

New indanyloxydihydrobenzofuranylacetic acids

Field of the invention

The present invention relates to novel indanyloxydihydrobenzofuranylacetic 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.

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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

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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, nephropathy, 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 insulintropic 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 indanyloxydihydrobenzofuranylacetic 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 indanyloxydihydrobenzofuranylacetic 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.

- 5 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
10 comprising at least one compound according to the invention.

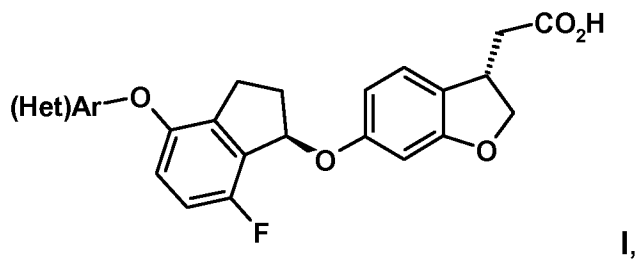
A further object of the present invention is to provide a combination of at least one compound according to the invention with one or more additional therapeutic agents.

- 15 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 2004041266 (EP 1559422), WO 2007033002, WO 2009157418 and WO
20 2012072691. The indanyloxydihydrobenzofuranylacetic 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. In particular, the present invention provides compounds of superior stability in acidic aqueous media compared to related
25 compounds disclosed in WO 2012072691.

Summary of the Invention

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



wherein

(Het)Ar is linked via a carbon atom and is selected from the group (Het)Ar-G1
 5 consisting of phenyl, naphthyl and a mono- or bicyclic heteroaromatic group
 having 5 to 10 ring member atoms of which 2 to 9 ring members are carbon
 atoms and either

one ring member is an unsubstituted or substituted heteroatom selected from N,
 10 NH, NR^N, O, S, S(=O) and S(=O)₂, or

one ring member is N and a second ring member is selected from N, NH, NR^N,
 O, S, S(=O) and S(=O)₂, or

two ring members are N and a third ring member is selected from N, NH, NR^N, O,
 S, S(=O) and S(=O)₂,

15 wherein in naphthyl the ring not attached to the indanyl-O atom of formula I
 may be partially saturated,

wherein in bicyclic heteroaromatic groups the ring not attached to the
 20 indanyl-O atom of formula I may be partially saturated, while at least one
 aromatic ring includes a heteroatom, and optionally

one ring member in the partially or fully saturated bridge is replaced by N,
 NH, NR^N, O, S, S(=O) or S(=O)₂, or

one ring member in the partially or fully saturated bridge is replaced by N,
 25 NH or NR^N and second ring member is replaced by NH, NR^N, O, S,
 C(=O), S(=O) or S(=O)₂, or

two not vicinal ring members in a fully saturated bridge are replaced by O
 atoms,

wherein any of these groups is optionally and independently substituted with 1 to 5 R^1 groups;

- 5 R^1 is selected from the group R^1 -G1 consisting of F, Cl, Br, I, CN, NO₂, NH₂, C₁₋₄-alkyl-NH-, (C₁₋₄-alkyl)₂N-, C₁₋₄-alkyl, C₂₋₄-alkenyl, C₂₋₄-alkynyl, OH, HO-C₁₋₄-alkyl, C₁₋₄-alkyl-O-, C₁₋₄-alkyl-O-C₁₋₄-alkyl, C₁₋₄-alkyl-S-, C₁₋₄-alkyl-S(=O)-, C₁₋₄-alkyl-S(=O)₂-, C₃₋₆-cycloalkyl, C₃₋₆-cycloalkyl-O-, wherein any alkyl and cycloalkyl group or submoiety is optionally substituted with 1 to 5 F atoms;

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R^N is selected from the group R^N -G1 consisting of C₁₋₄-alkyl, C₃₋₄-alkenyl, HO-C₁₋₄-alkyl, C₁₋₄-alkyl-O-C₁₋₄-alkyl, C₁₋₄-alkyl-C(=O)-, C₁₋₄-alkyl-S(=O)₂-, and C₃₋₆-cycloalkyl-, wherein any alkyl and cycloalkyl group or submoiety is optionally substituted with 1 to 5 F atoms;

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

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

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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.

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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
5 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.

10 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.

15 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
20 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.

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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.

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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 (Het)Ar, R¹ and R^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.

15 (Het)Ar:

(Het)Ar-G1:

The group (Het)Ar is preferably selected from the group (Het)Ar-G1 as defined hereinbefore.

20 **(Het)Ar-G2:**

According to one embodiment the group (Het)Ar is selected from the group (Het)Ar-G2 consisting of phenyl, naphthyl, and a mono- or bicyclic heteroaromatic group having 5 to 10 ring member atoms of which 2 to 9 ring members are carbon atoms and either

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one ring member is an unsubstituted or substituted heteroatom selected from N, NH, NR^N, O, S, S(=O) and S(=O)₂, or

one ring member is N and a second ring member is selected from N, NH, NR^N, O, S, S(=O) and S(=O)₂, or

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two ring members are N and a third ring member is selected from N, NH, NR^N, O, S, S(=O) and S(=O)₂,

wherein in naphthyl the ring not attached to the indanyl-O atom of formula I may be partially saturated,

wherein in bicyclic heteroaromatic groups the ring not attached to the indanyl-O atom of formula I may be partially saturated, while at least one

aromatic ring includes a heteroatom, and optionally

one ring member in the partially or fully saturated bridge is replaced by N, NH, NR^N, O or S, or

one ring member in the partially or fully saturated bridge is replaced by N, NH or NR^N and a second ring member is replaced by NH, NR^N, O or S,

wherein any of these groups is optionally and independently substituted with 1 to 5 R¹ groups;

(Het)Ar-G3:

According to one embodiment the group (Het)Ar is selected from the group (Het)Ar-G3 consisting of

phenyl, naphthyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, quinolinyl, isoquinolinyl, quinazolinyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, indolinyl, benzoimidazolyl, indazolyl, benzoxazolyl, benzoisoxazolyl and benzothiazolyl,

wherein each of these groups is optionally substituted with 1 to 3 groups independently selected from R¹ and wherein independently a NH group optionally is replaced by a NR^N group.

(Het)Ar-G4:

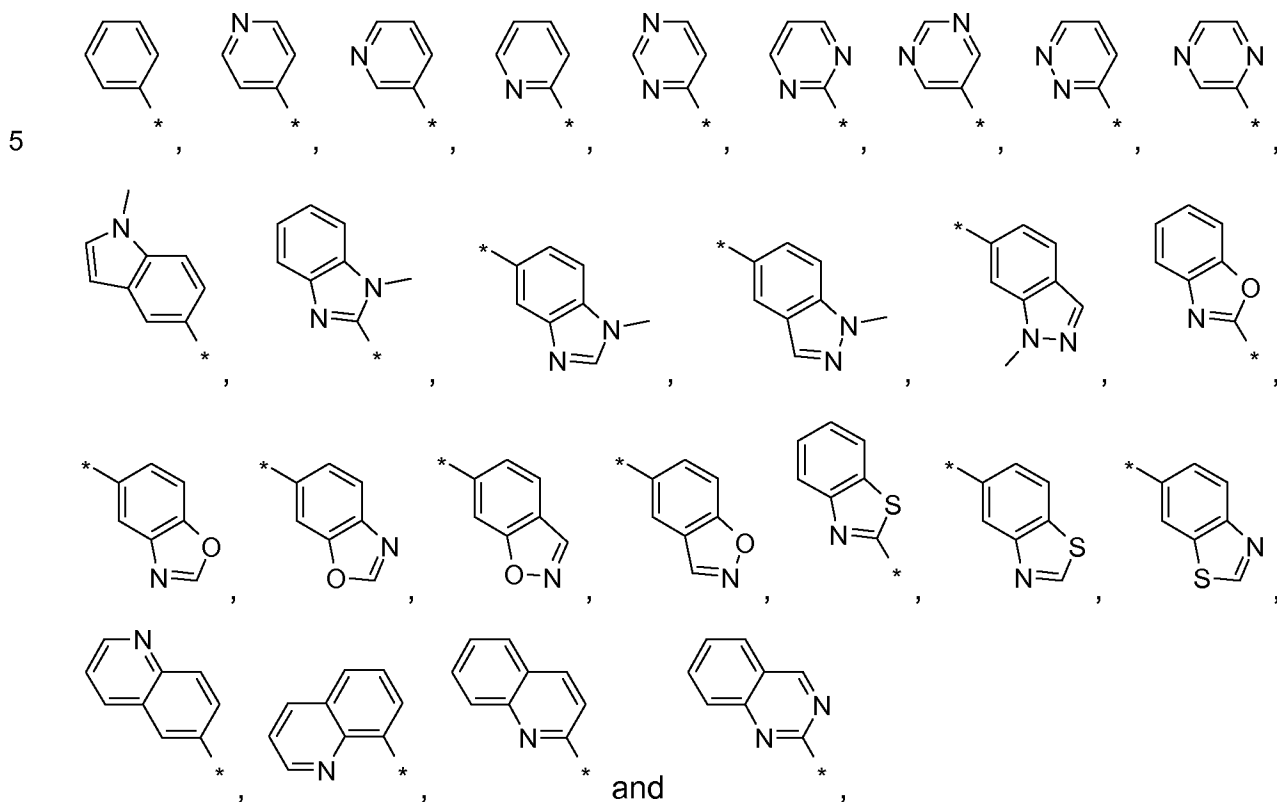
According to one embodiment the group (Het)Ar is selected from the group (Het)Ar-G4 consisting of

phenyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, quinolinyl, isoquinolinyl, quinazolinyl, indolinyl, benzoimidazolyl, indazolyl, benzoxazolyl, benzoisoxazolyl and

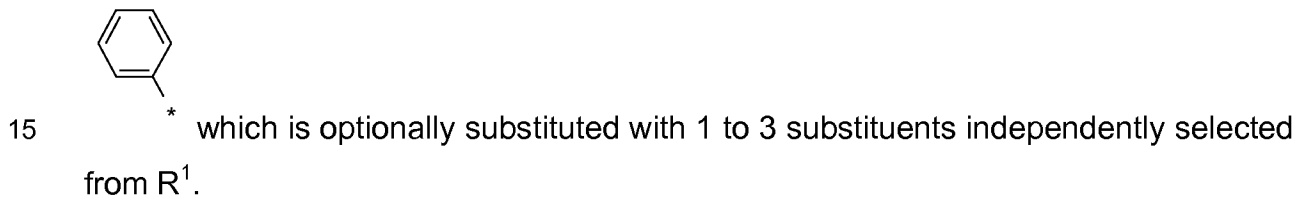
benzothiazolyl, wherein each of these groups is optionally substituted with 1 to 3 groups independently selected from R¹ and wherein independently a NH group optionally is replaced by a NR^N group.

