a solvent such as dichloromethane, 1,4-dioxane, isopropanol, or ethyl acetate. A benzyl ester is

advantageously cleaved using hydrogen in the presence of a transition metal, preferably palladium on carbon. Benzyl esters bearing electron donating groups, such as methoxy, on the aromatic ring may also be removed under oxidative conditions; ceric ammonium nitrate (CAN) or 2,3-dichloro-5,6-dicyanoquinone (DDQ) are two commonly used reagents for this approach. The carboxylic acid group may also be introduced at an earlier stage of the synthesis, e.g., prior to the coupling of the pyridine part with the benzyl amino residue or the C-C coupling of the two phenyl subgroups as described in the experimental section.

Scheme 1: Liberation of carboxylic acid function to access compounds of the invention



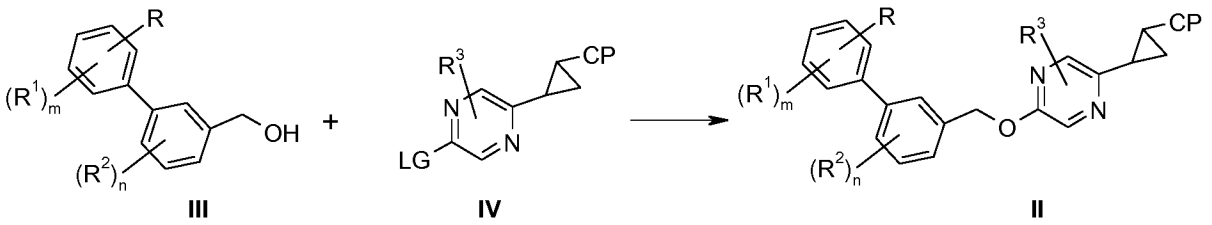
CP = masked or protected form of COOH, e.g., CO_2C_{1-4}-alkyl, CO_2CH_2aryl, $CON(C_{1-4}\text{-alkyl})_2$, CN, $CH{=}CH_2$, thiazol-2-yl, oxazol-2-yl

Compound **II**, in turn, may be obtained from benzylalcohol **III** and pyrazine **IV** which bears the carboxylic acid group or a precursor group thereof and a leaving group (Scheme 2); R, R^1, R^2, R^3, m, and n in Scheme 2 have the meanings as defined hereinbefore and hereinafter. The leaving group LG in **IV** is replaced with the O group in **III** via a nucleophilic substitution reaction on the pyrazine ring; suited LG may be F, Cl, Br, and I. The reaction is usually carried out in the presence of a base such as NaH and KH, a carbonate, e.g., K_2CO_3 and Cs_2CO_3, a hydroxide, e.g., NaOH and KOH, and an alcoholate, e.g., NaO*t*Bu and KO*t*Bu. Preferred solvents are dimethylsulfoxide, N,N-dimethylformamide, N,N-dimethylacetamide, N-methyl-pyrrolidinone, acetonitrile, 1,4-dioxane, tetrahydrofuran, toluene, alcohol, e.g., tert-BuOH, or mixtures thereof at temperatures of 0 to 220 °C.

Alternatively, coupling of benzylalcohol **III** and pyrazine **IV** is mediated by a transition metal catalyst. Suited pyrazines **IV** for this approach bear Cl, Br, or I as LG, and the catalyst is preferably derived from Cu or Pd. Suited catalyst precursors are CuI and palladium(II) acetate optionally combined with a ligand such as a bipyridine or a

phosphine. The reaction is commonly conducted in the presence of a base such as an alcoholate, e.g., NaO*t*Bu, K_3PO_4, a carbonate, e.g., Cs_2CO_3, or NaH in a solvent such as toluene, tetrahydrofuran, 1,4-dioxane, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidinone, dimethylsulfoxide, *t*BuOH, or mixtures thereof, at temperatures in the range of 20 to 180 °C.

Scheme 2: Preparation of precursor **II**



LG = leaving group, e.g., Cl, Br, I;

CP = COOH or masked or protected form of COOH, e.g., CO_2C_{1-4}-alkyl, CO_2CH_2aryl, $CON(C_{1-4}\text{-alkyl})_2$, CN, $CH{=}CH_2$, thiazol-2-yl, oxazol-2-yl

Compounds of general structure **IV** wherein R^3 has the meaning as defined hereinbefore and hereinafter and CP is a suitable carboxylic acid ester group can be synthesized as summarized in Scheme 4.

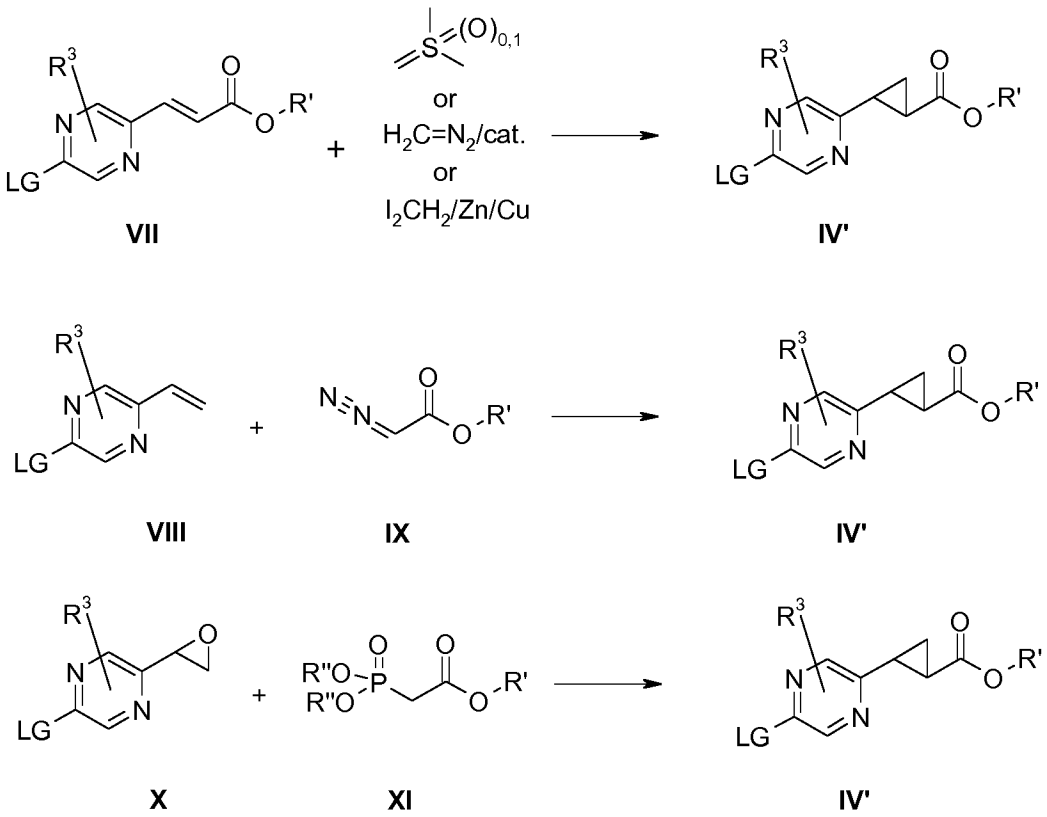
Acrylic acid ester **VII** is reacted with a methylene synthetic equivalent to give ester **IV'**. Suitable reagents for this transformation include diazomethane in the presence of a transition metal catalyst such as palladium diacetate (see, e.g., WO2011/94890), trimethyloxosulfonium halide in the presence of a base such as sodium hydride (see, e.g., WO2005/103032), and diiodomethane in the presence of copper and zinc (see, e.g., US628476). Generally, use of a *trans*-acrylic acid ester in these reactions leads to predominant formation of a *trans*-substituted cyclopropyl ester. Enantioselective variants of this type of reaction are reported in the literature such as the one using diazomethane and chiral copper complexes (see, e.g., *Tetrahedron Asymmetry* **2003**, *14*, 867-872).

The pyrazine **IV'** is also obtained from vinylpyrazine **VIII** and diazoacetic ester **IX** in the presence of a transition metal catalyst. Suitable catalyst systems for this transformation include, for example, palladium diacetate (see, e.g., WO2007/104717), cobalt(II) porphyrins (see, e.g., WO2006/103503), rhodium complexes (see, e.g., WO2006/87169), and copper complexes (see, e.g., WO2010/51819). Mixtures of *cis*- and *trans*-cyclopropyl esters are generally formed

with the *trans*-system predominant and the ratio depending on the catalyst system and substrates used. Enantioselective reactions of this type are reported using chiral transition metal catalysts derived from copper and cobalt (see, e.g., *J. Am. Chem Soc.* **1991**, *113*, 726-728) and variations thereof.

Another proceeding to access compound **IV'** employs epoxide **X** and phosphonoacetate **XI**. The reaction is commonly carried out in the presence of a base such as an alcoholate, e.g., NaOEt, NaOtBu, NaOtPent, KOtBu, and KOtPent, $LiN(iPr)_2$, $LiN(SiMe_3)_2$, NaH, or nBuLi, in a solvent such as hexane, benzene, toluene, tetrahydrofuran, 1,2-dimethoxyethane, 1,4-dioxane, dimethylsulfoxide, or mixtures thereof, at 0 to 160 °C. The epoxide **X** is accessed using standard procedures in organic synthesis such as epoxidation of the corresponding alkene, base induced cyclization of the corresponding chloro- or bromohydrin derivative, or Corey-Chaykovsky reaction of the corresponding pyrazinecarbaldehyde and an appropriate sulfur ylide.

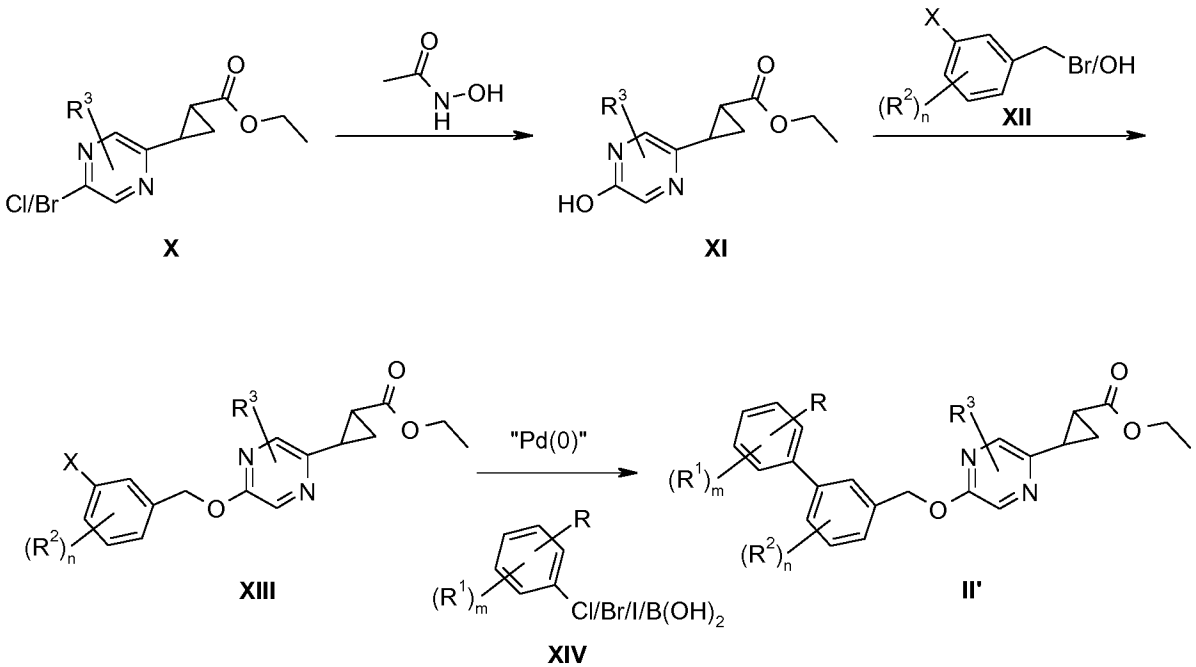
Scheme 4: Preparation of intermediate **IV**



LG = Leaving group, e.g., F, Cl, Br, I
R' = C_{1-4}-alkyl, CH_2aryl
R'' = C_{1-4}-alkyl

Alternatively, compounds of general structure **II** may be accessed as described in the experimental section (Scheme 4). Starting from pyrazine **X** compound **XI** is synthesized via substitution with an O-nucleophile such as N-acetylhydroxylamine in the presence of a base such as K_2CO_3. Product **XI** is then alkylated with a benzyl halide or pseudohalide **XII** that bears an additional group, e.g. Br or $B(OCMe_2CMe_2O)$, for carrying out a subsequent transition metal catalyzed C_{sp2}-C_{sp2} coupling reaction to attach an additional phenyl group. The alkylation is preferably conducted in the presence of a base and a Ag(I) salt, e.g., Ag_2CO_3, in a solvent such as toluene at 80 °C. Alternatively, a benzylalcohol instead of a halide **XII** and the conditions of the Mitsunobu reaction, using triphenylphosphine and diisopropyl azodicarboxylate, are used to prepare compounds **XIII**. Compounds **XIII**, bearing a leaving group such as Br, may be coupled with boronic acids **XIV** or boronic esters thereof using a transition metal catalyst, preferably a Pd derived catalyst, to provide compounds **II'**. The reactivity of the two coupling partners **XIII** and **XIV** may be reversed, i.e. compound **XIII** is employed as the nucleophilic, e.g., as boronic acid or ester, and compound **XIV** as the electrophilic partner, e.g., as bromide, to provide compounds **II'** under analogous reaction conditions.

Scheme 4: Alternative Approach for the synthesis of intermediate **II**



X = I, Br, Cl or $B(OCMe_2CMe_2O)$, $B(OH)_2$

The synthetic routes presented may rely on the use of protecting groups. For example, potentially reactive groups present, such as hydroxy, carbonyl, carboxy, amino, alkylamino, or imino, may be protected during the reaction by conventional protecting groups which are cleaved again after the reaction. Suitable protecting groups for the respective functionalities and their removal are well known to the one skilled in the art and are described in the literature of organic synthesis for example in "Protecting Groups", 3rd Edition, Philip J. Kocienski, Thieme, 2005, or "Protective Groups in Organic Synthesis", 4th Edition, Peter G. M. Wuts, Theodora W. Greene, John Wiley & Sons, 2006.

The compounds of general formula **I** may be resolved into their enantiomers and/or diastereomers as mentioned below. Thus, for example, *cis/trans* mixtures may be resolved into their *cis* and *trans* isomers and racemic compounds may be separated into their enantiomers.

The *cis/trans* mixtures may be resolved, for example, by chromatography into the *cis* and *trans* isomers thereof. The compounds of general formula I which occur as racemates may be separated by methods known *per se* into their optical antipodes and diastereomeric mixtures of compounds of general formula **I** may be resolved into their diastereomers by taking advantage of their different physico-chemical properties 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 below.

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.

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

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

Terms and definitions

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

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

The terms "treatment" and "treating" embrace both preventative, i.e. prophylactic, or therapeutic, i.e. curative and/or palliative, treatment. Thus the terms "treatment" and "treating" comprise therapeutic treatment of patients having already developed said condition, in particular in manifest form. Therapeutic treatment may be symptomatic treatment in order to relieve the symptoms of the specific indication or causal treatment in order to reverse or partially reverse the conditions of the indication or to

stop or slow down progression of the disease. Thus the compositions and methods of the present invention may be used for instance as therapeutic treatment over a period of time as well as for chronic therapy. In addition the terms "treatment" and "treating" comprise prophylactic treatment, i.e. a treatment of patients at risk to develop a condition mentioned hereinbefore, thus reducing said risk.

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

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

The terms "modulated" or "modulating", or "modulate(s)", as used herein, unless otherwise indicated, refer to the activation of the G-protein-coupled receptor GPR40 with one or more compounds of the present invention.

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

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

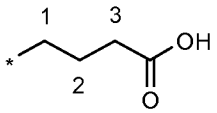
In the groups, radicals, or moieties defined below, the number of carbon atoms is often specified preceding the group, for example, C_{1-6}-alkyl means an alkyl group or radical having 1 to 6 carbon atoms. In general, for groups comprising two or more subgroups, the last named subgroup is the radical attachment point, for example, the

substituent "aryl-C_{1-3}-alkyl-" means an aryl group which is bound to a C_{1-3}-alkyl-group, the latter of which is bound to the core or to the group to which the substituent is attached.

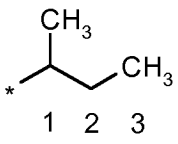
In case a compound of the present invention is depicted in form of a chemical name and as a formula in case of any discrepancy the formula shall prevail.

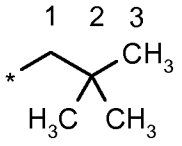
An asterisk may be used in sub-formulas to indicate the bond which is connected to the core molecule as defined.

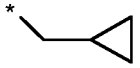
The numeration of the atoms of a substituent starts with the atom which is closest to the core or to the group to which the substituent is attached.
For example, the term “3-carboxypropyl-group” represents the following substituent:



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:



,


,


.

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

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^{ex} denotes H, C_{1-3}-alkyl, C_{3-6}-cycloalkyl, C_{3-6}-cycloalkyl-C_{1-3}-alkyl or C_{1-3}-alkyl-O-, wherein each alkyl group is optionally substituted with one or more L^{ex}." or the like means that in each of the beforementioned groups which comprise the term alkyl, i.e. in each of the groups C_{1-3}-alkyl, C_{3-6}-cycloalkyl-C_{1-3}-alkyl and C_{1-3}-alkyl-O-, the alkyl moiety may be substituted

with L^{ex} as defined.

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.

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.

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.

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

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

The term “C_{1-n}-alkyl”, wherein n is an integer from 1 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_{1-5}-alkyl embraces the radicals H_3C-, H_3C-CH_2-, H_3C-CH_2-CH_2-, H_3C-$CH(CH_3)$-, H_3C-CH_2-CH_2-CH_2-, H_3C-CH_2-$CH(CH_3)$-, H_3C-$CH(CH_3)$-CH_2-, H_3C-$C(CH_3)_2$-, H_3C-CH_2-CH_2-CH_2-CH_2-,

H_3C-CH_2-CH_2-$CH(CH_3)$-, H_3C-CH_2-$CH(CH_3)$-CH_2-, H_3C-$CH(CH_3)$-CH_2-CH_2-, H_3C-CH_2-$C(CH_3)_2$-, H_3C-$C(CH_3)_2$-CH_2-, H_3C-$CH(CH_3)$-$CH(CH_3)$- and H_3C-CH_2-$CH(CH_2CH_3)$-.

The term "C_{1-n}-alkylene" wherein n is an integer 1 to n, either alone or in combination with another radical, denotes an acyclic, straight or branched chain divalent alkyl radical containing from 1 to n carbon atoms. For example the term C_{1-4}-alkylene includes -(CH_2)-, -$(CH_2$-$CH_2)$-, -$(CH(CH_3))$-, -$(CH_2$-CH_2-$CH_2)$-, -$(C(CH_3)_2)$-, -$(CH(CH_2CH_3))$-, -$(CH(CH_3)$-$CH_2)$-, -$(CH_2$-$CH(CH_3))$-, -$(CH_2$-CH_2-CH_2-$CH_2)$-, -$(CH_2$-CH_2-$CH(CH_3))$-, -$(CH(CH_3)$-CH_2-$CH_2)$-, -$(CH_2$-$CH(CH_3)$-$CH_2)$-, -$(CH_2$-$C(CH_3)_2)$-, -$(C(CH_3)_2$-$CH_2)$-, -$(CH(CH_3)$-$CH(CH_3))$-, -$(CH_2$-$CH(CH_2CH_3))$-, -$(CH(CH_2CH_3)$-$CH_2)$-, -$(CH(CH_2CH_2CH_3))$- , -$(CHCH(CH_3)_2)$- and –$C(CH_3)(CH_2CH_3)$-.

The term “C_{2-n}-alkenyl”, is used for a group as defined in the definition for "C_{1-n}-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_{2-3}-alkenyl includes -$CH=CH_2$, -$CH=CH$-CH_3, -CH_2-$CH=CH_2$.

The term “C_{2-n}-alkynyl”, is used for a group as defined in the definition for "C_{1-n}-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_{2-3}-alkynyl includes -C≡CH, -C≡C-CH_3, -CH_2-C≡CH.

The term “C_{3-n}-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, norbonyl, norcaryl, adamantyl, etc.

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

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

IP_1 accumulation measurements using the IPOne assay system - 1321N1 cells stably expressing human GPR40 receptor (Euroscreen, Belgium) are seeded 24 h before the assay in white 384-well plates in culture medium containing 10% FCS, 1% Na-Pyruvate and 400 µg/mL G418. IP_1 is assayed according to the manufacturer's description (Cisbio Bioassays, France). In brief, the assay is started by substitution of the culture medium by stimulation buffer (Hepes 10 mM, $CaCl_2$ 1 mM, $MgCl_2$ 0.5 mM, KCl 4.2 mM, NaCl 146 mM, glucose 5.5 mM and LiCl 50 mM, pH 7.4). Cells are stimulated for 1 h at 37 °C, 5% CO_2 by addition of the compounds that are diluted in stimulation buffer containing LiCl. Assays are stopped by adding HTRF-conjugates (IP1-d2 and Anti-IP1 cryptate Tb) and lysis buffer, provided by the manufacturer. After an incubation time of 1 h at room temperature plates are measured using an EnVision™, Perkin Elmer. The obtained fluorescence ratios at 665/615 nM are then used to calculate the pEC_{50} values using Assay Explorer 3.3 Software (Accelrys, Inc.) by interpolation using an IP_1 reference curve and subsequent sigmoidal curve fitting allowing for a variable hill slope.

The compounds according to the invention typically have EC_{50} values in the range from about 1 nM to about 10 µM, preferably less than 1 µM, more preferably less than 100 nM.

EC_{50} values for compounds according to the invention are shown in the following table. The number of the compound corresponds to the number of the Example in the experimental section.

Table 2:

Example	EC_{50} [nM]	Example	EC_{50} [nM]	Example	EC_{50} [nM]	Example	EC_{50} [nM]
1	6	2	3	3	24	4	12
5	67	6	10	7	8	8	7

9	9	10	13	11	6	12	8
13	20	14	6	15	8	16	3
17	7	18	7	19	6	20	35
21	3	22	4				

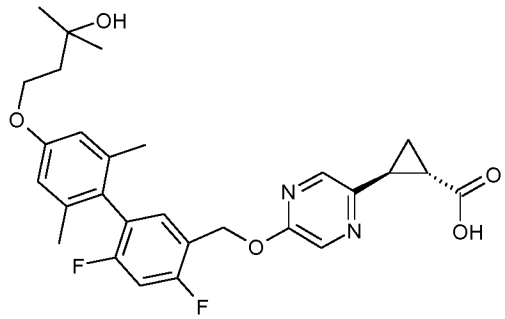
Solubility

The aqueous solubility of the compounds of the invention is determined by comparing the amount dissolved in buffer to the amount in an acetonitrile/water (1/1) solution. Starting from a 10 mM DMSO stock solution aliquots are diluted with acetonitrile/water (1/1) or buffer, respectively. After 24 h of shaking, the solutions are filtrated and analyzed by LC-UV. The amount dissolved in buffer is compared to the amount in the acetonitrile solution.

Solubility is usually being measured from 0.001 to 0.125 mg/mL at a DMSO concentration of 2.5%. If more than 90% of the compound is dissolved in buffer, the value is marked with ">".

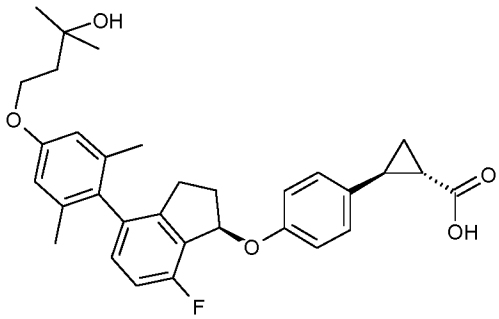
The compounds of the invention show higher solubility at medium pH value (pH 6.8) compared with their structural counterparts explicitly disclosed in WO 2013/178575. Their development and application is therefore more convenient and reliable. The following compilation shows the superiority of the compounds of this invention in terms of solubility at pH 6.8 by comparing selected compounds of this invention with their analogs from WO 2013/178575.

Example 1 in this invention:



Solubility at pH 6.8: 56 µg/mL

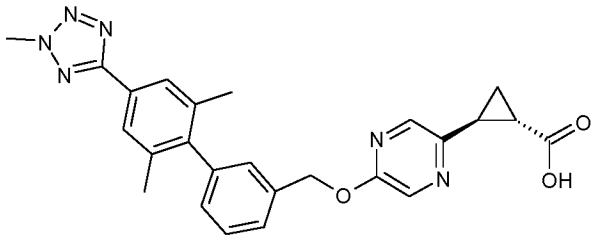
Example 17 in WO 2013/178575:



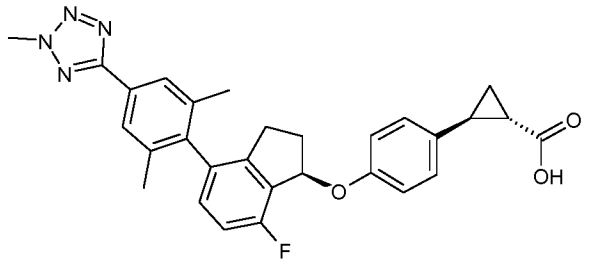
Solubility at pH 6.8: <1 µg/mL

Example 2 in this invention:

Example 45 in WO 2013/178575:



Solubility at pH 6.8: 16 µg/mL



Solubility at pH 6.8: <1 µg/mL

In view of their ability to modulate the activity of the G-protein-coupled receptor GPR40, 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 GPR40.

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

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 GPR40 in a patient, preferably in a human.

In yet another aspect the present invention relates to a method for treating a disease or condition mediated by the activation of the G-protein-coupled receptor GPR40 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.

Diseases and conditions mediated by agonists of the G-protein-coupled receptor GPR40 embrace metabolic diseases or conditions. 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.