(Het)Ar-G5:

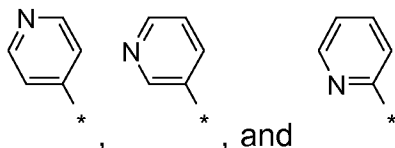
In another embodiment the group (Het)Ar is selected from the group (Het)Ar-G5 consisting of

**(Het)Ar-G5a:**

In another embodiment the group (Het)Ar is selected from the group (Het)Ar-G5a consisting of

**(Het)Ar-G5b:**

In another embodiment the group (Het)Ar is selected from the group (Het)Ar-G5b consisting of

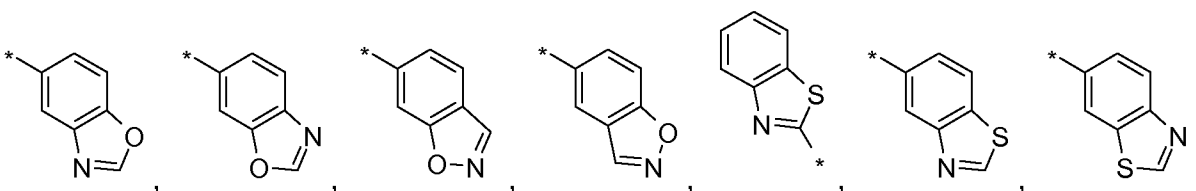
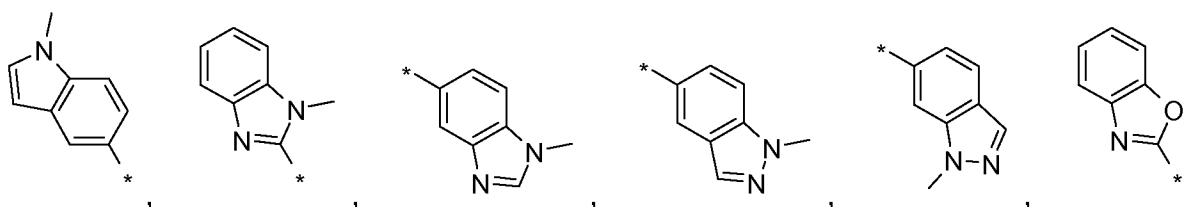


, and , wherein each of these groups is optionally substituted with 1 or 2 substituents independently selected from R¹.

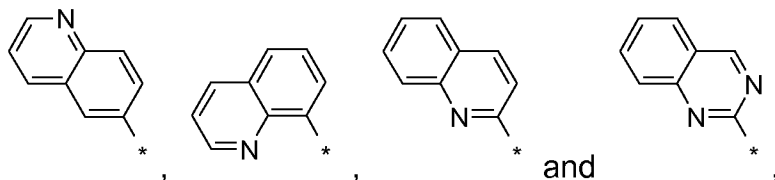
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(Het)Ar-G5c:

In another embodiment the group (Het)Ar is selected from the group (Het)Ar-G5c consisting of



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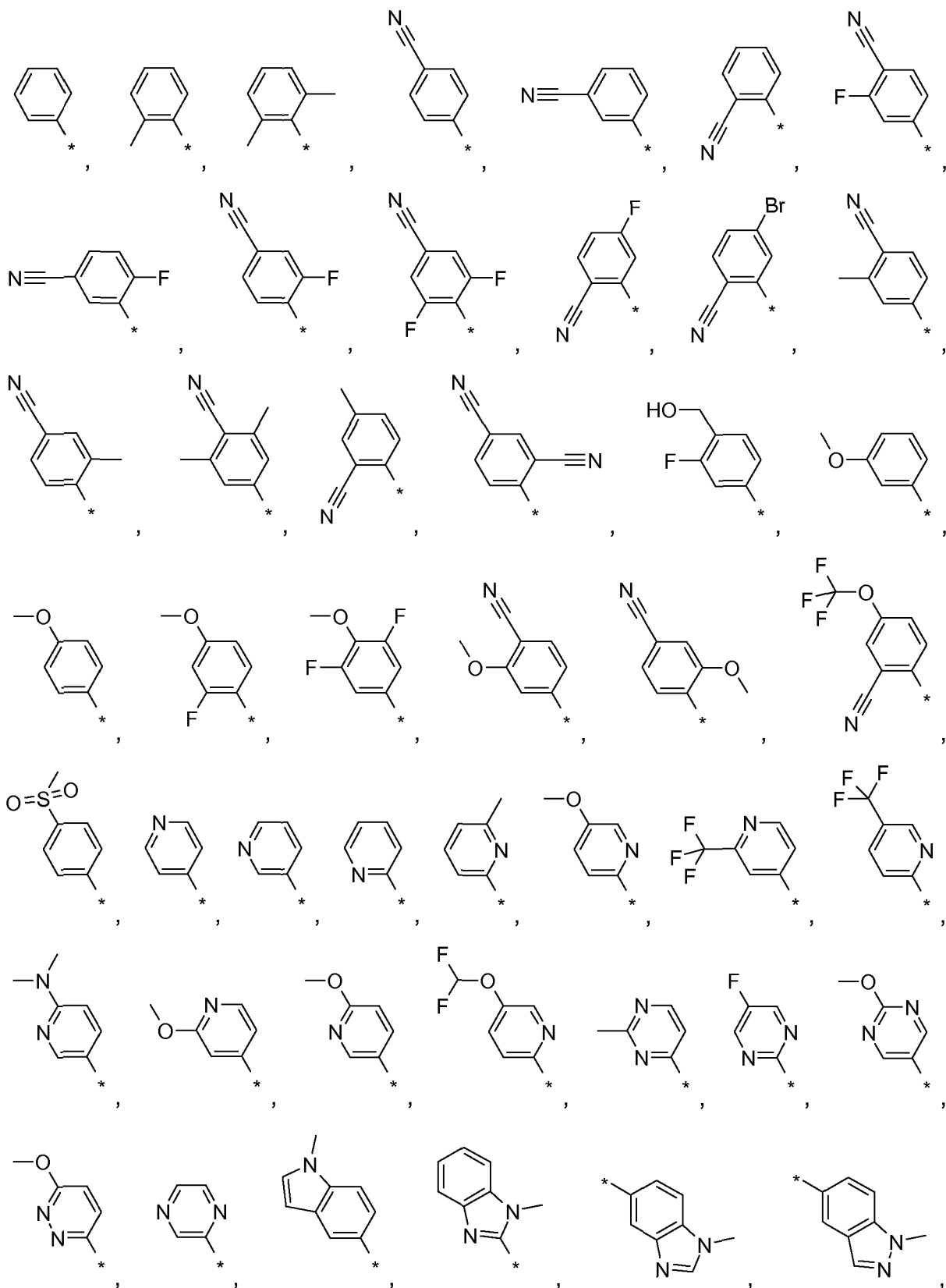


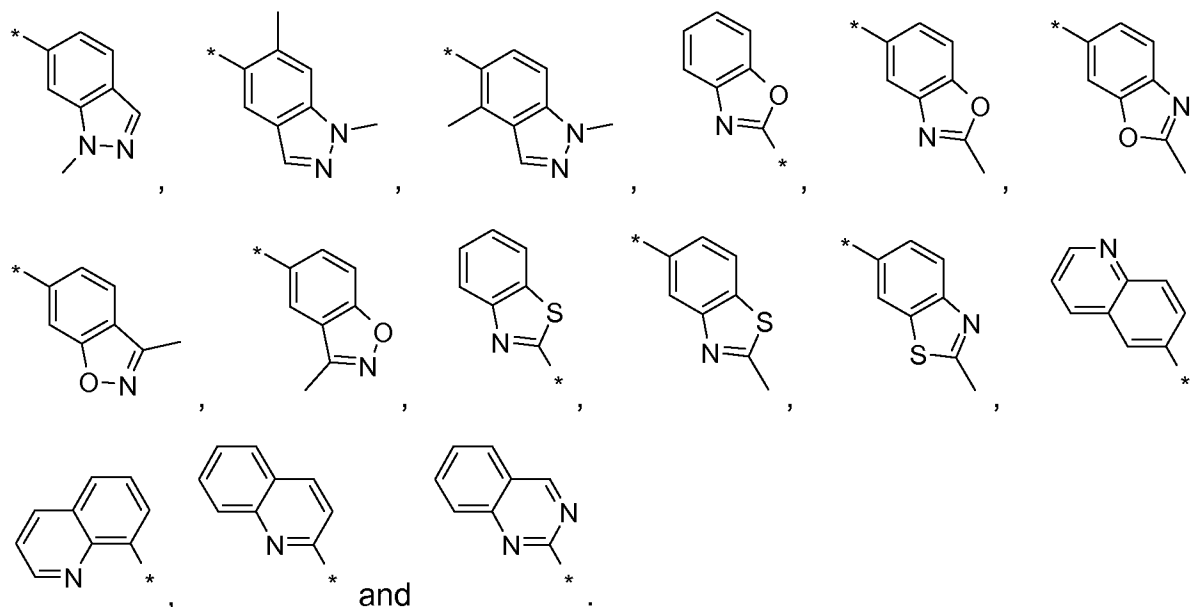
and

wherein each of these groups is optionally substituted with 1 to 3 substituents independently selected from R¹.

(Het)Ar-G6:

In another embodiment the group (Het)Ar is selected from the group (Het)Ar-G6 consisting of





5 **R¹:**

R¹-G1:

The group R¹ is preferably selected from the group R¹-G1 as defined hereinbefore.

R¹-G2:

- 10 In another embodiment the group R¹ is selected from the group R¹-G2 consisting of F, Cl, Br, C₁₋₄-alkyl, C₂₋₄-alkinyl, HO-C₁₋₄-alkyl, C₁₋₄-alkyl-O-C₁₋₄-alkyl, CN, NH₂, C₁₋₄-alkyl-NH-, (C₁₋₄-alkyl)₂N-, OH, C₁₋₄-alkyl-O-, C₁₋₄-alkyl-S(=O)-, C₁₋₄-alkyl-S(=O)₂-, C₃₋₆-cycloalkyl and C₃₋₆-cycloalkyl-O-, wherein any alkyl and cycloalkyl group or submoiety is optionally substituted with 1 to 3 F atoms.

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R¹-G3:

In another embodiment the group R¹ is selected from the group R¹-G3 consisting of F, Cl, Br, C₁₋₄-alkyl, F₂HC-, F₃C-, HO-C₁₋₄-alkyl, H₃C-O-C₁₋₄-alkyl, H₃C-NH-, (H₃C)₂N-, CN, OH, C₁₋₄-alkyl-O-, F₂HC-O-, F₃C-O-, H₃C-S(=O)-, H₃C-S(=O)₂-, C₃₋₅-cycloalkyl and C₅₋₆-cycloalkyl-O-.

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R¹-G4:

In another embodiment the group R¹ is selected from the group R¹-G4 consisting of

F, Cl, Br, C₁₋₃-alkyl, F₂HC-, F₃C-, HO-CH₂-, H₃C-O-CH₂-, H₃C-NH-, (H₃C)₂N-, CN, OH, C₁₋₃-alkyl-O-, F₂HC-O-, F₃C-O-, H₃C-S(=O)₂- and cyclopropyl.

R¹-G5:

- 5 In another embodiment the group R¹ is selected from the group R¹-G5 consisting of F, H₃C-, F₃C-, NC-, HO-H₂C-, (H₃C)₂N-, H₃C-O-, HF₂C-O-, F₃C-O- and H₃C-S(=O)₂-.

R¹-G6:

- 10 In another embodiment the group R¹ is selected from the group R¹-G6 consisting of F, H₃C-, F₃C-, NC-, H₃C-O-, HF₂C-O- and F₃C-O-.

R^N:**R^N-G1:**

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

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R^N-G2:

- 20 In another embodiment the group R^N is selected from the group R^N-G2 consisting of C₁₋₃-alkyl, HO-C₁₋₄-alkyl, C₁₋₃-alkyl-O-C₁₋₄-alkyl, C₁₋₃-alkyl-C(=O)-, C₁₋₃-alkyl-S(=O)₂-, and C₄₋₆-cycloalkyl-, wherein any alkyl group or submoiety is optionally substituted with 1 to 3 F atoms.

R^N-G3:

In another embodiment the group R^N is selected from the group R^N-G3 consisting of C₁₋₃-alkyl, HO-C₁₋₄-alkyl, H₃C-O-C₁₋₄-alkyl, H₃C-C(=O)-, and H₃C-S(=O)₂-.

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R^N-G4:

In another embodiment the group R^N is selected from the group R^N-G4 consisting of C₁₋₃-alkyl, HO-C₁₋₄-alkyl, and H₃C-C(=O)-.

30 R^N-G5:

In another embodiment the group R^N is selected from the group R^N-G5 consisting of C₁₋₃-alkyl, preferably methyl.

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

Embodiment	(Het)Ar-	R ¹ -	R ^N -
E-1	(Het)Ar-G1	R ¹ -G1	R ^N -G1
E-2	(Het)Ar-G2	R ¹ -G3	R ^N -G3
E-3	(Het)Ar-G2	R ¹ -G4	R ^N -G4
E-4	(Het)Ar-G2	R ¹ -G5	R ^N -G5
E-5	(Het)Ar-G3	R ¹ -G1	R ^N -G2
E-6	(Het)Ar-G3	R ¹ -G2	R ^N -G3
E-7	(Het)Ar-G3	R ¹ -G4	R ^N -G4
E-8	(Het)Ar-G3	R ¹ -G5	R ^N -G5
E-9	(Het)Ar-G4	R ¹ -G1	R ^N -G2
E-10	(Het)Ar-G4	R ¹ -G2	R ^N -G3
E-11	(Het)Ar-G4	R ¹ -G3	R ^N -G3
E-12	(Het)Ar-G4	R ¹ -G4	R ^N -G4
E-13	(Het)Ar-G4	R ¹ -G5	R ^N -G5
E-14	(Het)Ar-G5	R ¹ -G1	-
E-15	(Het)Ar-G5	R ¹ -G2	-
E-16	(Het)Ar-G5	R ¹ -G3	-
E-17	(Het)Ar-G5	R ¹ -G4	-
E-18	(Het)Ar-G5	R ¹ -G5	-
E-19	(Het)Ar-G5	R ¹ -G6	-
E-20	(Het)Ar-G6	-	-

Preferred are those compounds of formula I, wherein

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(Het)Ar is selected from the group consisting of

phenyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, quinolinyl, isoquinolinyl, quinazolinyl, indolinyl, benzoimidazolyl, indazolyl, benzoxazolyl, benzoisoxazolyl and benzothiazolyl, wherein each of these groups is optionally substituted with 1 to 3 groups independently selected from R¹;

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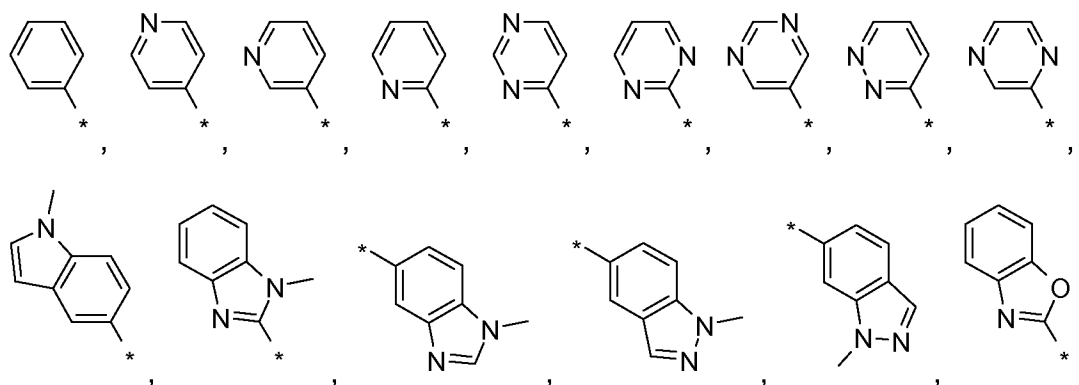
R¹ is selected from the group consisting of F, Cl, Br, C₁₋₄-alkyl, C₂₋₄-alkynyl, HO-C₁₋₄-alkyl, C₁₋₄-alkyl-O-C₁₋₄-alkyl, CN, NH₂, C₁₋₄-alkyl-NH-, (C₁₋₄-alkyl)₂N-, OH, C₁₋₄-alkyl-O-, C₁₋₄-alkyl-S(=O)-, C₁₋₄-alkyl-S(=O)₂-, C₃₋₆-cycloalkyl and C₃₋₆-cycloalkyl-O-, wherein any alkyl and cycloalkyl group or submoiety is optionally substituted with 1 to 3 F atoms; and

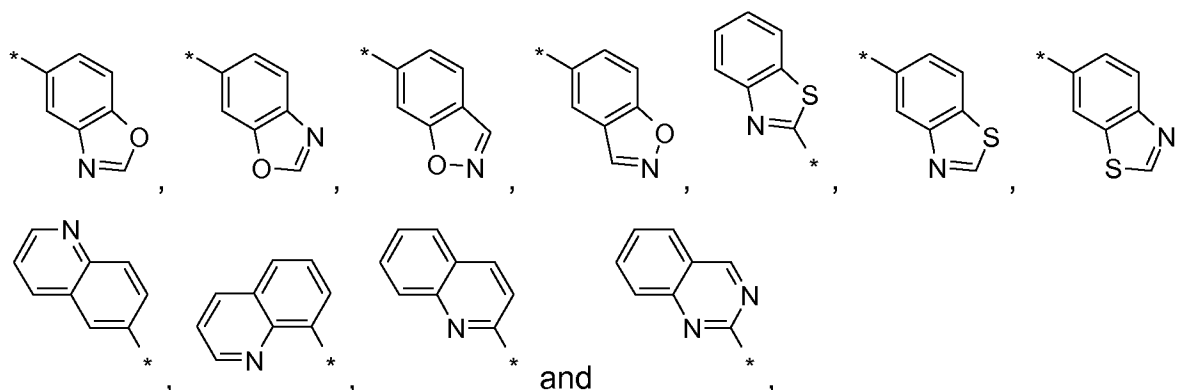
R^N is selected from the group consisting of C₁₋₃-alkyl, HO-C₁₋₄-alkyl, H₃C-O-C₁₋₄-alkyl, H₃C-S(=O)₂-, and C₁₋₃-alkyl-C(=O)-;

15 and the pharmaceutically acceptable salts thereof.

More preferred are those compounds of formula I, wherein

(Het)Ar is selected from the group consisting of





wherein each of these groups is optionally substituted with 1 to 3 substituents independently selected from R^1 ; and

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R^1 is selected from the group consisting of F, Cl, Br, C_{1-4} -alkyl, F_2HC- , F_3C- , $HO-C_{1-4}$ -alkyl, H_3C-O-C_{1-4} -alkyl, H_3C-NH- , $(H_3C)_2N-$, CN, OH, C_{1-4} -alkyl-O-, F_2HC-O- , F_3C-O- , $H_3C-S(=O)-$, $H_3C-S(=O)_2-$, C_{3-5} -cycloalkyl and C_{5-6} -cycloalkyl-O-;

10 and the pharmaceutically acceptable salts thereof.

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

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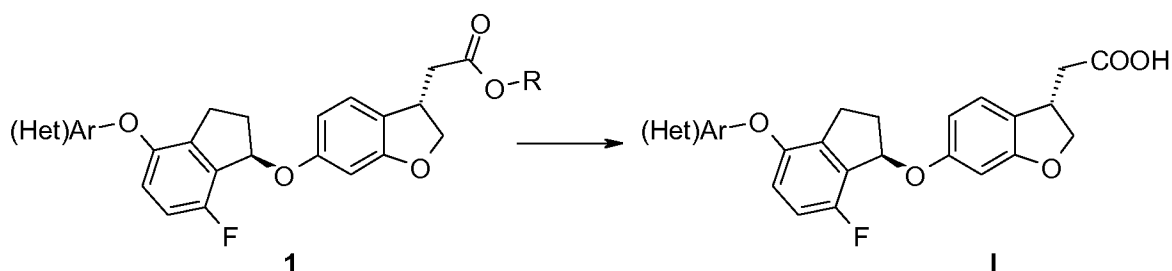
The compounds according to the invention and their intermediates may be obtained using methods of synthesis which are known to the one skilled in the art and described in the literature of organic synthesis. Preferably the compounds are obtained analogously to the methods of preparation explained more fully hereinafter, 20 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 25 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.

- 5 The compounds of the invention I are preferably accessed from a precursor **1** that bears the carboxylic acid protected as ester (Scheme 1); (Het)Ar has the meaning as defined hereinbefore and hereinafter. The ester group may be hydrolysed in the presence of an acid, such as hydrochloric acid or sulfuric acid, or an alkali metal hydroxide, such as lithium hydroxide, sodium hydroxide, or potassium hydroxide, to
 10 yield the carboxylic acid. The hydrolysis is preferably conducted in aqueous solvents, such as water combined with 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, 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
 15 a transition metal, preferably palladium on carbon. Benzyl esters bearing electron donating groups on the phenyl ring, such as methoxy, may also be removed under oxidative conditions; ceric ammonium nitrate (CAN) or 2,3-dichloro-5,6-dicyanoquinone (DDQ) are reagents commonly used for this approach.