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.

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.

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.

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

- 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);
- for improving glycaemic control and/or reducing fasting plasma glucose, postprandial plasma glucose and/or the glycosylated haemoglobin HbA1c;
- for preventing, delaying, slowing or reversing the progression of disrupted glucose tolerance, insulin resistance and/or metabolic syndrome to type 2 diabetes;

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

In particular, the compounds and pharmaceutical compositions according to the invention are suitable for the treatment of obesity, diabetes (comprising type 1 and type 2 diabetes, preferably type 2 diabetes mellitus) and/or complications of diabetes (such as for example retinopathy, nephropathy or neuropathies, diabetic foot, ulcers or macroangiopathies).

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

The dose range of the compounds of general formula **I** applicable per day is usually from 0.001 to 10 mg per kg body weight, for example from 0.01 to 8 mg per kg body weight of the patient. Each dosage unit may conveniently contain from 0.1 to 1000 mg, for example 0.5 to 500 mg.

The actual therapeutically effective amount or therapeutic dosage will of course depend on factors known by those skilled in the art such as age and weight of the patient, route of administration and severity of disease. In any case the compound or composition will be administered at dosages and in a manner which allows a therapeutically effective amount to be delivered based upon patient's unique condition.

The compounds, compositions, including any combinations with one or more additional therapeutic agents, according to the invention may be administered by

oral, transdermal, inhalative, parenteral or sublingual route. Of the possible methods of administration, oral or intravenous administration is preferred.

Pharmaceutical Compositions

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.

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

The compounds of the invention may further be combined with one or more, preferably one additional therapeutic agent. According to one embodiment the additional therapeutic agent is selected from the group of therapeutic agents useful in the treatment of diseases or conditions described hereinbefore, in particular associated with metabolic diseases or conditions such as for example diabetes mellitus, obesity, diabetic complications, hypertension, hyperlipidemia. Additional therapeutic agents which are suitable for such combinations include in particular

those which for example potentiate the therapeutic effect of one or more active substances with respect to one of the indications mentioned and/or which allow the dosage of one or more active substances to be reduced.

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

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

Therapeutic agents for the treatment of overweight and/or obesity are for example antagonists of the cannabinoid1 receptor, MCH-1 receptor antagonists, MC4 receptor agonists, NPY5 or NPY2 antagonists, β3-agonists, leptin or leptin mimetics, agonists of the 5HT2c receptor.

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, β-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.

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

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.

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 GPR40, in particular diseases or conditions as described hereinbefore and hereinafter.

In yet another aspect the present invention relates a method for treating a disease or condition mediated by the activation of the G-protein-coupled receptor GPR40 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 in hereinbefore and hereinafter,

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

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.

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.

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:

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

As a rule, ^{1}H-NMR and/or mass spectra have been obtained for the compounds prepared.

Intermediates and Examples reported in the following bearing a basic or acidic group may be obtained as a corresponding salt or neutral compound depending on the purification method and conditions employed. Salts can be transformed into their neutral counterparts by standard procedures known to the one skilled in the art.

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

Method:	1			
Device	Agilent 1200 with DA- and MS-Detector			
Column:	Sunfire C18, 3 x 30 mm, 2.5 µm			
Column Supplier:	Waters			
Gradient/Solvent Time [min]	% Solvent [H_2O,0.1%TFA]	% Solvent [Acetonitrile]	Flow [ml/min]	Temperature [°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

Method:	2			
Device	Waters Acquity, QDa Detector			
Column:	XBridge C18_3.0 x 30 mm_2.5 µm			
Column Supplier:	Waters			
Gradient/Solvent Time [min]	% Solvent [H_2O,0.1%NH_3]	% Solvent [Acetonitrile]	Flow [ml/min]	Temperature [°C]
0	95	5	1.5	60
1.3	0	100	1.5	60

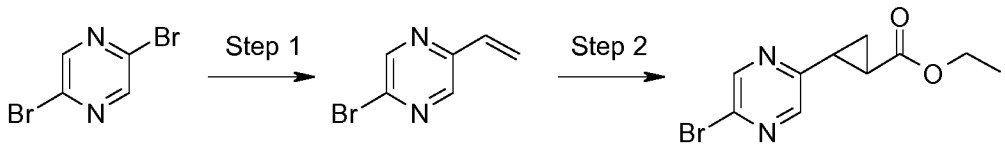
1.5	0	100	1.5	60
1.6	95	5	1.5	60

Method:	3			
Device	Waters Acquity, QDa Detector			
Column:	Sunfire C18_3.0 x 30 mm_2.5 µm			
Column Supplier:	Waters			
Gradient/Solvent Time [min]	% Solvent [H_2O,0.1%TFA]	% Solvent [Acetonitrile]	Flow [ml/min]	Temperature [°C]
0	95	5	1.5	60
1.3	0	100	1.5	60
1.5	0	100	1.5	60
1.6	95	5	1.5	60

Method:	4			
Device	Waters Acquity, QDa Detector			
Column:	XBridge C18_3.0 x 30 mm_2.5 µm			
Column Supplier:	Waters			
Gradient/Solvent Time [min]	% Solvent [H_2O,0.1%TFA]	% Solvent [Acetonitrile]	Flow [ml/min]	Temperature [°C]
0	95	5	1.5	60
1.3	0	100	1.5	60
1.5	0	100	1.5	60
1.6	95	5	1.5	60
0	95	5	1.5	60

Intermediate 1

trans-2-(5-Bromo-pyrazin-2-yl)-cyclopropanecarboxylic acid ethyl ester



Step 1: 2-Bromo-5-vinyl-pyrazine

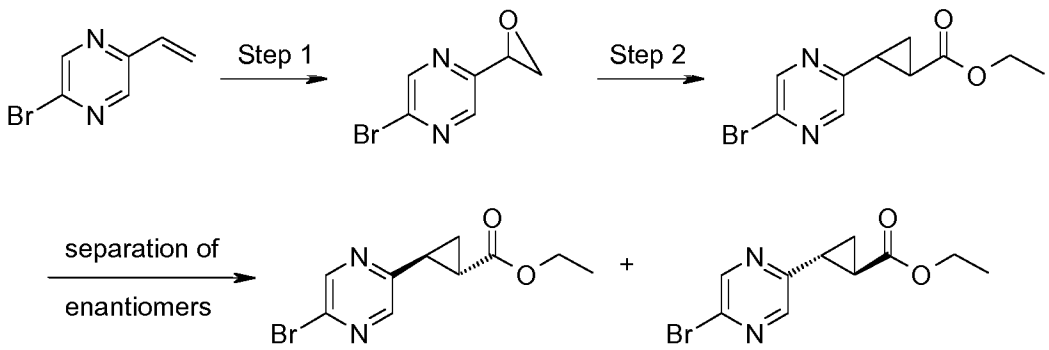
Na_2CO_3 solution (2 mol/L in water, 5.3 mL) is added to a flask charged with a stir bar, 2,5-dibromo-pyrazine (1.00 g), potassium vinyltrifluoroborate (0.56 g), tetrahydrofuran (6 mL), and toluene (2 mL) at room temperature. The mixture is purged with Ar for 5 min prior to the addition of 1,1'-bis(diphenylphosphino)ferrocene-dichloropalladium(II) (0.15 g). The mixture is stirred at 80 °C overnight. After cooling to room temperature, water and ethyl acetate are added, and the resulting mixture is filtered. The organic phase is separated and carefully concentrated. The residue is chromatographed on silica gel (cyclohexane/ethyl acetate 49:1→7:3) to give the title compound. Mass spectrum (ESI^+): m/z = 185/187 (Br) $[M+H]^+$.

Step 2: *trans*-2-(5-Bromo-pyrazin-2-yl)-cyclopropanecarboxylic acid ethyl ester

A mixture of ethyl diazoacetate (13% in dichloromethane; 2.2 mL), 2-bromo-5-vinyl-pyrazine (0.45 g), and xylene (5 mL) is stirred at 100 °C for 4 h. After cooling to room temperature, aqueous 1 M HCl solution is added, and the resulting mixture is vigorously stirred for 15 min. The mixture is extracted with ethyl acetate, and the organic extract is concentrated. The residue is chromatographed on silica gel (cyclohexane/ethyl acetate 49:1→4:1) to give the racemic *trans* configured title compound. Mass spectrum (ESI^+): m/z = 271/273 (Br) $[M+H]^+$.

Intermediate 2 and Intermediate 3

(1*S*,2*S*)-2-(5-Bromo-pyrazin-2-yl)-cyclopropanecarboxylic acid ethyl ester (Intermediate 2) and (1*R*,2*R*)-2-(5-Bromo-pyrazin-2-yl)-cyclopropanecarboxylic acid ethyl ester (Intermediate 3)



Step 1: 2-Bromo-5-oxiranyl-pyrazine

N-Bromosuccinimide (NBS, 2.51 g) is added to a flask charged with a stir bar, 2-bromo-5-vinyl-pyrazine (2.50 g), tert-butanol (18 mL), and water (38 mL) at room temperature. The mixture is stirred at 55 °C for 1.5 h. After cooling to room temperature, the mixture is cooled in an ice bath, and NaOH solution (4 mol/L in

water, 10 mL) is dropwise added. The mixture is stirred in the cooling bath for 15 min prior to the addition of water, aqueous $Na_2S_2O_3$ solution, and diethyl ether. The organic phase is separated, washed with water, and dried (Na_2SO_4). The solvent is carefully removed, and the residue is chromatographed on silica gel (cyclohexane/ethyl acetate 49:1→3:1) to give the title compound. Mass spectrum (ESI^+): m/z = 201/203 (Br) $[M+H]^+$.

Step 2: *trans*-2-(5-Bromo-pyrazin-2-yl)-cyclopropanecarboxylic acid ethyl ester

A solution of sodium tert-pentoxide (30% in 2-methyltetrahydrofuran, 6.9 mL) is added dropwise to a flask charged with a stir bar, triethyl phosphonoacetate (3.3 mL), and toluene (50 mL) at room temperature. The mixture is stirred at ca. 35 °C for 20 min prior to the addition of 2-bromo-5-oxiranyl-pyrazine (3.20 g) in toluene (15 mL). The mixture is stirred at 105 °C for 1 h. After cooling to room temperature, the mixture is washed with aqueous 1 M H_3PO_4 solution and brine and dried ($MgSO_4$). The mixture is concentrated, and the residue is chromatographed on silica gel (cyclohexane/ethyl acetate 49:1→7:3) to give the title compound. Mass spectrum (ESI^+): m/z = 271/273 (Br) $[M+H]^+$.

Chromatographic separation of the enantiomers:

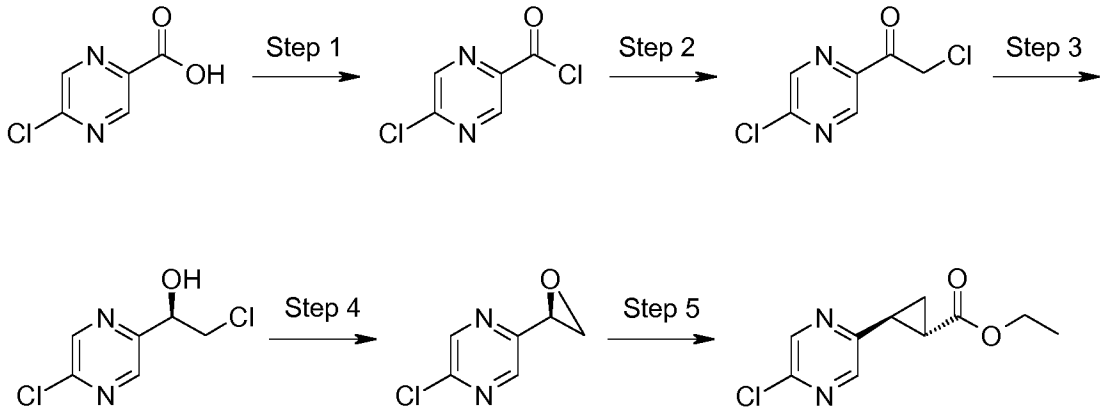
The pure enantiomers are obtained from the racemic mixture upon SFC separation on chiral phase (column: LUX® Amylose – 2 (Phenomenex Inc.), 5 µm, 250 mm x 20 mm; eluent: $scCO_2$/methanol 95:5, 40 °C, 150 bar, 60 mL/min):

(1*S*,2*S*)-2-(5-Bromo-pyrazin-2-yl)-cyclopropanecarboxylic acid ethyl ester: t_R = 2.26 min

(1*R*,2*R*)-2-(5-Bromo-pyrazin-2-yl)-cyclopropanecarboxylic acid ethyl ester: t_R = 2.00 min

Intermediate 4

(1*S*,2*S*)-2-(5-Chloro-pyrazin-2-yl)-cyclopropanecarboxylic acid ethyl ester



Step 1: 5-Chloro-pyrazine-2-carbonyl chloride

N,N-dimethylformamide (1 drop) is added to a flask charged with a stir bar, 5-chloro-pyrazine-2-carboxylic acid (13.17 g), thionyl chloride (25 mL), and toluene (200 mL) at room temperature. The mixture is stirred at 60 °C overnight. After cooling to room temperature, the mixture is concentrated, and the remainder is freed from volatile residues by three times repeated evaporation with toluene.