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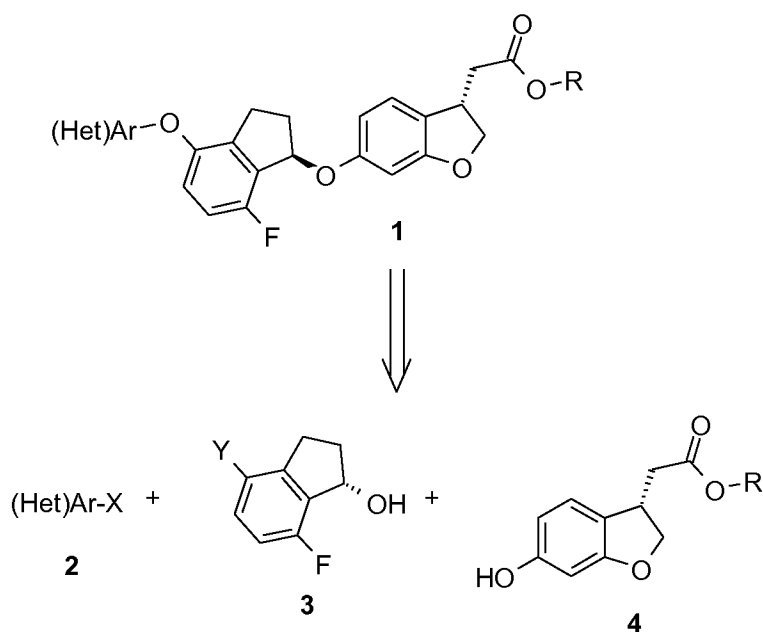
Scheme 1



R = C₁₋₄-alkyl, optionally substituted with one or more F atoms;
 CH₂-phenyl, wherein phenyl is optionally substituted with one or more F atoms
 and/or one or two groups independently selected from Cl, Br, CH₃, OCH₃, and NO₂;
 allyl

Compound 1 may be assembled using building blocks 2, 3 and 4 (Scheme 2); (Het)Ar has the meaning as defined hereinbefore and hereinafter.

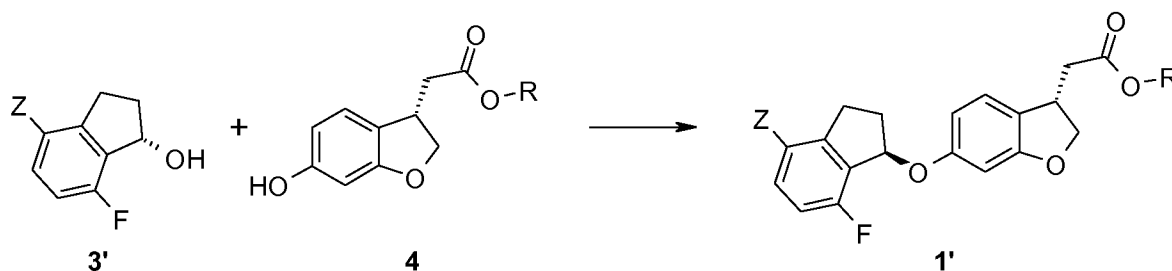
Scheme 2



X = e.g., OH, B(OH)₂, F, Cl, Br, I;
 Y = e.g., OH, O-PG, B(OH)₂, BF₃K, B(OCMe₂CMe₂O), Cl, Br, I;
 PG = protective group, e.g., CH₃, tert-Bu, CH₂-Ph, allyl, Si(C₁₋₄-alkyl)₃;
 R = as defined in Scheme 1

Building blocks 3 and 4 may be combined in a stereoselective fashion employing the conditions of the Mitsunobu reaction or variations thereof (Scheme 3); (Het)Ar has the meaning as defined hereinbefore and hereinafter. The reaction is usually conducted with a phosphine and an azodicarboxylic ester or amide in tetrahydrofuran, 1,4-dioxane, diethyl ether, toluene, benzene, dichloromethane, or mixtures thereof, at -30 to 100 °C. Phosphines often used are triphenylphosphine and tributylphosphine, which are commonly combined with dimethyl azodicarboxylate, diethyl azodicarboxylate, diisopropyl azodicarboxylate, di-(4-chlorobenzyl) azodicarboxylate, dibenzyl azodicarboxylate, di-tert-butyl azodicarboxylate, azodicarboxylic acid bis-(dimethylamide), azodicarboxylic acid dipiperidide, or azodicarboxylic acid dimorpholide.

Scheme 3



Z = e.g., (Het)Ar-O or Y'

Y' = e.g., O-PG, B(OCMe₂CMe₂O), Cl, Br, I;

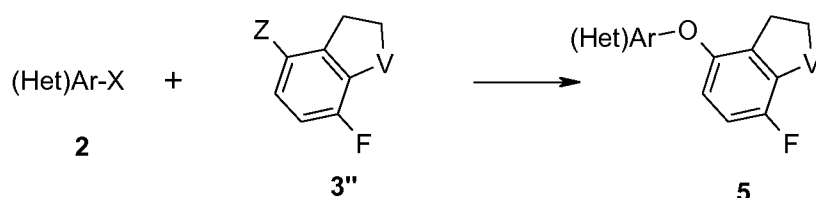
PG = protective group, e.g., CH₂-Ph, allyl, Si(C₁₋₄-alkyl)₃;

R is as defined in Scheme 1

The group (Het)Ar may be attached to the indane moiety via an oxygen starting from various precursors (Scheme 4); (Het)Ar has the meaning as defined hereinbefore and hereinafter. The two parts may be linked using one of them decorated with a hydroxy group (X or Z denotes OH) and the other one with a boronic acid group (X or Z denotes B(OH)₂). The two building blocks accordingly equipped may be coupled employing copper(II) acetate in the presence of a base, e.g. pyridine or triethylamine, molecular sieves, optionally a co-oxidant, e.g. oxygen, in a solvent, e.g. dichloromethane, at 0 to 60 °C. Alternatively, the linkage between (Het)Ar and indane via oxygen is formed after coupling the indane moiety, bearing an OH group (Z = OH), and (Het)Ar, bearing a leaving group (X = e.g., F, Br, Cl, I). The O of the OH group replaces the leaving group by nucleophilic substitution or a transition metal catalyzed reaction. The former proceeding is particularly suited for electron deficient (Het)Ar groups which are coupled with the hydroxylated indane in the presence of a base, e.g. Cs₂CO₃, K₂CO₃, KOH, triethylamine or NaH, preferably in a solvent, e.g. toluene, tetrahydrofuran, 1,2-dimethoxyethane, 1,4-dioxane, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidinone, alcohol, water or mixtures thereof, at 0 to 220 °C. The transition metal catalyzed coupling is used for (Het)Ar groups bearing Cl, Br or I as leaving group. Suitable transition metal catalysts are commonly derived from palladium or copper. The active catalyst may be an elemental form of the transition metal or formed from a salt of the transition metal, such as fluoride, chloride, bromide, iodide, acetate, triflate or trifluoroacetate, which are optionally combined with ligands, such as phosphines, e.g. tri-*tert*-butylphosphine,

tricyclohexylphosphine, optionally substituted biphenyl-dicyclohexyl-phosphines, optionally substituted biphenyl-di-*tert*-butyl-phosphines, 1,1'-bis(diphenylphosphino)-ferrocene, triphenylphosphine, tritolylphosphine, or trifurylphosphine, phosphites, 1,3-disubstituted imidazole carbenes, 1,3-disubstituted imidazolidine carbenes, pyridines or phenanthrolines. The reaction is usually carried out in the presence of a base, e.g. NaOH, KOH, Na₂CO₃, K₂CO₃, Cs₂CO₃, triethylamine or ethyldiisopropylamine, in toluene, tetrahydrofuran, 1,2-dimethoxyethane, 1,4-dioxane, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidinone, alcohol, water, or mixtures thereof, preferably at 10 to 180 °C.

Scheme 4



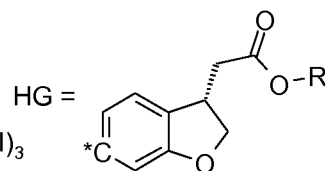
X = e.g., OH, B(OH)₂, F, Cl, Br, I;

Z = e.g., OH, B(OH)₂, Cl, Br, I;

V = C=O, CH-OH, CH-O-PG, CH-O-HG

PG = protective group, e.g., CH₂-Ph, allyl, Si(C₁₋₄-alkyl)₃

R is as defined in Scheme 1



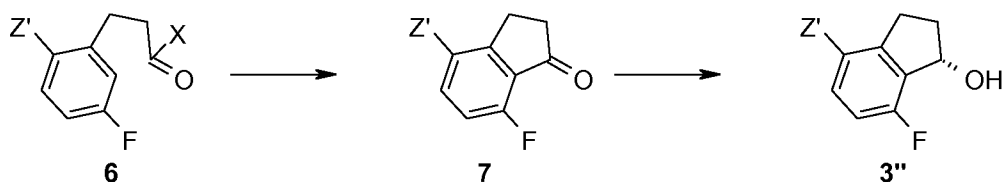
Intermediate **3** or derivatives thereof, as **3''**, may be obtained from indanone **7**, which, in turn, may be prepared from phenylpropionic acid derivative **6** (Scheme 5). For the intramolecular acylation (Friedel-Crafts acylation), **6**→**7**, a considerable number of approaches has been reported. The reaction may be performed starting with a carboxylic acid, carboxylic ester, carboxylic anhydride, carboxylic chloride or fluoride, or a nitrile using a Lewis acid as catalyst. The following Lewis acids are some of the more often used ones: hydrobromic acid, hydroiodic acid, hydrochloric acid, sulfuric acid, phosphoric acid, P₄O₁₀, trifluoroacetic acid, methanesulfonic acid, toluenesulfonic acid, trifluoromethanesulfonic acid, ClSO₃H, Sc(OSO₂CF₃)₃, Tb(OSO₂CF₃)₃, SnCl₄, FeCl₃, AlBr₃, AlCl₃, SbCl₅, BCl₃, BF₃, ZnCl₂, montmorillonites, POCl₃, and PCl₅. The reaction may be conducted, e.g., in dichloromethane, 1,2-dichloroethane, nitrobenzene, chlorobenzene, carbon disulfide, mixtures thereof, or

without an additional solvent in an excess of the Lewis acid, at 0 to 180 °C. Carboxylic acids are preferably reacted in polyphosphoric acid at 0 to 120 °C, while carboxylic chlorides are preferably reacted with AlCl₃ in dichloromethane or 1,2-dichloroethane at 0 to 80 °C.

- 5 The subsequent reduction of the keto group in compound **7** providing the alcohol **3''** in enantiomerically enriched or pure form may be accomplished using hydrogen or a hydrogen source, such as formate or silane, and a transition metal catalyst derived from, e.g., Ir, Rh, Ru or Fe and a chiral auxiliary. For instance, a ruthenium complex, such as chloro{[(1S,2S)-(-)-2-amino-1,2-diphenylethyl](4-toluenesulfonyl)-amido}-
10 (mesitylene)ruthenium(II), may deliver the hydroxy compound **3''** with high enantiomeric excess using, e.g., formic acid in the presence of a base, e.g. triethylamine, in dichloromethane, at -20 to 60 °C. Alternatively, boranes combined with an enantiomerically pure [1,3,2]oxazaborol may be used as reducing agent (Corey-Bakshi-Shibata reaction or Corey-Itsuno reaction). Typical reaction conditions
15 for this approach are borane (complexed with, e.g., dimethyl sulfide) and (*R*)- or (*S*)-3,3-diphenyl-1-methyltetrahydro-1H,3H-pyrrolo[1,2-c][1,3,2]oxazaborol in, e.g., dichloromethane, toluene, methanol, tetrahydrofuran, or mixtures thereof, at 0 to 60 °C.

20

Scheme 5



Z' = e.g. Cl, Br, I, O-PG; PG = protective group, e.g., Me, CH₂-Ph

25

The synthetic routes presented may rely on the use of protecting groups. For example, potentially reactive groups present, such as hydroxy, carbonyl, carboxy, amino, alkylamino, or imino, may be protected during the reaction by conventional protecting groups which are cleaved again after the reaction. Suitable protecting groups for the respective functionalities and their removal are well known to the one skilled in the art and are described in the literature of organic synthesis.

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
5 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
10 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
20 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
25 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.

30 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.

20

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.

10 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.

15 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.

20 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.

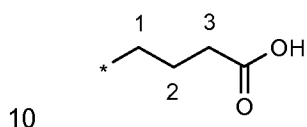
25 In the groups, radicals, or moieties defined below, the number of carbon atoms is often specified preceding the group, for example, C₁₋₆-alkyl means an alkyl group or radical having 1 to 6 carbon atoms. In general, for groups comprising two or more subgroups, the last named subgroup is the radical attachment point, for example, the substituent "aryl-C₁₋₃-alkyl-" means an aryl group which is bound to a C₁₋₃-alkyl-
30 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.

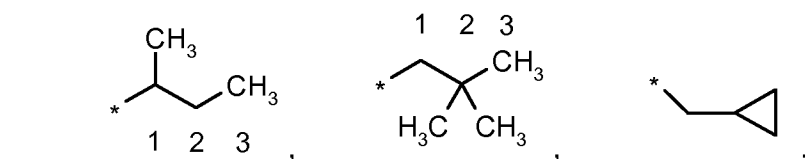
An asterisk may be used in sub-formulas to indicate the bond which is connected to
5 the core molecule as defined.

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, C₁₋₃-alkyl, C₃₋₆-cycloalkyl, C₃₋₆-cycloalkyl-C₁₋₃-alkyl or C₁₋₃-alkyl-O-, wherein each alkyl group is optionally substituted with one or more L^{ex}." or the like means that in each of the
25 beforementioned groups which comprise the term alkyl, i.e. in each of the groups C₁₋₃-alkyl, C₃₋₆-cycloalkyl-C₁₋₃-alkyl and C₁₋₃-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
5 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.

10 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
15 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
20 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.

25 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
30 hydrocarbon radical with 1 to n C atoms. For example the term C₁₋₅-alkyl embraces the radicals H₃C-, H₃C-CH₂-, H₃C-CH₂-CH₂-, H₃C-CH(CH₃)-, H₃C-CH₂-CH₂-CH₂-, H₃C-CH₂-CH(CH₃)-, H₃C-CH(CH₃)-CH₂-, H₃C-C(CH₃)₂-, H₃C-CH₂-CH₂-CH₂-CH₂-,

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

- 5 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 $-(\text{CH}_2)-$, $-(\text{CH}_2-\text{CH}_2)-$, $-(\text{CH}(\text{CH}_3))-$, $-(\text{CH}_2-\text{CH}_2-\text{CH}_2)-$, $-(\text{C}(\text{CH}_3)_2)-$, $-(\text{CH}(\text{CH}_2\text{CH}_3))-$, $-(\text{CH}(\text{CH}_3)-\text{CH}_2)-$, $-(\text{CH}_2-\text{CH}(\text{CH}_3))-$, $-(\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2)-$,
 10 $-(\text{CH}_2-\text{CH}_2-\text{CH}(\text{CH}_3))-$, $-(\text{CH}(\text{CH}_3)-\text{CH}_2-\text{CH}_2)-$, $-(\text{CH}_2-\text{CH}(\text{CH}_3)-\text{CH}_2)-$, $-(\text{CH}_2-\text{C}(\text{CH}_3)_2)-$, $-(\text{C}(\text{CH}_3)_2-\text{CH}_2)-$, $-(\text{CH}(\text{CH}_3)-\text{CH}(\text{CH}_3))-$, $-(\text{CH}_2-\text{CH}(\text{CH}_2\text{CH}_3))-$, $-(\text{CH}(\text{CH}_2\text{CH}_3)-\text{CH}_2)-$, $-(\text{CH}(\text{CH}_2\text{CH}_2\text{CH}_3))-$, $-(\text{CHCH}(\text{CH}_3)_2)-$ and $-\text{C}(\text{CH}_3)(\text{CH}_2\text{CH}_3)-$.

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 $-\text{CH}=\text{CH}_2$, $-\text{CH}=\text{CH}-\text{CH}_3$, $-\text{CH}_2-\text{CH}=\text{CH}_2$.

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 $-\text{C}\equiv\text{CH}$, $-\text{C}\equiv\text{C}-\text{CH}_3$, $-\text{CH}_2-\text{C}\equiv\text{CH}$.

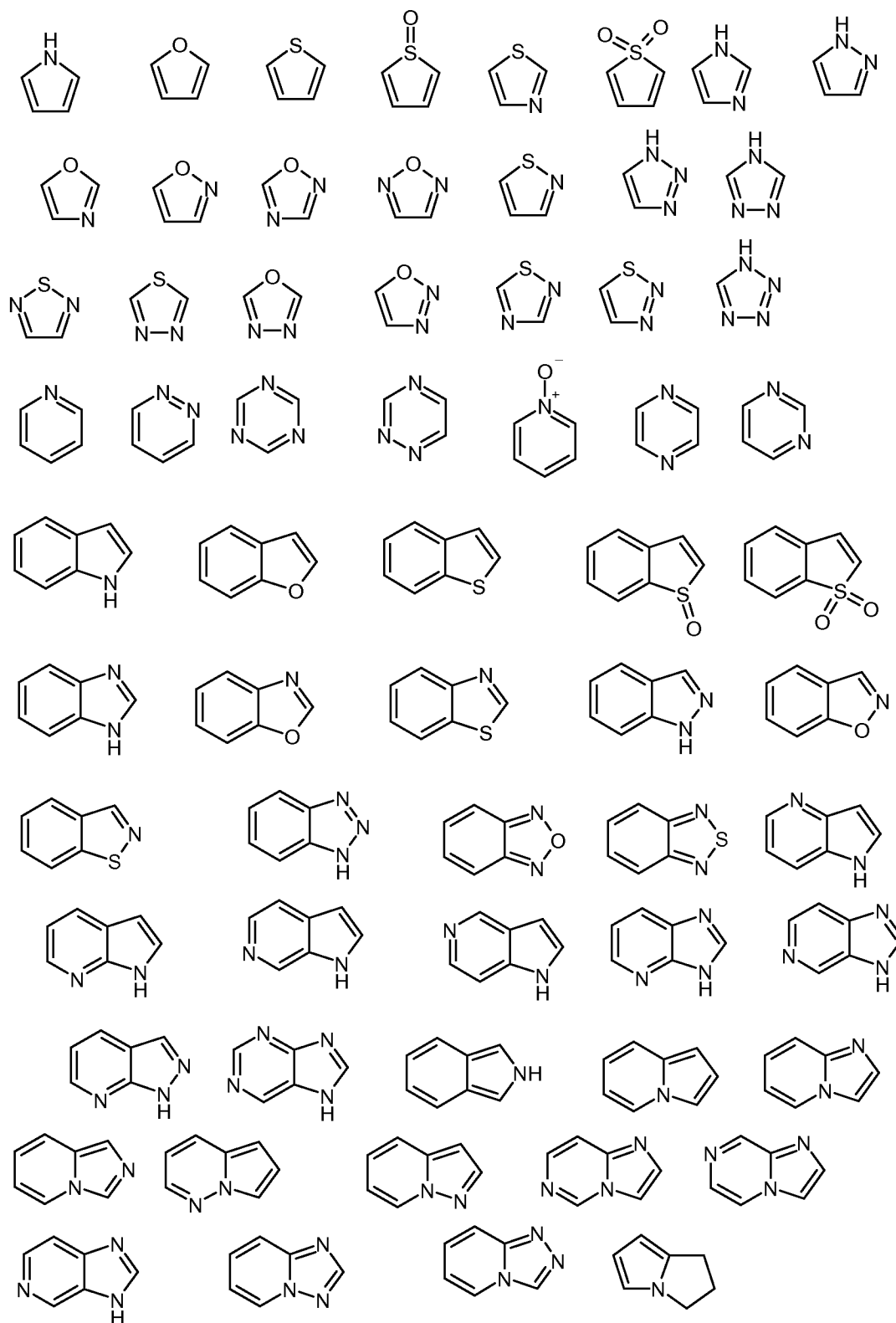
The term " C_{3-n} -carbocyclyl" as used either alone or in combination with another radical, denotes a monocyclic, bicyclic or tricyclic, saturated or unsaturated hydrocarbon radical with 3 to n C atoms. The hydrocarbon radical is preferably nonaromatic. Preferably the 3 to n C atoms form one or two rings. In case of a bicyclic or tricyclic ring system the rings may be attached to each other via a single bond or may be fused or may form a spirocyclic or bridged ring system. For example
 25 the term C_{3-10} -carbocyclyl includes C_{3-10} -cylcoalkyl, C_{3-10} -cycloalkenyl, octahydropentalenyl, octahydroindenyl, decahydronaphthyl, indanyl,
 30

tetrahydronaphthyl. Most preferably the term C_{3-n} -carbocyclyl denotes C_{3-n} -cylcoalkyl, in particular C_{3-7} -cycloalkyl.

5 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,
10 adamantyl, etc.

The term "heteroaryl" or heteroaromatic group, unless specified otherwise, means a mono- or polycyclic, preferably mono- or bicyclic-ring system containing one or more heteroatoms selected from N, NH, NR^N , O or $S(O)_r$ with $r=0, 1$ or 2 wherein at least
15 one of the heteroatoms is part of an aromatic ring, R^N preferably is a C_{1-3} -alkyl group, and wherein said ring system may have a carbonyl group. More preferably the term "heteroaryl" as used herein, either alone or in combination with another radical, means a mono- or bicyclic-ring system containing 1, 2 or 3 heteroatoms selected from N, NH, NR^N , O or $S(O)_r$ with $r=0, 1$ or 2 wherein at least one of the heteroatoms
20 is part of an aromatic ring, R^N preferably is a methyl group, and wherein said ring system may have a carbonyl group. The term "heteroaryl" is intended to include all the possible isomeric forms.

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



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

Chemical Stability

Degradation kinetics is used to simulate chemical stability of compounds in the acidic part of the gastro intestinal tract. The compounds of the invention show superior
5 chemical stability in acidic aqueous media (pH value ca. 1.2) compared to the bulk of compounds explicitly disclosed in WO 2012072691. Their application as medical drugs to treat human diseases is therefore less restricted and troublesome.