Step 2: 2-Chloro-1-(5-chloro-pyrazin-2-yl)-ethanone

Trimethylsilyldiazomethane (2 mol/L in hexane, 50 mL) is added dropwise over a period of 3.5 h to a stirred solution of 5-chloro-pyrazine-2-carbonyl chloride (11.80 g) in tetrahydrofuran chilled in an ice bath. After complete disappearance of the starting material (TLC or HPLC), the mixture is cooled to ca. -15 °C, and HCl in 1,4-dioxane (4 mol/L, 50 mL) is added within 1 min. The mixture is stirred for 10 min prior to the addition of water. The organic phase is separated, and the aqueous phase is extracted with ethyl acetate (80 mL). The combined organic phases are washed with water and aqueous $NaHCO_3$ solution until neutral and dried ($MgSO_4$). The mixture is filtered, and the drying agent is washed with ethyl acetate (80 mL) to give a combined solution of the title compound that is used as is in the next reaction step.

Step 3: (*R*)-1-(5-Chloro-pyrazin-2-yl)-2-chloro-ethanol

(1*S*,2*S*)-Cp*RhCl(TsNCHPhCHPhNH$_2$) (0.33 g; prepared from (1*S*,2*S*)-(+)-N-(4-toluenesulfonyl)-1,2-diphenylethylenediamine and pentamethyl-cyclopentadienyl-rhodium chloride dimer as described in, e.g., Organometallics 2009, 28, 1435-1446 or Chem. Commun. 2015, 52, 362-365; alternatively, the catalyst is prepared in situ by combining the two components in the reaction flask) is added to the solution of 2-chloro-1-(5-chloro-pyrazin-2-yl)-ethanone prepared in Step 2, and the resulting mixture is cooled to -30 °C. To this mixture is added dropwise a mixture of triethylamine and formic acid, prepared by adding triethylamine (45 mL) to formic acid

(12 mL) at room temperature and stirring the mixture for 5 min. The mixture is stirred while warming to room temperature overnight. 1 M aqueous $NaHCO_3$ solution is added, and the mixture is vigorously stirred. The mixture is filtered over Celite, and the organic phase of the filtrate is separated. The aqueous phase is extracted with ethyl acetate, and the organic phases are combined. The organic phase is washed with water and brine and dried ($MgSO_4$). The solvent is evaporated to give the title compound that is used as is in the next reaction step.

Step 4: (*R*)-2-Chloro-5-oxiranyl-pyrazine

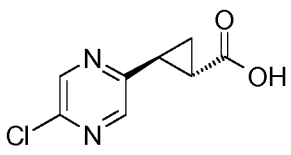
Aqueous NaOH solution (4 mol/L, 20 mL) is added to a flask charged with a stir bar, (*R*)-1-(5-chloro-pyrazin-2-yl)-2-chloro-ethanol (12.9 g), and tetrahydrofuran (80 mL) at room temperature. The mixture is stirred overnight. The mixture is diluted with ethyl acetate, and the resulting mixture is washed with 1 M aqueous H_3PO_4 solution and brine, dried ($MgSO_4$), and concentrated. The residue is chromatographed on silica gel (petrol ether/ethyl acetate) to give the title compound. Mass spectrum (ESI^+): m/z = 157/159 (Cl) $[M+H]^+$.

Step 5: (1*S*,2*S*)-2-(5-Chloro-pyrazin-2-yl)-cyclopropanecarboxylic acid ethyl ester

A solution of sodium tert-pentoxide (70 g) in tetrahydrofuran (250 mL) is added over 15 min to a flask charged with a stir bar and triethyl phosphonoacetate (125 mL) chilled in an ice bath. The mixture is stirred with cooling for 15 min and at room temperature for 30 min. The mixture is then added dropwise over a period of 45 min to a solution of (*R*)-2-chloro-5-oxiranyl-pyrazine (34.3 g) in toluene (125 mL) at 90 °C. The mixture is stirred at 90 °C for additional 15 min and then at room temperature for 1 h. The mixture is slightly acidified (pH ca. 5-6) with aqueous 1 M H_3PO_4 solution. The organic phase is separated, and the aqueous phase is extracted with ethyl acetate. The combined organic phases are washed with water and brine, dried ($MgSO_4$), and concentrated. The residue is chromatographed on silica gel (petrol ether/ethyl acetate) to give the title compound. Mass spectrum (ESI^+): m/z = 227/229 (Cl) $[M+H]^+$.

Intermediate 5

(1S,2S)-2-(5-Chloro-pyrazin-2-yl)-cyclopropanecarboxylic acid



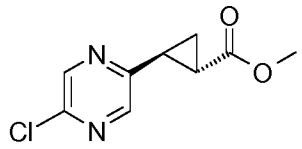
Aqueous 4 M NaOH solution (45 mL) is added to a flask charged with a stir bar, (1S,2S)-2-(5-chloro-pyrazin-2-yl)-cyclopropanecarboxylic acid ethyl ester (27.2 g), and tetrahydrofuran (160 mL) at room temperature. The mixture is stirred at room temperature overnight. Water (80 mL) is added, and most of the tetrahydrofuran is evaporated. The aqueous residue is washed with diethylether and then adjusted to pH value 4-5 using aqueous 4 M HCl solution. The mixture is stirred for 30 min, and the precipitate formed is separated by filtration, washed with water, and dried in a desiccator to give a first batch of the title compound. The aqueous filtrate is adjusted to pH value 1 with aqueous 4 M HCl solution and extracted with ethyl acetate. The combined extract is washed with brine, dried ($MgSO_4$), and concentrated to give a second batch of the title compound. Mass spectrum (ESI^-): m/z = 197/199 (Cl) $[M-H]^-$.

The enantiomeric purities (ee) of batches of Intermediate 5, obtained from Intermediate 4 and hydrolyzed as described above, are commonly between 40% and 80%.

The enantiomeric purity of batches of Intermediate 5 may be increased to >95% ee by employing the following procedure:
(*S*)-1-Phenylethylamine (11.6 mL) is added to a solution of (1S,2S)-2-(5-chloro-pyrazin-2-yl)-cyclopropanecarboxylic acid (18.1 g) in isopropanol (270 mL) at 80 °C. The solution is stirred at 80 °C for 15 min and then left standing without stirring at room temperature overnight. The precipitate is separated by filtration, washed with isopropanol, and dried at 40 °C to give (*S*)-1-phenylethylammonium (1S,2S)-2-(5-chloro-pyrazin-2-yl)-cyclopropanecarboxylate (if the diasteromeric purity of the ammonium salt is not sufficient the precipitate is again recrystallized from isopropanol).
The (*S*)-1-phenylethylammonium carboxylate (14.8 g) is suspended in ethyl acetate (60 mL), and aqueous 1 M HCl solution (47 mL) is added. The mixture is stirred until all solid is dissolved. The organic phase is separated and washed with brine. The organic phase is dried ($MgSO_4$) and concentrated. The residue is recrystallized form diethyl ether/pentane to give (1S,2S)-2-(5-chloro-pyrazin-2-yl)-cyclopropane-carboxylic acid in up to enantiomerically pure form.

Intermediate 6

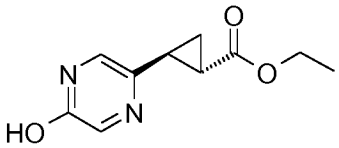
(1S,2S)-2-(5-Chloro-pyrazin-2-yl)-cyclopropanecarboxylic acid methyl ester



Trimethylsilyldiazomethane (2 mol/L in hexane, 15.7 mL) is added dropwise to a flask charged with a stir bar, (1S,2S)-2-(5-chloro-pyrazin-2-yl)-cyclopropanecarboxylic acid (5.00 g), dichloromethane (90 mL), and methanol (10 mL) chilled in an ice bath. The mixture is stirred in the cooling bath for 15 min and then at room temperature for 30 min. Methanol (40 mL) is added, and the solution is stirred for 20 min. The solution is concentrated to give the title compound. Mass spectrum (ESI^-): m/z = 213/215 (Cl) $[M-H]^-$.

Intermediate 7

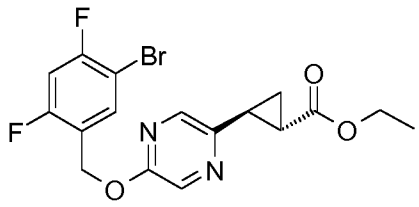
(1*S*,2*S*)-2-(5-Hydroxy-pyrazin-2-yl)-cyclopropanecarboxylic acid ethyl ester



Acetoxyhydroxamic acid (0.93 g) and K_2CO_3 (2.84 g) are added to a flask charged with a stir bar, (1*S*,2*S*)-2-(5-chloro-pyrazin-2-yl)-cyclopropanecarboxylic acid ethyl ester (0.93 g) and dimethylsulfoxide (8 mL) at room temperature. The mixture is stirred at 85 °C for 0.5 h. After cooling to room temperature, water is added, and the resulting mixture is extracted with ethyl acetate. The aqueous phase is acidified (pH ca. 5) with aqueous 1 M H_3PO_4 and extracted again with ethyl acetate. The combined extracts are concentrated and treated with little ethyl acetate and diethyl ether. The precipitate is separated by filtration and dried at reduced pressure to give a first batch of the title compound. The filtrate is concentrated and chromatographed (HPLC; water/acetonitrile/trifluoroacetic acid) to give a second batch of the title compound. Mass spectrum (ESI^+): m/z = 209 $[M+H]^+$.

Intermediate 8

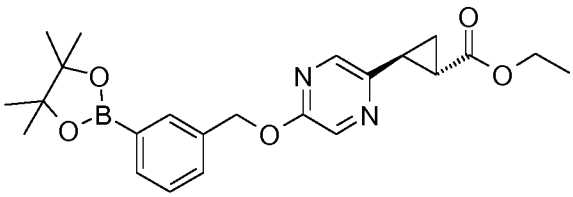
(1*S*,2*S*)-2-[5-(5-Bromo-2,4-difluoro-benzyloxy)-pyrazin-2-yl]-cyclopropanecarboxylic acid ethyl ester



Diisopropyl azodicarboxylate (57 µL) is added to a flask charged with a stir bar, (5-bromo-2,4-difluoro-phenyl)-methanol (54 mg), (1*S*,2*S*)-2-(5-hydroxy-pyrazin-2-yl)-cyclopropanecarboxylic acid ethyl ester (50 mg), triphenylphosphine (76 mg), and toluene (2 mL) at room temperature. The mixture is stirred at room temperature for 30 min. Water is added, and the resulting mixture is extracted with ethyl acetate. The combined organic extracts are concentrated, and the residue is chromatographed (HPLC; water/acetonitrile/trifluoroacetic acid) to give the title compound. Mass spectrum (ESI$^+$): m/z = 413/415 (Br) $[M+H]^+$.

Intermediate 9

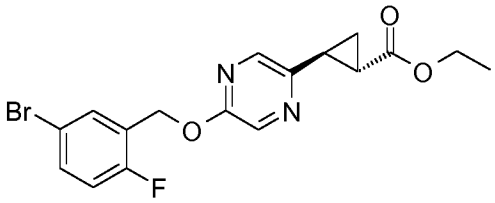
(1*S*,2*S*)-2-{5-[3-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzyloxy]-pyrazin-2-yl}-cyclopropanecarboxylic acid ethyl ester



A mixture of Ag_2CO_3 (1.39 g), (1*S*,2*S*)-2-(5-hydroxy-pyrazin-2-yl)-cyclopropanecarboxylic acid ethyl ester (0.70 g), and toluene (2 mL) is stirred at 80 °C overnight. After cooling to room temperature, water and ethyl acetate are added, and the mixture is filtered. The filtrate is extracted with ethyl acetate, and the combined extracts are concentrated. The residue is chromatographed on silica gel (cyclohexane/ethyl acetate 4:1) to give the title compound. Mass spectrum (ESI$^+$): m/z = 425 $[M+H]^+$.

Intermediate 10

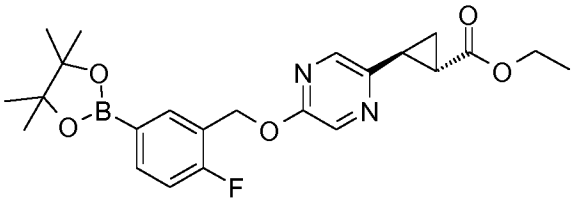
(1*S*,2*S*)-2-[5-(5-Bromo-2-fluoro-benzyloxy)-pyrazin-2-yl]-cyclopropanecarboxylic acid ethyl ester



The title compound is prepared from (1*S*,2*S*)-2-(5-hydroxy-pyrazin-2-yl)-cyclopropanecarboxylic acid ethyl ester and 4-bromo-2-bromomethyl-1-fluoro-benzene following a procedure analogous to that described for Intermediate 9. Mass spectrum (ESI$^+$): m/z = 395/397 (Br) $[M+H]^+$.