The chemical stability of the compounds of the invention at pH value of ca. 1.2 is
10 determined as follows:

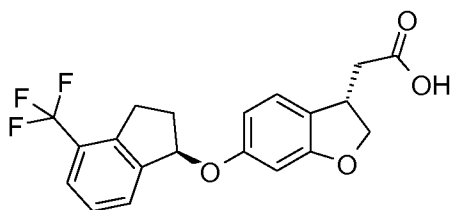
Compound is dissolved in an HPLC vial either in a mixture of acetonitrile/0.1 M aqueous HCl (2:3; pH ca. 1.2) or in a mixture of acetonitrile/McIlvaine buffer pH 7.4 (2:3) to get a concentration of approximately 0.25 mg/ml. The vial was then transferred into an HPLC autosampler system and maintained at a temperature of 37
15 °C. A first sample is taken and injected immediately into a standard HPLC system with a UV DAD detector. Further samples are injected after 2, 4, 6, 8 and 10 hours. Degradation of the compound is measured by determining the recovery rate of compound [%] for each injection using an HPLC standard gradient method. Therefore the peak area of the main peak for the first injection (AU_{t_0}) is determined
20 and set as 100%. Peak area of the main peak is determined also for the further injections ($AU_{t_n, n=2, 4, 6, 8, 10}$) and expressed as fraction of $(AU_{t_0}) / (AU_{t_n, n=2, 4, 6, 8, 10})$ [%].

The recovery rate of the compounds according to the invention after 2 h at pH value
25 of ca. 1.2 determined as described above is typically above 90%, preferably above 95%, more preferably at least 98%.

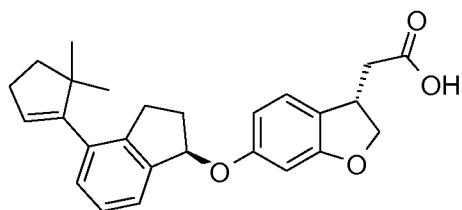
The following table compares the recovery rate after 2 h at pH value of ca. 1.2 of compounds according to the invention and compounds of WO 2012072691.

Example in this invention	Recovery rate after 2 h	Example in WO 2012072691	Recovery rate after 2 h
1	98.5%	2	88%
2	98.0%	25	98%
3	98.0%	29	1%
4	97.5%	32	2%
8	>99.5%	37	95%
12	>99.5%	42	0%
15	>99.5%	43	0%
21	>99.5%	60	74%
27	>99.5%	64	82%
28	99.5%	68	82%
29	>99.5%	84	81%
33	99.5%		
36	>99.5%		
37	>99.5%		
45	98.0%		
46	99.0%		

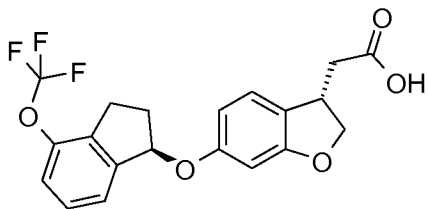
Chemical structures of the examples of case WO 2012072691 listed in the table above:



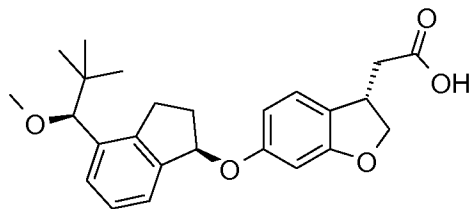
Example 2



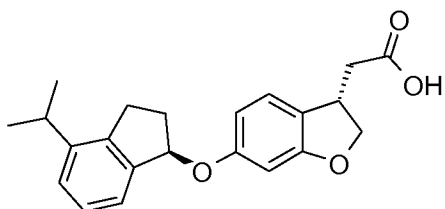
Example 42



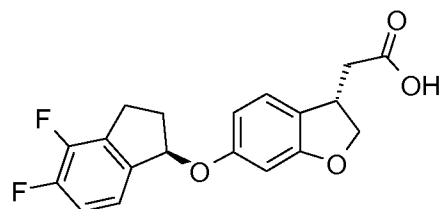
Example 25



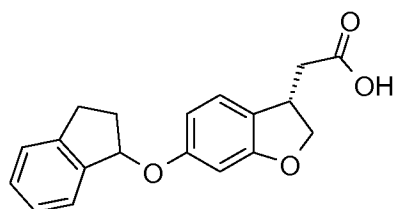
Example 29



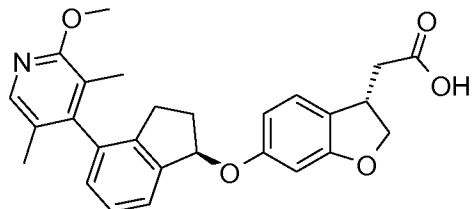
Example 32



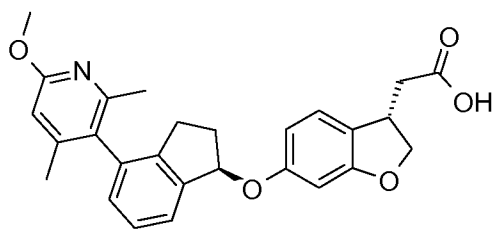
Example 37



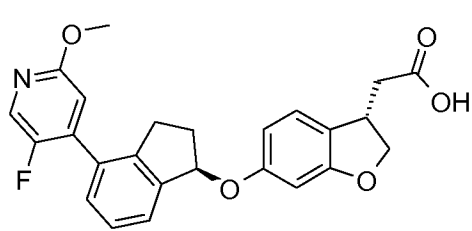
Example 43



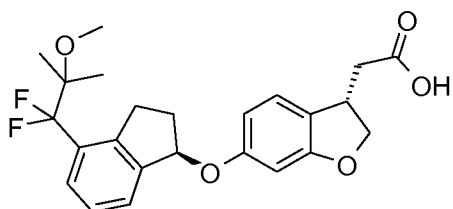
Example 60



Example 64



Example 68



Example 84

Pharmacological Activity

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

- 5 IP₁ 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. IP₁ is assayed according to the manufacturer's description (Cisbio Bioassays, France). In brief, the assay is started by substitution of
 - 10 the culture medium by stimulation buffer (Hepes 10 mM, CaCl₂ 1 mM, MgCl₂ 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% CO₂ 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.
 - 15 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 pEC₅₀ values using Assay Explorer 3.3 Software (Accelrys, Inc.) by interpolation using an IP₁ reference curve and subsequent sigmoidal curve fitting allowing for a variable hill slope.

20

The compounds according to the invention typically have EC₅₀ values in the range from about 1 nM to about 10 µM, preferably less than 1 µM, more preferably less than 100 nM.

- 25 EC₅₀ values for compounds according to the invention are shown in the following table. The number of the compound corresponds to the number of the Example in the experimental section.

Example	EC ₅₀ [nM]	Example	EC ₅₀ [nM]	Example	EC ₅₀ [nM]	Example	EC ₅₀ [nM]
1	4	2	6	3	3	4	6
5	70	6	33	7	32	8	4

9	155	10	35	11	18	12	12
13	216	14	26	15	31	16	138
17	4	18	41	19	13	20	6
21	4	22	3	23	7	24	3
25	13	26	30	27	7	28	8
29	6	30	11	31	120	32	6
33	31	34	5	35	79	36	4
37	5	38	6	39	21	40	22
41	17	42	891	43	34	44	19
45	7	46	3	47	26	48	7
49	12	50	6	51	18	52	6
53	69	54	29	55	6	56	6
57	7	58	3	59	5	60	3
61	3						

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
5 suitable for the treatment of all those diseases or conditions which may be affected or which are mediated by the activation of the G-protein-coupled receptor GPR40.

Accordingly, the present invention relates to a compound of general formula I as a
10 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
15 human.

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

5 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
10 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.

15

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
20 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
25 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,
30 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.

5

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
5 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

10 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
15 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.

20 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.

25 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,
30 cycloset, 11 β -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, α 2-antagonists, CCR-2 antagonists or glucokinase activators. One or more lipid lowering agents are also suitable as combination
5 partners, such as for example HMG-CoA-reductase inhibitors, fibrates, nicotinic acid and the derivatives thereof, PPAR-(α , γ or α/γ) agonists or modulators, PPAR- δ 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
10 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, β 3-agonists, leptin or leptin mimetics, agonists
15 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,
20 antagonists of the α -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.

25 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
30 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
5 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
10 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.
15

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.
20

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
25 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.
30

Examples

Preliminary remarks:

- 5 As a rule, ¹H-NMR and/or mass spectra have been obtained for the compounds prepared. The R_f values are determined using Merck silica gel 60 F₂₅₄ plates and UV light at 254 nm.

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

10

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

Method:		1		
Device:		Agilent 1200 with DA and MS detector		
Column:		XBridge C18, 3 x 30 mm, 2.5 µm		
Column Supplier:		Waters		
Gradient/Solvent Time [min]	% Solvent [H ₂ O,0.1%TFA]	% Solvent [Methanol]	Flow [mL/min]	Temperature [°C]
0.0	95	5	2.2	60
0.05	95	5	2.2	60
1.40	0	100	2.2	60
1.80	0	100	2.2	60

Method:		2		
Device:		Agilent 1200 with DA and MS detector		
Column:		XBridge C18, 3 x 30 mm, 2.5 µm		
Column Supplier:		Waters		
Gradient/Solvent Time [min]	% Solvent [H ₂ O,0.1% FA]	% 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:		3		
Device:		Agilent 1200 with DA and MS detector		
Column:		XBridge C18, 3 x 30 mm, 2.5 µm		
Column Supplier:		Waters		
Gradient/Solvent Time [min]	% Solvent [H ₂ O,0.1%TFA]	% Solvent [Acetonitrile]	Flow [mL/min]	Temperature [°C]
0.00	50	50	2.2	60
0.20	50	50	2.2	60
1.20	0	100	2.2	60
1.25	0	100	3	60
1.40	0	100	3	60

Method:		4		
Device:		Agilent 1200 with DA and MS detector		
Column:		XBridge C18, 3 x 30 mm, 2.5 µm		
Column Supplier:		Waters		
Gradient/Solvent Time [min]	% Solvent [H ₂ O,0.1% FA]	% Solvent [Acetonitrile]	Flow [ml/min]	Temperature [°C]
0.00	50	50	2.2	60
0.20	50	50	2.2	60
1.20	0	100	2.2	60
1.25	0	100	3	60
1.40	0	100	3	60

Method:		5		
Device:		Agilent 1200 with DA and MS detector		

Column:		XBridge C18, 3 x 30 mm, 2.5 µm		
Column Supplier:		Waters		
Gradient/Solvent Time [min]	% Solvent [H ₂ O,0.1%NH ₃]	% 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:		6		
Device:		Agilent 1200 with DA and MS detector		
Column:		XBridge C18, 3 x 30 mm, 2.5 µm		
Column Supplier:		Waters		
Gradient/Solvent Time [min]	% Solvent [H ₂ O,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:		7		
Device:		Agilent 1200 with DA and MS detector		
Column:		XBridge C18, 3 x 30 mm, 2.5 µm		
Column Supplier:		Waters		
Gradient/Solvent Time [min]	% Solvent [H ₂ O,0.1% NH ₃]	% Solvent [Acetonitrile]	Flow [ml/min]	Temperature [°C]
0.00	50	50	2.2	60
0.20	50	50	2.2	60
1.20	0	100	2.2	60