Intermediate 11

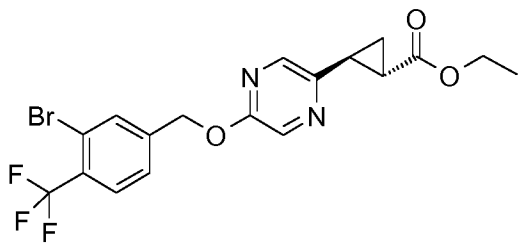
(1*S*,2*S*)-2-{5-[2-Fluoro-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzyloxy]-pyrazin-2-yl}-cyclopropanecarboxylic acid ethyl ester



A flask charged with a stir bar, (1*S*,2*S*)-2-[5-(5-bromo-2-fluoro-benzyloxy)-pyrazin-2-yl]-cyclopropanecarboxylic acid ethyl ester (1.20 g), bis(pinacolato)diboron (0.77 g), potassium acetate (0.60 g), and 1,4-dioxane (20 mL) is purged with Ar for 10 min. 1,1'-Bis(diphenylphosphino)ferrocene-dichloropalladium(II) (44 mg) is added, and the mixture is stirred at reflux temperature for 1 h. After cooling to room temperature, the mixture is diluted with water and extracted with ethyl acetate. The combined organic phase is treated with charcoal, filtered, and concentrated. The residue is chromatographed on silica gel (cyclohexane/ethyl acetate 49:1->3:1) to give the title compound. Mass spectrum (ESI$^+$): m/z = 443 $[M+H]^+$.

Intermediate 12

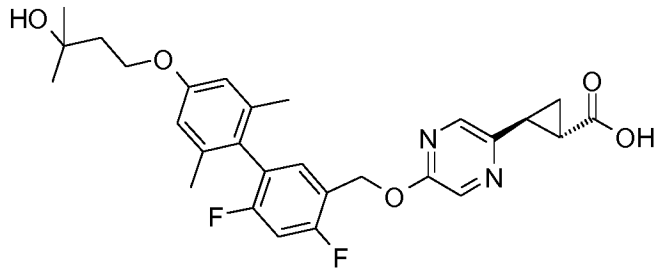
(1*S*,2*S*)-2-[5-(3-Bromo-4-trifluoromethyl-benzyloxy)-pyrazin-2-yl]-cyclopropane-carboxylic acid ethyl ester



The title compound is prepared from (1*S*,2*S*)-2-(5-hydroxy-pyrazin-2-yl)-cyclopropanecarboxylic acid ethyl ester and 2-bromo-4-bromomethyl-1-trifluoromethyl-benzene following a procedure analogous to that described for Intermediate 9. Mass spectrum (ESI^+): m/z = 445/447 (Br) $[M+H]^+$.

Example 1

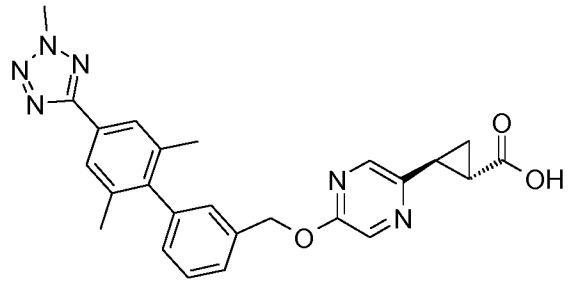
(1*S*,2*S*)-2-{5-[4,6-Difluoro-4'-(3-hydroxy-3-methyl-butoxy)-2',6'-dimethyl-biphenyl-3-ylmethoxy]-pyrazin-2-yl}-cyclopropanecarboxylic acid



A vial charged with a stir bar, (1*S*,2*S*)-2-[5-(5-bromo-2,4-difluoro-benzyloxy)-pyrazin-2-yl]-cyclopropanecarboxylic acid ethyl ester (50% ee; 50 mg), [4-(3-hydroxy-3-methyl-butoxy)-2,6-dimethyl-phenyl]-boronic acid (32 mg), K_3PO_4 (131 mg), water (1 mL), and 1,4 dioxane (3 mL) is purged with Ar for 10 min. Bis[di-tert-butyl-(4-dimethylaminophenyl)-phosphine]dichloropalladium(II) ($PdCl_2(Amphos)_2$; 3 mg) is added, and the mixture is stirred at 90 °C for 1 h. After cooling to room temperature, 4 M aqueous NaOH solution (0.5 mL) and methanol (1 mL) are added, and the mixture is stirred for 1 h. 4 M aqueous HCl solution (0.5 mL) is added, and the resulting mixture is filtered. The filtrate is chromatographed (HPLC; acetonitrile/water/ammonia) to give the title compound. LC (method 1): t_R = 0.83 min; Mass spectrum (ESI^-): m/z = 511 $[M-H]^-$.

Example 2

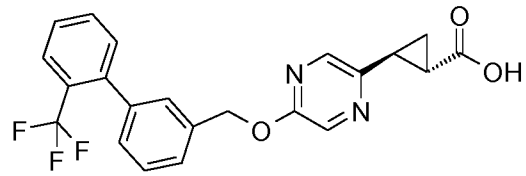
(1*S*,2*S*)-2-{5-[2',6'-Dimethyl-4'-(2-methyl-2H-tetrazol-5-yl)-biphenyl-3-ylmethoxy]-pyrazin-2-yl}-cyclopropanecarboxylic acid



A vial charged with a stir bar, (1*S*,2*S*)-2-{5-[3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzyloxy]-pyrazin-2-yl}-cyclopropanecarboxylic acid ethyl ester (50% ee; 50 mg), 5-(4-bromo-3,5-dimethyl-phenyl)-2-methyl-2H-tetrazole (31 mg), K_3PO_4 (128 mg), water (1 mL), and 1,4 dioxane (3 mL) is purged with Ar for 10 min. Bis[di-tert-butyl-(4-dimethylaminophenyl)-phosphine]dichloropalladium(II) ($PdCl_2(Amphos)_2$; 3 mg) is added, and the mixture is stirred at 90 °C for 1 h. After cooling to room temperature, 4 M aqueous NaOH solution (0.5 mL) and methanol (1 mL) are added, and the mixture is stirred for 1 h. 4 M aqueous HCl solution (0.5 mL) is added, and the resulting mixture is filtered. The filtrate is chromatographed (HPLC; acetonitrile/water/trifluoroacetic acid) to give the title compound. LC (method 1): t_R = 1.12 min; Mass spectrum (ESI^+): m/z = 457 $[M+H]^+$.

Example 3

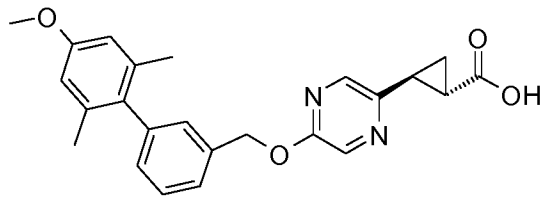
(1*S*,2*S*)-2-[5-(2'-Trifluoromethyl-biphenyl-3-ylmethoxy)-pyrazin-2-yl]-cyclopropanecarboxylic acid



The title compound is prepared from (1*S*,2*S*)-2-{5-[3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzyloxy]-pyrazin-2-yl}-cyclopropanecarboxylic acid ethyl ester (50% ee) and 2-iodobenzotrifluoride following a procedure analogous to that described for Example 1. LC (method 2): t_R = 0.56 min; Mass spectrum (ESI^+): m/z = 415 $[M+H]^+$.

Example 4

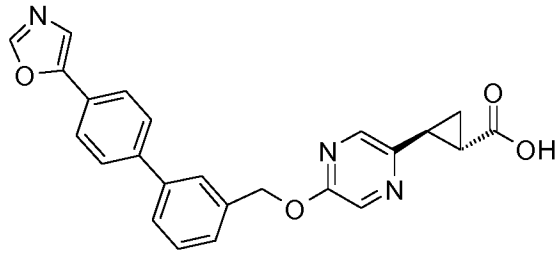
(1*S*,2*S*)-2-[5-(4'-Methoxy-2',6'-dimethyl-biphenyl-3-ylmethoxy)-pyrazin-2-yl]-cyclopropanecarboxylic acid



The title compound is prepared from (1*S*,2*S*)-2-{5-[3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzyloxy]-pyrazin-2-yl}-cyclopropanecarboxylic acid ethyl ester (50% ee) and 4-bromo-3,5-dimethyl-anisole following a procedure analogous to that described for Example 1. LC (method 2): t_R = 0.56 min; Mass spectrum (ESI$^+$): m/z = 405 $[M+H]^+$.

Example 5

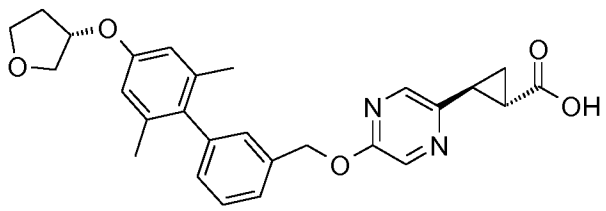
(1*S*,2*S*)-2-[5-(4'-Oxazol-5-yl-biphenyl-3-ylmethoxy)-pyrazin-2-yl]-cyclopropane-carboxylic acid



The title compound is prepared from (1*S*,2*S*)-2-{5-[3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzyloxy]-pyrazin-2-yl}-cyclopropanecarboxylic acid ethyl ester (50% ee) and 5-(4-bromophenyl)-1,3-oxazole following a procedure analogous to that described for Example 1. LC (method 2): t_R = min; Mass spectrum (ESI$^+$): m/z = 414 $[M+H]^+$.

Example 6

(1*S*,2*S*)-2-(5-{2',6'-Dimethyl-4'-[(*S*)-(tetrahydro-furan-3-yl)oxy]-biphenyl-3-ylmethoxy}-pyrazin-2-yl)-cyclopropanecarboxylic acid

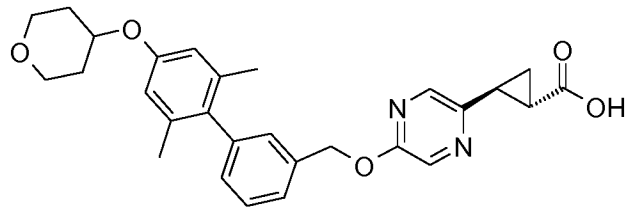


The title compound is prepared from (1*S*,2*S*)-2-{5-[3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzyloxy]-pyrazin-2-yl}-cyclopropanecarboxylic acid ethyl

ester (50% ee) and (*S*)-3-(4-bromo-3,5-dimethyl-phenoxy)-tetrahydrofuran following a procedure analogous to that described for Example 1. LC (method 2): t_R = 0.55 min; Mass spectrum (ESI^+): m/z = 461 $[M+H]^+$.

Example 7

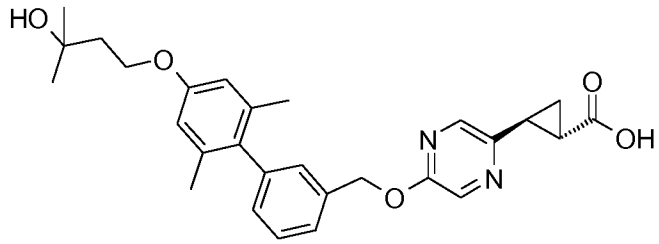
(1*S*,2*S*)-2-{5-[2',6'-Dimethyl-4'-(tetrahydro-pyran-4-yloxy)-biphenyl-3-ylmethoxy]-pyrazin-2-yl}-cyclopropanecarboxylic acid



The title compound is prepared from (1*S*,2*S*)-2-{5-[3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzyloxy]-pyrazin-2-yl}-cyclopropanecarboxylic acid ethyl ester (50% ee) and 4-(4-bromo-3,5-dimethyl-phenoxy)-tetrahydropyran following a procedure analogous to that described for Example 1. LC (method 2): t_R = min; Mass spectrum (ESI^+): m/z = 475 $[M+H]^+$.

Example 8

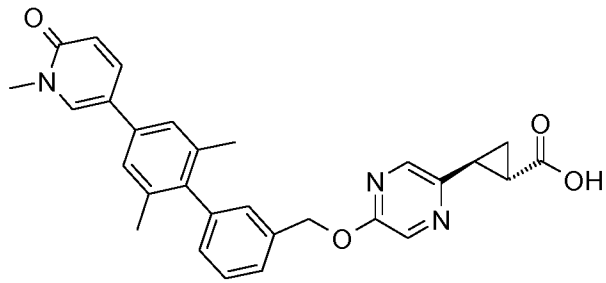
(1*S*,2*S*)-2-{5-[4'-(3-Hydroxy-3-methyl-butoxy)-2',6'-dimethyl-biphenyl-3-ylmethoxy]-pyrazin-2-yl}-cyclopropanecarboxylic acid



The title compound is prepared from (1*S*,2*S*)-2-{5-[3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzyloxy]-pyrazin-2-yl}-cyclopropanecarboxylic acid ethyl ester (50% ee) and 4-(4-bromo-3,5-dimethyl-phenoxy)-2-methyl-butan-2-ol following a procedure analogous to that described for Example 1. LC (method 2): t_R = 0.56 min; Mass spectrum (ESI^+): m/z = 477 $[M+H]^+$.