1.25	0	100	3	60
1.40	0	100	3	60

Method:		8		
Device:		Waters Acquity with 3100 MS		
Column:		Sunfire C18, 2.1 x 50 mm, 2.5 µm		
Column supplier:		Waters		
Gradient/Solvent Time [min]	% Solvent [H ₂ O, 0.1% TFA]	% Solvent [Acetonitrile, 0.08% TFA]	Flow [ml/min]	Temperature [°C]
0.0	95.0	5.0	1.5	60.0
0.75	0.0	100.0	1.5	60.0
0.85	0.0	100.0	1.5	60.0

Method:		9		
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 ₂ O, 0.1% FA]	% 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:		10		
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 ₂ O, 0.1% FA]	% Solvent [Acetonitrile]	Flow [ml/min]	Temperature [°C]

0.00	50	50	2.2	60
0.20	50	50	2.2	60
1.20	0	100	2.2	60
1.25	0	100	3	60
1.40	0	100	3	60

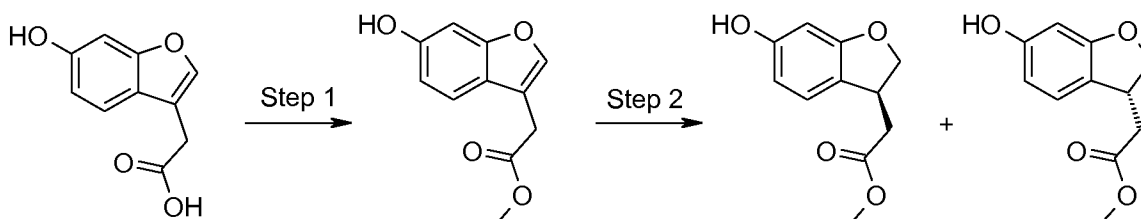
Method Name:		11		
Device:		Agilent 1200 with DA and MS detector		
Column:		Sunfire, 3 x 30 mm, 2.5 µm		
Column Supplier:		Waters		
Gradient/Solvent Time [min]	% Solvent [H ₂ O,0.1%TFA]	% Solvent [Acetonitrile]	Flow [ml/min]	Temperature [°C]
0.00	50	50	2.2	60
0.20	50	50	2.2	60
1.20	0	100	2.2	60
1.25	0	100	3	60
1.40	0	100	3	60

Method Name:		12		
Device:		Agilent 1200 with DA and MS detector		
Column:		Sunfire, 3 x 30 mm, 2.5 µm		
Column Supplier:		Waters		
Gradient/Solvent Time [min]	% Solvent [H ₂ O,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

The Examples that follow are intended to illustrate the present invention without restricting it:

Intermediate 1

5 [(S)-6-Hydroxy-2,3-dihydro-benzofuran-3-yl]-acetic acid methyl ester



Step 1: (6-hydroxy-benzofuran-3-yl)-acetic acid methyl ester

A mixture of (6-hydroxy-benzofuran-3-yl)-acetic acid (for preparation see WO 2008001931; 14.0 g), concentrated sulfuric acid (5 mL), and methanol (250 mL) is stirred at reflux temperature for 4 h. After cooling to room temperature, the mixture is concentrated. Ethyl acetate is added to the residue, and the resulting mixture is washed with water, saturated aqueous NaHCO₃ solution and brine and dried (MgSO₄). The solvent is evaporated, and the residue is chromatographed on silica gel (cyclohexane/ethyl acetate 2:1→1:2) to give the title compound. Mass spectrum (ESI⁺): m/z = 207 [M+H]⁺.

Step 2: (6-hydroxy-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester

A mixture of (6-hydroxy-benzofuran-3-yl)-acetic acid methyl ester (5.00 g), 10% palladium on carbon (0.50 g), and methanol (50 mL) is shaken under hydrogen atmosphere (3 bar) at room temperature for 3 h. The catalyst is separated by filtration and the filtrate is concentrated. The residue is chromatographed on silica gel (cyclohexane/ethyl acetate 4:1→1:1) to give the racemic title compound. Mass spectrum (ESI⁺): m/z = 209 [M+H]⁺.

The enantiomers may be separated by SFC on chiral phase (column: Daicel ADH, 5 μm, 250 mm x 20 mm; eluent: scCO₂/(isopropanol+0.2% diethylamine) 80:20, 70 mL/min):

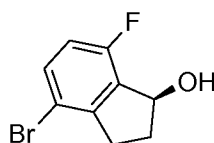
(S)-(6-Hydroxy-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester: t_R = 2.33 min.

(R)-(6-Hydroxy-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester: t_R = 2.75 min.

Alternatively, the pure enantiomer may be obtained as described in WO 2008001931.

Intermediate 2

(S)-4-Bromo-7-fluoro-2,3-dihydro-1H-inden-1-ol



5

Formic acid (8.1 mL) is added to a solution of triethylamine (25.6 mL) in dichloromethane (50 mL) chilled in an ice bath. 4-Bromo-7-fluoro-2,3-dihydro-1H-inden-1-one (14.0 g) is added, the solution is warmed to room temperature, and the flask is purged with argon for 5 min. Chloro{[(1S,2S)-(-)-2-amino-1,2-diphenylethyl](4-toluenesulfonyl)amido}-(mesitylene)ruthenium(II) (0.85 g; alternatively, the catalyst is formed *in situ* from dichloro(p-cymene)-ruthenium(II) dimer and N-[(1S,2S)-2-amino-1,2-diphenylethyl]-4-methylbenzenesulfonamide) is added, and the mixture is stirred at room temperature for 16 h. Water is added and the resulting mixture is extracted with dichloromethane. The combined extract is washed with saturated aqueous

10

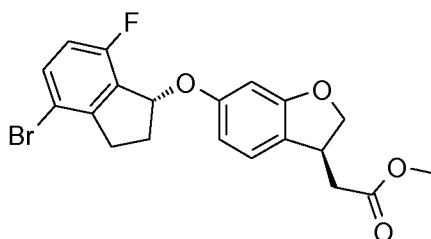
15

NaHCO₃ solution and dried (MgSO₄). The solvent is evaporated and the residue is chromatographed on silica gel (cyclohexane/ethyl acetate 90:10→50:50) to give the title compound.

LC (method 1): $t_R = 1.04$ min; Mass spectrum (ESI⁺): $m/z = 213/215$ (Br) $[M+H-H_2O]^+$.

20 Intermediate 3

{(S)-6-[(R)-4-Bromo-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester



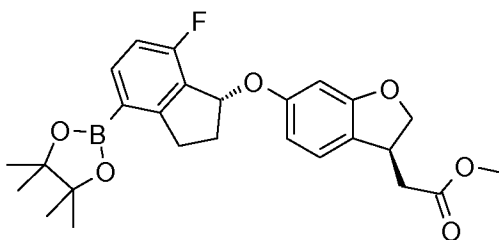
25

A solution of di-tert-butyl azodicarboxylate (18.0 g) in tetrahydrofuran (80 mL) is added dropwise over 45 min to a solution of [(S)-6-hydroxy-2,3-dihydro-benzofuran-3-yl]-acetic acid methyl ester (11.0 g), (S)-4-bromo-7-fluoro-2,3-dihydro-1H-inden-1-ol

(12.0 g) and tributylphosphine (19.3 mL) in tetrahydrofuran (320 mL) at -10 °C. The resulting solution is stirred for 30 min and then poured into saturated aqueous NaHCO₃ solution. The mixture is extracted with dichloromethane, and the combined organic phases are dried (MgSO₄) and concentrated. The residue is chromatographed on silica gel (cyclohexane/ethyl acetate 90:10→70:30) to give the title compound. LC (method 1): t_R = 1.41 min; Mass spectrum (ESI⁺): m/z = 421 [M+H]⁺.

Intermediate 4

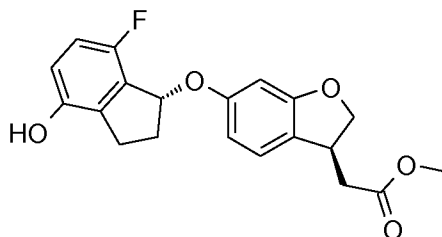
{{(S)-6-[(R)-7-Fluoro-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester}



A microwave vial charged with a stir bar, {{(S)-6-[(R)-4-bromo-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester (7.0 g), bis-(pinacolato)-diboron (5.6 g), potassium acetate (4.2 g) and 1,4-dioxane (100 mL) is purged with argon for 10 min. [1,1'-Bis(diphenylphosphino)-ferrocene]-dichloropalladium(II) (0.60 g) is added, the vial is sealed, and the mixture is stirred at 100 °C for 4 h. After cooling to room temperature, saturated aqueous NH₄Cl solution is added and the resulting mixture is extracted with diethyl ether. The combined extracts are dried (MgSO₄) and concentrated. The residue is chromatographed on silica gel (cyclohexane/ethyl acetate 99:1→70:30) to give the title compound. LC (method 1): t_R = 1.48 min; Mass spectrum (ESI⁺): m/z = 469 [M+H]⁺.

Intermediate 5

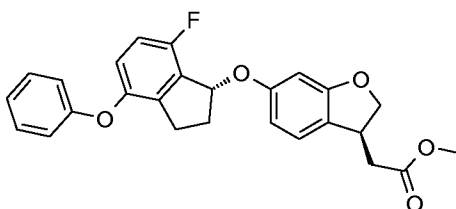
{{(S)-6-[(R)-7-Fluoro-4-hydroxy-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester}



Aqueous hydrogen peroxide solution (35%, 3.7 mL) is added dropwise to a solution of {(S)-6-[(R)-7-fluoro-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester (5.0 g) in acetic acid (30 mL)
 5 chilled in an ice bath. The solution is stirred with cooling for 0.5 h and at room temperature for another 2 h. Ice-cold water (50 mL) and 2 N aqueous NaOH solution (20 mL) are added, and the mixture is stirred at room temperature overnight. The mixture is extracted with ethyl acetate, and the combined extracts are washed with brine and dried (MgSO₄). The solvent is evaporated and the residue is
 10 chromatographed on silica gel (cyclohexane/ethyl acetate 80:20→60:40) to give the title compound. LC (method 2): $t_R = 1.01$ min; Mass spectrum (ESI⁺): $m/z = 359$ [M+H]⁺.

Intermediate 6

15 {(S)-6-[(R)-7-Fluoro-4-phenoxy-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester

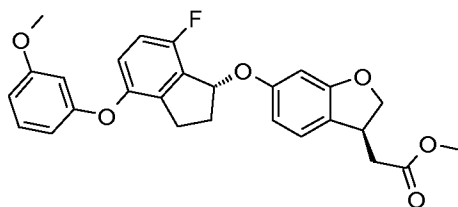


Triethylamine (0.4 mL) is added to a mixture of {(S)-6-[(R)-7-fluoro-4-hydroxy-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester (0.15 g), phenylboronic acid (0.10 g), freshly activated molecular sieves 4A (1.0 g), copper(II) acetate (78 mg) and dichloromethane (8 mL) at room temperature. The flask is purged with O₂
 20 and sealed. The mixture is stirred under O₂ atmosphere (1 bar) at room temperature for 16 h. The mixture is diluted with dichloromethane, filtered and concentrated. The residue is chromatographed on silica gel (cyclohexane/ethyl acetate 90:10→80:20) to

give the title compound. LC (method 3): $t_R = 0.81$ min; Mass spectrum (ESI^+): $m/z = 435$ $[M+H]^+$.