Example 9

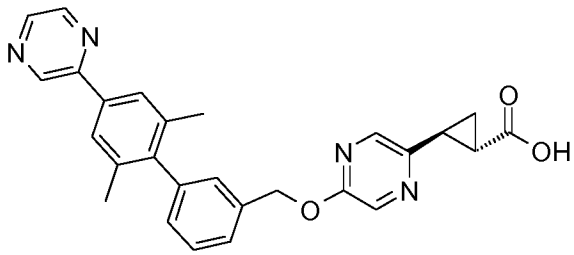
(1*S*,2*S*)-2-{5-[2',6'-Dimethyl-4'-(1-methyl-6-oxo-1,6-dihydro-pyridin-3-yl)-biphenyl-3-ylmethoxy]-pyrazin-2-yl}-cyclopropanecarboxylic acid



The title compound is prepared from (1*S*,2*S*)-2-{5-[3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzyloxy]-pyrazin-2-yl}-cyclopropanecarboxylic acid ethyl ester (50% ee) and 5-(4-bromo-3,5-dimethyl-phenyl)-1-methyl-1H-pyridin-2-one following a procedure analogous to that described for Example 2. LC (method 3): t_R = min; Mass spectrum (ESI^+): m/z = 482 $[M+H]^+$.

Example 10

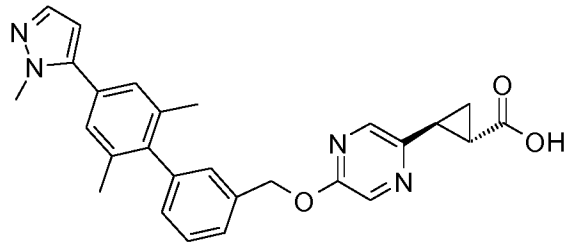
(1*S*,2*S*)-2-[5-(2',6'-Dimethyl-4'-pyrazin-2-yl-biphenyl-3-ylmethoxy)-pyrazin-2-yl]-cyclopropanecarboxylic acid



The title compound is prepared from (1*S*,2*S*)-2-{5-[3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzyloxy]-pyrazin-2-yl}-cyclopropanecarboxylic acid ethyl ester (50% ee) and 2-(4-bromo-3,5-dimethyl-phenyl)-pyrazine following a procedure analogous to that described for Example 1. LC (method 2): t_R = 0.53 min; Mass spectrum (ESI^+): m/z = 453 $[M+H]^+$.

Example 11

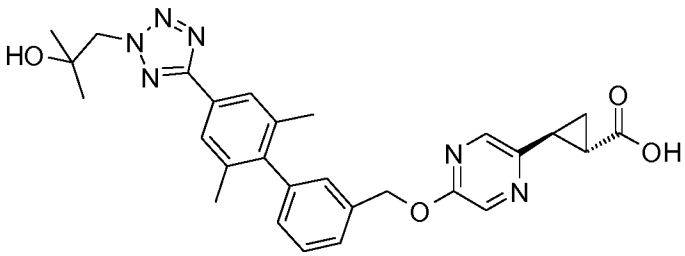
(1*S*,2*S*)-2-{5-[2',6'-Dimethyl-4'-(2-methyl-2H-pyrazol-3-yl)-biphenyl-3-ylmethoxy]-pyrazin-2-yl}-cyclopropanecarboxylic acid



The title compound is prepared from (1*S*,2*S*)-2-{5-[3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzyloxy]-pyrazin-2-yl}-cyclopropanecarboxylic acid ethyl ester (50% ee) and 5-(4-bromo-3,5-dimethyl-phenyl)-1-methyl-1H-pyrazole following a procedure analogous to that described for Example 1. LC (method 2): t_R = 0.55 min; Mass spectrum (ESI^+): m/z = 455 $[M+H]^+$.

Example 12

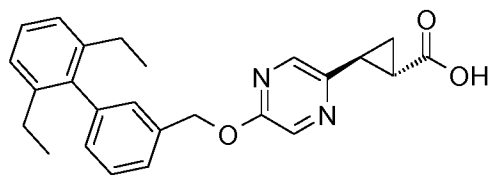
(1*S*,2*S*)-2-(5-{4'-[2-(2-Hydroxy-2-methyl-propyl)-2H-tetrazol-5-yl]-2',6'-dimethyl-biphenyl-3-ylmethoxy}-pyrazin-2-yl)-cyclopropanecarboxylic acid



The title compound is prepared from (1*S*,2*S*)-2-{5-[3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzyloxy]-pyrazin-2-yl}-cyclopropanecarboxylic acid ethyl ester (50% ee) and 1-[5-(4-bromo-3,5-dimethyl-phenyl)-tetrazol-2-yl]-2-methyl-propan-2-ol following a procedure analogous to that described for Example 1. LC (method 2): t_R = 0.51 min; Mass spectrum (ESI^+): m/z = 515 $[M+H]^+$.

Example 13

(1*S*,2*S*)-2-[5-(2',6'-Diethyl-biphenyl-3-ylmethoxy)-pyrazin-2-yl]-cyclopropane-carboxylic acid

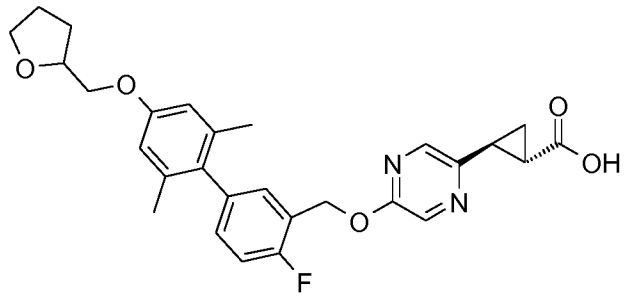


The title compound is prepared from (1*S*,2*S*)-2-{5-[3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzyloxy]-pyrazin-2-yl}-cyclopropanecarboxylic acid ethyl

ester (50% ee) and 2-bromo-2,6-diethyl-benzene following a procedure analogous to that described for Example 2. LC (method 3): t_R = 1.16 min; Mass spectrum (ESI^+): m/z = 403 $[M+H]^+$.

Example 14

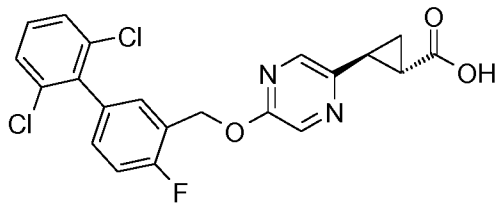
(1*S*,2*S*)-2-{5-[4-Fluoro-2',6'-dimethyl-4'-(tetrahydro-furan-2-ylmethoxy)-biphenyl-3-ylmethoxy]-pyrazin-2-yl}-cyclopropanecarboxylic acid



The title compound is prepared from (1*S*,2*S*)-2-{5-[2-fluoro-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzyloxy]-pyrazin-2-yl}-cyclopropanecarboxylic acid ethyl ester (47% ee) and 2-(4-bromo-3,5-dimethyl-phenoxymethyl)-tetrahydrofuran following a procedure analogous to that described for Example 1. LC (method 4): t_R = 0.56 min; Mass spectrum (ESI^+): m/z = 493 $[M+H]^+$.

Example 15

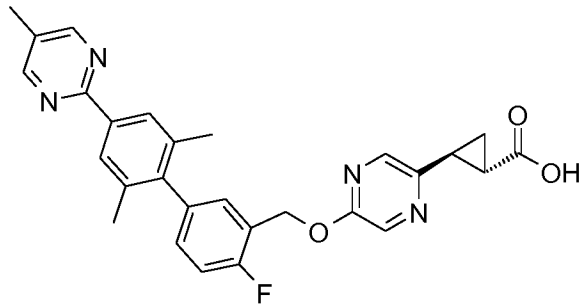
(1*S*,2*S*)-2-[5-(2',6'-Dichloro-4-fluoro-biphenyl-3-ylmethoxy)-pyrazin-2-yl]-cyclopropanecarboxylic acid



The title compound is prepared from (1*S*,2*S*)-2-{5-[2-fluoro-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzyloxy]-pyrazin-2-yl}-cyclopropanecarboxylic acid ethyl ester (47% ee) and 2,6-dichloro-iodobenzene following a procedure analogous to that described for Example 1. LC (method 4): t_R = 0.54 min; Mass spectrum (ESI^+): m/z = 433/435/437 (2 Cl) $[M+H]^+$.

Example 16

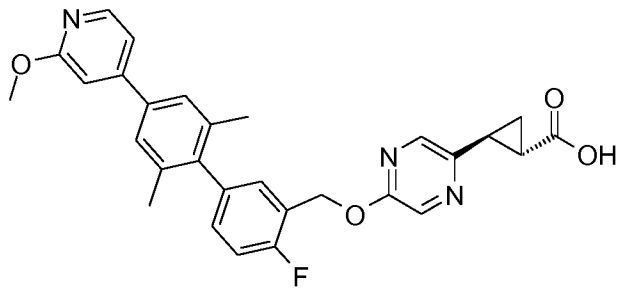
(1*S*,2*S*)-2-{5-[4-Fluoro-2',6'-dimethyl-4'-(5-methyl-pyrimidin-2-yl)-biphenyl-3-ylmethoxy]-pyrazin-2-yl}-cyclopropanecarboxylic acid



The title compound is prepared from (1*S*,2*S*)-2-{5-[2-fluoro-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzyloxy]-pyrazin-2-yl}-cyclopropanecarboxylic acid ethyl ester (47% ee) and 2-(4-chloro-3,5-dimethyl-phenyl)-5-methyl-pyrimidine following a procedure analogous to that described for Example 1. LC (method 2): t_R = 0.56 min; Mass spectrum (ESI^+): m/z = 485 $[M+H]^+$.

Example 17

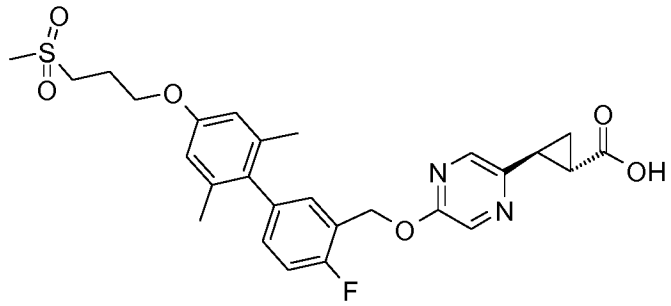
(1*S*,2*S*)-2-{5-[4-Fluoro-4'-(2-methoxy-pyridin-4-yl)-2',6'-dimethyl-biphenyl-3-ylmethoxy]-pyrazin-2-yl}-cyclopropanecarboxylic acid



The title compound is prepared from (1*S*,2*S*)-2-{5-[2-fluoro-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzyloxy]-pyrazin-2-yl}-cyclopropanecarboxylic acid ethyl ester (47% ee) and 5-(4-bromo-3,5-dimethyl-phenyl)-2-methoxy-pyridine following a procedure analogous to that described for Example 1. LC (method 4): t_R = 0.60 min; Mass spectrum (ESI^+): m/z = 500 $[M+H]^+$.

Example 18

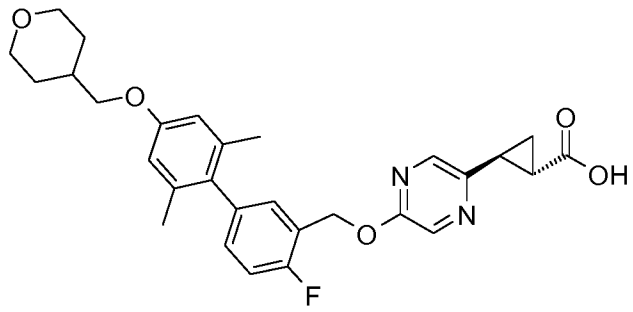
(1*S*,2*S*)-2-{5-[4-Fluoro-4'-(3-methanesulfonyl-propoxy)-2',6'-dimethyl-biphenyl-3-ylmethoxy]-pyrazin-2-yl}-cyclopropanecarboxylic acid



The title compound is prepared from (1*S*,2*S*)-2-{5-[2-fluoro-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzyloxy]-pyrazin-2-yl}-cyclopropanecarboxylic acid ethyl ester (47% ee) and 2-bromo-5-(3-methanesulfonyl-propoxy)-1,3-dimethyl-benzene following a procedure analogous to that described for Example 1. LC (method 4): t_R = 0.50 min; Mass spectrum (ESI^+): m/z = 529 $[M+H]^+$.

Example 19

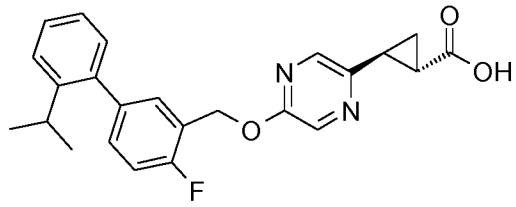
(1*S*,2*S*)-2-{5-[4-Fluoro-2',6'-dimethyl-4'-(tetrahydro-pyran-4-ylmethoxy)-biphenyl-3-ylmethoxy]-pyrazin-2-yl}-cyclopropanecarboxylic acid



The title compound is prepared from (1*S*,2*S*)-2-{5-[2-fluoro-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzyloxy]-pyrazin-2-yl}-cyclopropanecarboxylic acid ethyl ester (47% ee) and 4-(4-bromo-3,5-dimethyl-phenoxymethyl)-tetrahydropyrane following a procedure analogous to that described for Example 1. LC (method 4): t_R = 0.58 min; Mass spectrum (ESI^+): m/z = 507 $[M+H]^+$.

Example 20

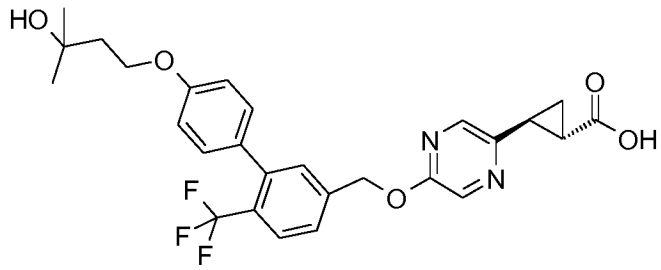
(1*S*,2*S*)-2-[5-(4-Fluoro-2'-isopropyl-biphenyl-3-ylmethoxy)-pyrazin-2-yl]-cyclopropanecarboxylic acid



The title compound is prepared from (1*S*,2*S*)-2-{5-[2-fluoro-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzyloxy]-pyrazin-2-yl}-cyclopropanecarboxylic acid ethyl ester (47% ee) and 1-bromo-2-isopropyl-benzene following a procedure analogous to that described for Example 1. LC (method 4): t_R = 0.57 min; Mass spectrum (ESI$^+$): m/z = 407 $[M+H]^+$.

Example 21

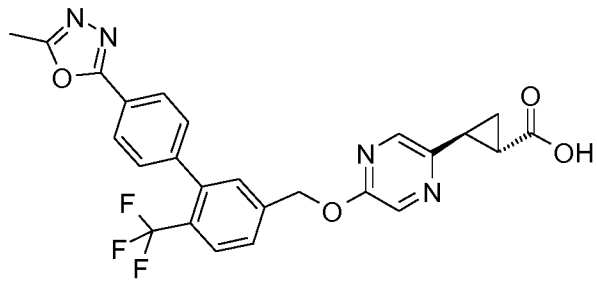
(1*S*,2*S*)-2-{5-[4'-(3-Hydroxy-3-methyl-butoxy)-6-trifluoromethyl-biphenyl-3-ylmethoxy]-pyrazin-2-yl}-cyclopropanecarboxylic acid



The title compound is prepared from (1*S*,2*S*)-2-[5-(3-bromo-4-trifluoromethyl-benzyloxy)-pyrazin-2-yl]-cyclopropane-carboxylic acid ethyl ester (47% ee) and 2-methyl-4-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenoxy]-butan-2-ol following a procedure analogous to that described for Example 1. LC (method 1): t_R = 1.15 min; Mass spectrum (ESI$^+$): m/z = 499 $[M-OH]^+$.

Example 22

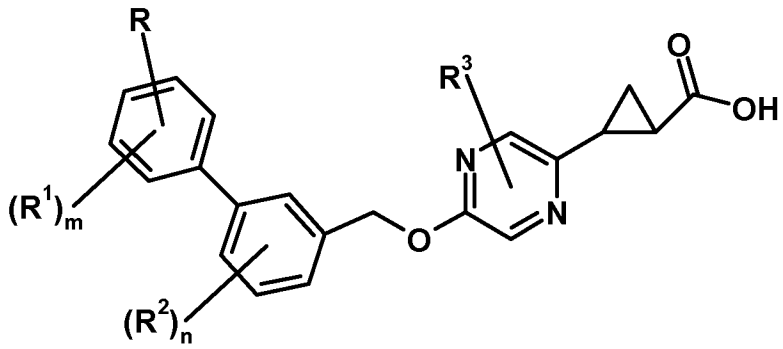
(1*S*,2*S*)-2-{5-[4'-(5-Methyl-[1,3,4]oxadiazol-2-yl)-6-trifluoromethyl-biphenyl-3-ylmethoxy]-pyrazin-2-yl}-cyclopropanecarboxylic acid



The title compound is prepared from (1*S*,2*S*)-2-[5-(3-bromo-4-trifluoromethyl-benzyloxy)-pyrazin-2-yl]-cyclopropane-carboxylic acid ethyl ester (47% ee) and 4-(5-methyl-[1,3,4]oxadiazol-2-yl)-phenylboronic acid following a procedure analogous to that described for Example 1. LC (method 1): t_R = 1.10 min; Mass spectrum (ESI^+): m/z = 497 $[M+H]^+$.

Claims

1. A compound of formula (**I**)



I,

wherein

R is selected from the group consisting of
H, F, Cl, Br, I, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{3-6}-cycloalkyl, NC-, HNR^N-C(=O)-, C_{1-4}-alkyl-NR^N-C(=O)-, C_{3-6}-cycloalkyl-NR^N-C(=O)-, heterocyclyl-NR^N-C(=O)-, heteroaryl-NR^N-C(=O)-, HOOC-, C_{1-4}-alkyl-O-C(=O)-, O_2N-, HR^NN-, C_{1-4}-alkyl-R^NN-, C_{1-4}-alkyl-C(=O)NR^N-, C_{3-6}-cycloalkyl-C(=O)NR^N-, heterocyclyl-C(=O)NR^N-, heteroaryl-C(=O)NR^N-, C_{1-4}-alkyl-$S(=O)_2NR^N$-, C_{3-6}-cycloalkyl-$S(=O)_2NR^N$-, heterocyclyl-$S(=O)_2NR^N$-, heteroaryl-$S(=O)_2NR^N$-, HO-, C_{1-6}-alkyl-O-, HOOC-C_{1-3}-alkyl-O-, C_{3-6}-cycloalkyl-C_{1-3}-alkyl-O-, heterocyclyl-C_{1-3}-alkyl-O-, phenyl-C_{1-3}-alkyl-O-, C_{3-6}-cycloalkyl-O-, heterocyclyl-O-, heteroaryl-O-, C_{1-4}-alkyl-S-, C_{3-6}-cycloalkyl-S-, heterocyclyl-S-, C_{1-4}-alkyl-S(=O)-, C_{3-6}-cycloalkyl-S(=O)-, heterocyclyl-S(=O)-, C_{1-4}-alkyl-$S(=O)_2$-, C_{3-6}-cycloalkyl-$S(=O)_2$-, heterocyclyl-$S(=O)_2$-, phenyl-$S(=O)_2$-, heteroaryl-$S(=O)_2$-, HNR^N-$S(=O)_2$-, C_{1-4}-alkyl-NR^N-$S(=O)_2$-, heterocyclyl, phenyl, and heteroaryl,
wherein each alkyl, cycloalkyl, and heterocyclyl group or sub-group within the groups forming R is optionally substituted with 1 or more F atoms and optionally substituted with 1 to 3 groups independently selected from Cl, C_{1-3}-alkyl, NC-, $(R^N)_2N$-, HO-, C_{1-3}-alkyl-O-, and C_{1-3}-alkyl-$S(=O)_2$-; and
wherein each phenyl and heteroaryl group or sub-group within the groups forming R is optionally substituted with 1 to 5 substituents independently

selected from F, Cl, C_{1-3}-alkyl, HF_2C-, F_3C-, NC-, $(R^N)_2N$-, HO-, C_{1-3}-alkyl-O-, F_3C-O-, and C_{1-3}-alkyl-$S(=O)_2$-;

wherein each heterocyclyl group or sub-group within the groups forming R is selected from

a cyclobutyl group wherein 1 CH_2 group is replaced by -NR^N- or -O-;

a C_{5-6}-cycloalkyl group wherein 1 CH_2 group is replaced by -C(=O)-, -NR^N-, -O-, -S- or -$S(=O)_2$- and/or 1 CH group is replaced by N;

a C_{5-6}-cycloalkyl group wherein 1 CH_2 group is replaced by -NR^N- or -O-, a second CH_2 group is replaced by -NR^N-, -C(=O)- or -$S(=O)_2$- and/or 1 CH group is replaced by N; and

a C_{5-6}-cycloalkyl group wherein 2 CH_2 groups are replaced by -NR^N- or 1 CH_2 group by -NR^N- and the other by -O- and a third CH_2 group is replaced by -C(=O)- or -$S(=O)_2$- and/or 1 CH group is replaced by N;

wherein each heteroaryl group or sub-group within the groups forming R is selected from

tetrazolyl 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-, wherein in heteroaromatic groups containing a -HC=N- unit this group is optionally replaced by -NR^N-C(=O)-;

wherein in heteroaryl and heterocyclyl rings with one or more NH groups, each of said NH groups is replaced by NR^N;

R^1 is selected from the group consisting of H, F, Cl, C_{1-4}-alkyl, C_{3-6}-cycloalkyl-, HO-C_{1-4}-alkyl, C_{1-4}-alkyl-O-C_{1-4}-alkyl, NC-, HO-, C_{1-4}-alkyl-O-, C_{3-6}-cycloalkyl-O-, C_{1-4}-alkyl-S-, C_{1-4}-alkyl-S(O)-, and C_{1-4}-alkyl-$S(O)_2$-,

wherein any alkyl and cycloalkyl group or sub-group within the groups forming R^1 is optionally substituted with 1 or more F atoms, and wherein multiple R^1 may be identical or different if m is 2, 3 or 4;

m is an integer selected from 1, 2, 3, and 4;

R^2 is selected from the group consisting of H, F, Cl, C_{1-4}-alkyl, NC-, and C_{1-4}-alkyloxy,

wherein any alkyl group or sub-group within the groups forming R^2 is optionally substituted with 1 or more F atoms, and wherein multiple R^2 may be identical or different if n is 2 or 3;

R^3 is selected from the group consisting of H, F, Cl, C_{1-4}-alkyl, NC-, and C_{1-4}-alkyl-O-,

wherein each alkyl group or sub-group within the groups forming R^3 is optionally substituted with 1 or more F atoms;

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

R^N is independently of each other selected from the group consisting of H, C_{1-4}-alkyl, HO-C_{1-4}-alkyl-(H_2C)-, C_{1-3}-alkyl-O-C_{1-4}-alkyl-, C_{1-4}-alkyl-C(=O)-, C_{1-4}-alkyl-NH-C(=O)-, C_{1-4}-alkyl-N(C_{1-4}-alkyl)-C(=O)-, C_{1-4}-alkyl-O-C(=O)-, and C_{1-4}-alkyl-$S(=O)_2$-,

wherein each alkyl group or sub-group within the groups forming R^N is optionally substituted with 1 or more F atoms;

wherein in any definition mentioned hereinbefore, if not specified otherwise, any alkyl group or sub-group may be straight-chained or branched,

or a salt thereof.

2. A compound according to claim 1, wherein

R is selected from the group consisting of H, F, Cl, C_{1-4}-alkyl, NC-, H_2N-C(=O)-, C_{1-3}-alkyl-NR^N-C(=O)-, HOOC-, H_2N-, C_{1-3}-alkyl-C(=O)NR^N-, C_{1-4}-alkyl-$S(=O)_2NR^N$-, HO-, C_{1-5}-alkyl-O-, HOOC-CH_2-O-, C_3-cycloalkyl-H_2C-O-, heterocyclyl-CH_2-O-, phenyl-CH_2-O-, C_{3-6}-cycloalkyl-O-, heterocyclyl-O-, heteroaryl-O-, heterocyclyl-$S(=O)_2$-, heterocyclyl, and heteroaryl,

wherein each alkyl, cycloalkyl, and heterocyclyl group or sub-group within the groups forming R is optionally substituted with 1 or more F atoms and optionally substituted with 1 group selected from Cl, H_3C-, NC-, R^NHN-, HO-, H_3C-O-, and H_3C-$S(=O)_2$-;

wherein each heteroaryl group or sub-group within the groups forming R is optionally substituted with 1 to 2 substituents independently selected from F, Cl, H_3C-, F_3C-, NC-, $(R^N)_2N$-, HO-, H_3C-O-, F_3C-O-, and H_3C-S(=O)$_2$-;

wherein each heterocyclyl or sub-group within the groups forming R is selected from

a cyclobutyl group wherein 1 CH_2 group is replaced by -NR^N- or -O-;

a C_{5-6}-cycloalkyl group wherein 1 CH_2 group is replaced by -C(=O)-, -NR^N-, -O-, -S- or -S(=O)$_2$- and/or 1 CH group is replaced by N;

wherein each heteroaryl group or sub-group within the groups forming R is selected from tetrazolyl, a 5-membered heteroaromatic ring which contains 1, 2 or 3 heteroatoms independently of each other selected from =N-, -NH-, O and S, and a 6-membered heteroaromatic ring which contains 1 or 2 =N- atoms, wherein a -HC=N- unit is optionally replaced by -NH-C(=O)-;

and wherein in each heteroaryl and heterocyclyl group or sub-group mentioned before containing one or more NH, said NH group(s) is/are replaced by NR^N;

or a salt thereof.

3. A compound according to claim 1, wherein

H_3C-O- optionally monosubstituted with C_{1-4}-alkyl, tetrahydrofuranyl, or tetrahydropyranyl,

wherein the C_{1-4}-alkyl group optionally attached to H_3C-O- is optionally monosubstituted with HO- or H_3C-S(=O)$_2$-;

tetrahydrofuranyl-O- and tetrahydropyranyl-O-; and

a heteroaryl group selected from pyrazolyl, oxazolyl, oxadiazolyl, tetrazolyl, pyridyl, pyridin-2-onyl, pyrazinyl, and pyrimidinyl,

wherein each of said heteroaryl groups is optionally monosubstituted with H_3C- or H_3C-O-, and

wherein each H-N group in said heteroaryl groups is optionally replaced with H_3C-N or $(H_3C)_2C(OH)$-H_2C-N;

or a salt thereof.

4. A compound according to claim 1, 2 or 3, wherein
R^1 is H, F, Cl, H_3C-, H_3C-H_2C-, $(H_3C)_2HC$-, F_3C-, NC-, or H_3C-O-;
m is 2;
R^2 is H, F, or F_3C-;
n is 2; and
R^3 is H;
or a salt thereof.

5. A compound according to claim 1, 2, 3 or 4, wherein R^1 is H or H_3C-; or a salt thereof.

6. A compound according to claim 1, wherein R is selected from the group consisting of H, Cl, C_{1-3}-alkyl optionally substituted with 1 or more F;

H_3C-O- optionally monosubstituted with C_{1-4}-alkyl, tetrahydrofuranyl, or tetrahydropyranyl,

wherein the C_{1-4}-alkyl group optionally attached to H_3C-O- is optionally monosubstituted with HO- or H_3C-$S(=O)_2$-;

tetrahydrofuranyl-O- and tetrahydropyranyl-O-; and

a heteroaryl group selected from pyrazolyl, oxazolyl, oxadiazolyl, tetrazolyl, pyridyl, pyridin-2-onyl, pyrazinyl, and pyrimidinyl,

wherein each of said heteroaryl groups is optionally monosubstituted with H_3C- or H_3C-O-, and

wherein each H-N group in said heteroaryl groups is optionally replaced with H_3C-N or $(H_3C)_2C(OH)$-H_2C-N;

R^1 is selected from the group consisting of H, F, Cl, H_3C-, H_3C-H_2C-, $(H_3C)_2HC$-, F_3C-, NC-, and H_3C-O-;

m is 2;

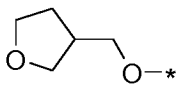
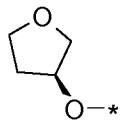
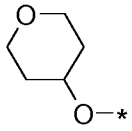
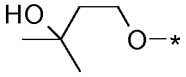
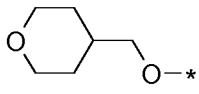
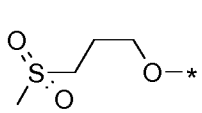
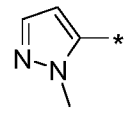
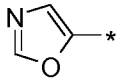
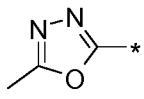
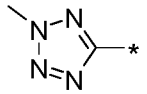
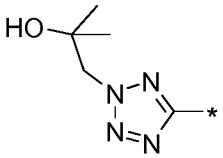
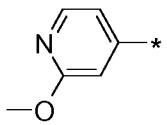
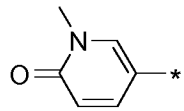
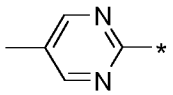
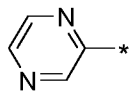
R^2 is H, F, or F_3C-;

n is 2; and

R^3 is H;

or a salt thereof.

7. A compound according to claim 1, wherein R is selected from the group consisting of

H, Cl, H_3C-H_2C-, $(H_3C)_2CH$-, F_3C-, H_3C-O-,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , and  ,

wherein the asterisk (-*) indicates the site/point of attachment;

R^1 is H or H_3C-;

m is 2;

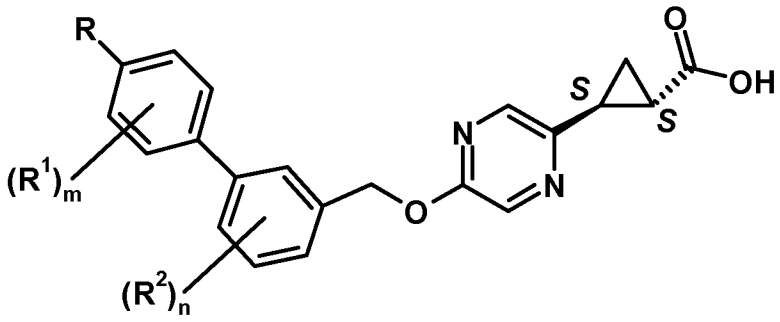
R^2 is H, F, or F_3C-;

n is 2; and

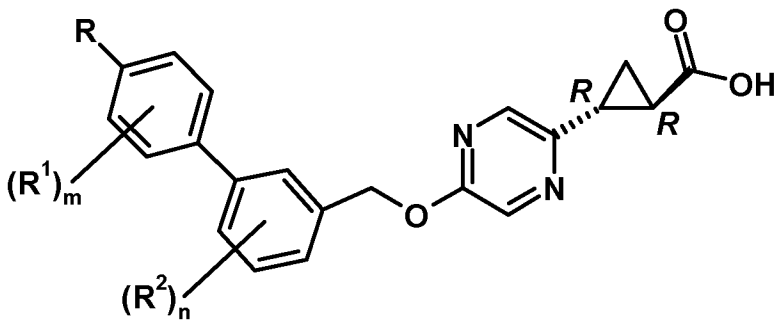
R^3 is H;

or a salt thereof.

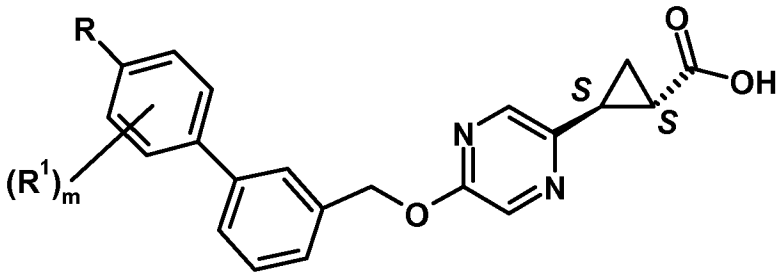
8. A compound according to any one of claims 1 to 7, with the structure and stereochemistry shown in formulae I.1, I.2, I.3, I.4, I.5, or I.6



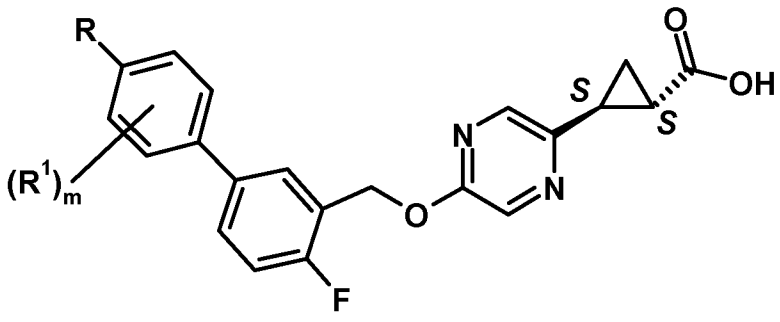
I.1



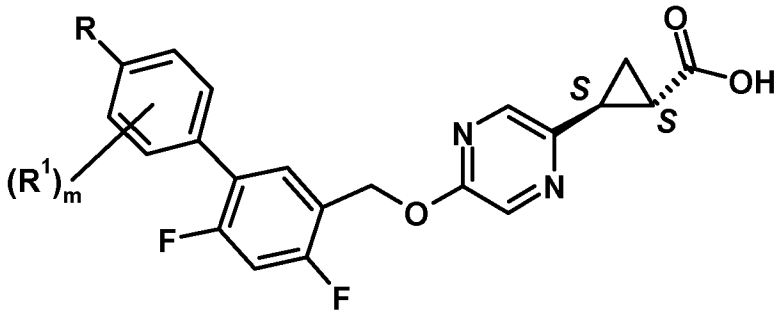
I.2



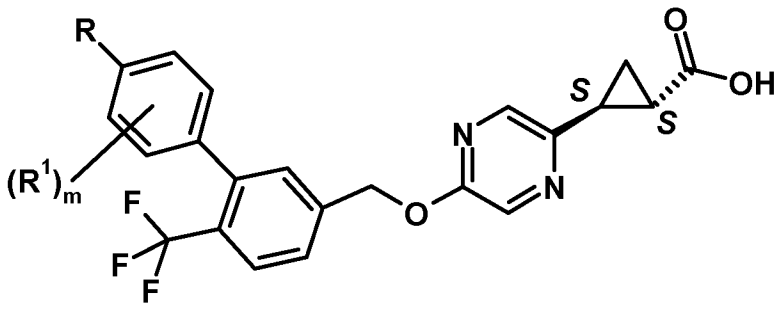
I.3



I.4



I.5



I.6

or a salt thereof.

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

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

11. A method for treating diseases or conditions which can be influenced by the modulation of the function of GPR40, particularly, for the prophylaxis and/or therapy of metabolic diseases, such as diabetes, more specifically type 2 diabetes mellitus, and conditions associated with the disease, including insulin resistance, obesity, cardiovascular disease and dyslipidemia in a patient in need thereof, characterized in that a compound according to one or more of the claims 1 to 8 or a pharmaceutically acceptable salt thereof is administered to the patient.

12. A compound according to one or more of the claims 1 to 8 or a pharmaceutically acceptable salt thereof for use as a medicament.

13. A compound according to one or more of the claims 1 to 8 or a pharmaceutically acceptable salt thereof for use in the treatment of diseases or conditions which can be influenced by the modulation of the function of GPR40, particularly, for use in the prophylaxis and/or therapy of metabolic diseases, such as diabetes, more specifically type 2 diabetes mellitus, and conditions associated with the disease, including insulin resistance, obesity, cardiovascular disease and dyslipidemia.

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

15. A pharmaceutical composition according to claim 14 wherein the additional therapeutic agents are 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.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2018/051390

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D403/12 C07D401/12 C07D405/12 C07D413/12 C07D241/18
A61P3/04 A61P9/04 A61P9/12 A61P3/10 A61K31/4965
A61K31/497

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61P

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 1 916 234 A1 (TAKEDA PHARMACEUTICAL [JP]) 30 April 2008 (2008-04-30) abstract examples 2, 3, 5, 7, 9, 11, 13, 15 pages 41-42 claims 1-19	1-15
A	US 2013/324514 A1 (HAMPRECHT DIETER [IT] ET AL) 5 December 2013 (2013-12-05) cited in the application abstract page 16; table 2 pages 63-91; examples 1-64; table 9 claims 1-17	1-15

-/--

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 April 2018	17/04/2018

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Dunet, Guillaume

1

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2016/009677 A1 (LEE JU YOUNG [KR] ET AL) 14 January 2016 (2016-01-14) abstract examples 1-147 pages 162-191; table 1 page 192; tables 2, 3 claims 1-10	1-15
Y	US 2010/152165 A1 (NEGORO KENJI [JP] ET AL) 17 June 2010 (2010-06-17) abstract examples 1-40 examples 41-478 claims 1-17	1-15
Y	US 2011/190330 A1 (BROWN SEAN P [US] ET AL) 4 August 2011 (2011-08-04) abstract examples 1-158 * table *; pages 244-303 claims 1-53	1-15

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2018/051390

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 1916234 A1	30-04-2008	EP 1916234 A1	30-04-2008
		JP 5084503 B2	28-11-2012
		JP WO2007013689 A1	12-02-2009
		US 2010144806 A1	10-06-2010
		WO 2007013689 A1	01-02-2007
US 2013324514 A1	05-12-2013	EP 2855419 A1	08-04-2015
		JP 6163695 B2	19-07-2017
		JP 2015523339 A	13-08-2015
		US 2013324514 A1	05-12-2013
		WO 2013178575 A1	05-12-2013
US 2016009677 A1	14-01-2016	AU 2014221489 A1	08-10-2015
		CA 2900348 A1	04-09-2014
		CN 105209448 A	30-12-2015
		EP 2963027 A1	06-01-2016
		JP 2016513135 A	12-05-2016
		KR 20140108179 A	05-09-2014
		US 2016009677 A1	14-01-2016
		WO 2014133361 A1	04-09-2014
US 2010152165 A1	17-06-2010	AR 064049 A1	11-03-2009
		AU 2007326449 A1	05-06-2008
		CA 2671080 A1	05-06-2008
		CN 101553469 A	07-10-2009
		EP 2096109 A1	02-09-2009
		JP WO2008066097 A1	11-03-2010
		KR 20090083935 A	04-08-2009
		RU 2009125019 A	10-01-2011
		TW 200838526 A	01-10-2008
		US 2010152165 A1	17-06-2010
		WO 2008066097 A1	05-06-2008
		ZA 200903646 B	25-08-2010
US 2011190330 A1	04-08-2011	AU 2009303475 A1	22-04-2010
		CA 2739888 A1	22-04-2010
		EP 2358656 A2	24-08-2011
		ES 2450567 T3	25-03-2014
		JP 5551707 B2	16-07-2014
		JP 2012505896 A	08-03-2012
		US 2011190330 A1	04-08-2011
		WO 2010045258 A2	22-04-2010