Intermediate 7

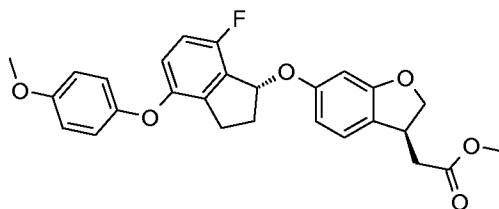
- 5 {{(S)-6-[(R)-7-Fluoro-4-(3-methoxy-phenoxy)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester



- The title compound is prepared from {{(S)-6-[(R)-7-fluoro-4-hydroxy-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester and 3-methoxy-phenylboronic acid following a procedure analogous to that described for Intermediate 6. LC
10 (method 3): $t_R = 0.82$ min; Mass spectrum (ESI^+): $m/z = 487$ $[M+Na]^+$.

Intermediate 8

- 15 {{(S)-6-[(R)-7-Fluoro-4-(4-methoxy-phenoxy)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester

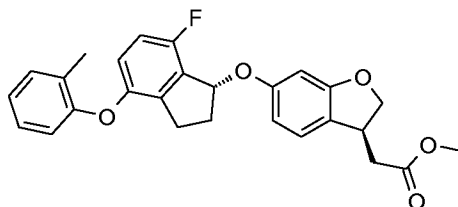


- The title compound is prepared from {{(S)-6-[(R)-7-fluoro-4-hydroxy-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester and 4-methoxy-phenylboronic acid following a procedure analogous to that described for Intermediate 6. LC
20 (method 3): $t_R = 0.78$ min; Mass spectrum (ESI^+): $m/z = 487$ $[M+Na]^+$.

Intermediate 9

{{(S)-6-[(R)-7-Fluoro-4-(2-methyl-phenoxy)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester

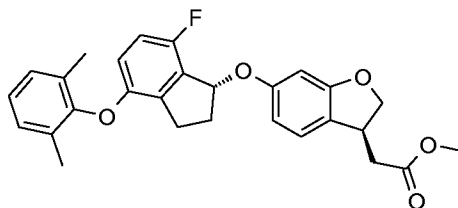
53



The title compound is prepared from {(S)-6-[(R)-7-fluoro-4-hydroxy-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester and 2-methyl-phenylboronic acid following a procedure analogous to that described for Intermediate 6. LC (method 3): $t_R = 0.90$ min; Mass spectrum (ESI⁺): $m/z = 471$ [M+Na]⁺.

Intermediate 10

{(S)-6-[(R)-7-Fluoro-4-(2,6-dimethyl-phenoxy)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester



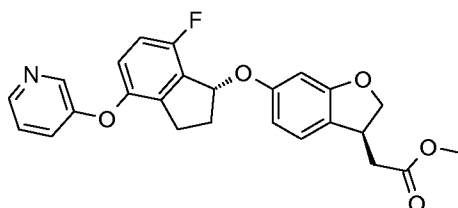
10

The title compound is prepared from {(S)-6-[(R)-7-fluoro-4-hydroxy-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester and 2,6-dimethyl-phenylboronic acid following a procedure analogous to that described for Intermediate 6. LC (method 3): $t_R = 0.96$ min; Mass spectrum (ESI⁺): $m/z = 485$ [M+Na]⁺.

15

Intermediate 11

{(S)-6-[(R)-7-Fluoro-4-pyrid-3-yloxy-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester

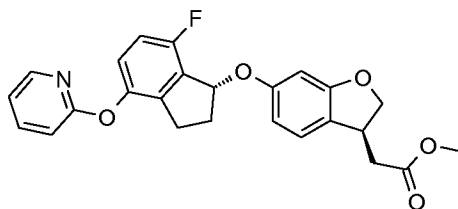


20 The title compound is prepared from {(S)-6-[(R)-7-fluoro-4-hydroxy-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester and pyridine-3-boronic acid

following a procedure analogous to that described for Intermediate 6. LC (method 2): $t_R = 1.08$ min; Mass spectrum (ESI^+): $m/z = 436$ $[M+H]^+$.

Intermediate 12

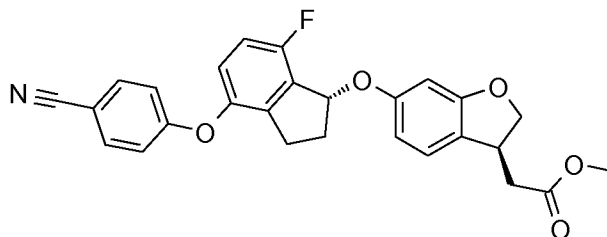
5 {{(S)-6-[(R)-7-Fluoro-4-pyrid-2-yloxy-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester}



A microwave vial is charged with a stir bar, {{(S)-6-[(R)-7-fluoro-4-hydroxy-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester (0.10 g), 2-fluoro-pyridine
10 (27 mg), Cs_2CO_3 (91 mg) and N,N-dimethylformamide (2 mL; alternatively N-methylpyrrolidinone is used). The mixture is stirred at 130 °C for 30 min by irradiation in a microwave oven. After cooling to room temperature, the mixture is concentrated and the residue is chromatographed on silica gel (cyclohexane/ethyl acetate 99:1→80:20) to give the title compound. LC (method 2): $t_R = 1.15$ min; Mass spectrum (ESI^+): m/z
15 = 436 $[M+H]^+$.

Intermediate 13

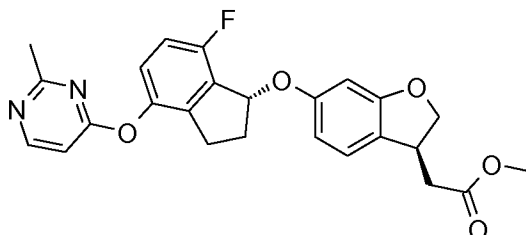
{{(S)-6-[(R)-4-(4-Cyano-phenoxy)-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester}



The title compound is prepared from {{(S)-6-[(R)-7-fluoro-4-hydroxy-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester and 4-fluoro-benzonitrile following a procedure analogous to that described for Intermediate 12. LC (method 2): $t_R = 1.18$ min; Mass spectrum (ESI^+): $m/z = 460$ $[M+H]^+$.

Intermediate 14

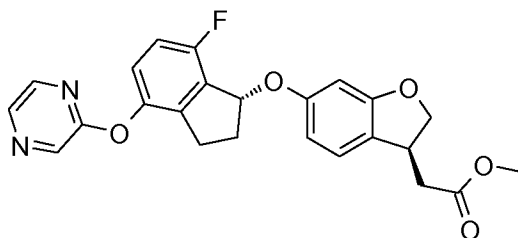
{{(S)-6-[(R)-7-Fluoro-4-(2-methyl-pyrimid-4-yloxy)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester



- 5 The title compound is prepared from {{(S)-6-[(R)-7-fluoro-4-hydroxy-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester and 4-chloro-2-methylpyrimidine following a procedure analogous to that described for Intermediate 12. LC (method 2): $t_R = 1.00$ min; Mass spectrum (ESI^+): $m/z = 451$ $[M+H]^+$.

10 Intermediate 15

{{(S)-6-[(R)-7-Fluoro-4-pyrazin-2-yloxy-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester

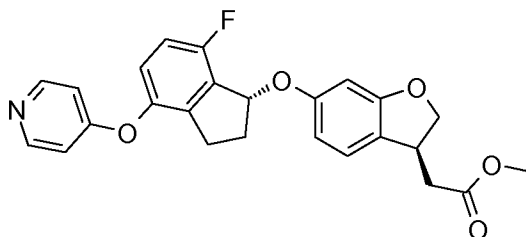


- 15 The title compound is prepared from {{(S)-6-[(R)-7-fluoro-4-hydroxy-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester and 2-fluoro-pyrazine following a procedure analogous to that described for Intermediate 12. LC (method 2): $t_R = 1.11$ min; Mass spectrum (ESI^+): $m/z = 437$ $[M+H]^+$.

Intermediate 16

- 20 {{(S)-6-[(R)-7-Fluoro-4-pyrid-4-yloxy-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester

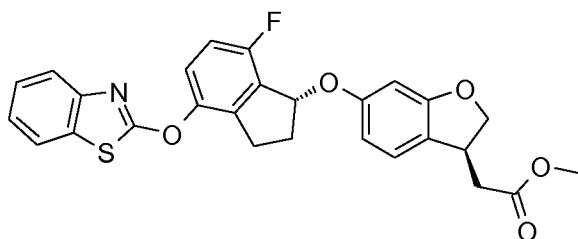
56



The title compound is prepared from {(S)-6-[(R)-7-fluoro-4-hydroxy-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester and 4-fluoro-pyridine following a procedure analogous to that described for Intermediate 12. LC (method 2): t_R = 0.93 min; Mass spectrum (ESI⁺): m/z = 436 [M+H]⁺.

Intermediate 17

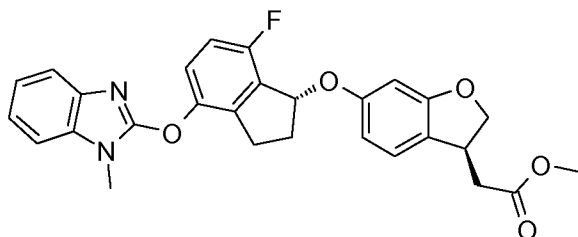
{(S)-6-[(R)-4-Benzothiazol-2-yloxy-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester



The title compound is prepared from {(S)-6-[(R)-7-fluoro-4-hydroxy-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester and 2-chloro-benzothiazole following a procedure analogous to that described for Intermediate 12; K₂CO₃ and acetonitrile are used as base and solvent, respectively, at 90 °C. LC (method 3): t_R = 0.78 min; Mass spectrum (ESI⁺): m/z = 492 [M+H]⁺.

Intermediate 18

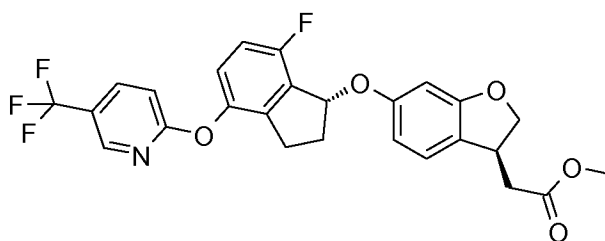
{(S)-6-[(R)-7-Fluoro-4-(1-methyl-1H-benzoimidazol-2-yloxy)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester



The title compound is prepared from {(S)-6-[(R)-7-fluoro-4-hydroxy-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester and 2-chloro-1-methyl-1H-benzoimidazole following a procedure analogous to that described for Intermediate 12; K₂CO₃ and acetonitrile are used as base and solvent, respectively, at 110 °C. LC (method 4): t_R = 0.72 min; Mass spectrum (ESI⁺): m/z = 489 [M+H]⁺.

Intermediate 19

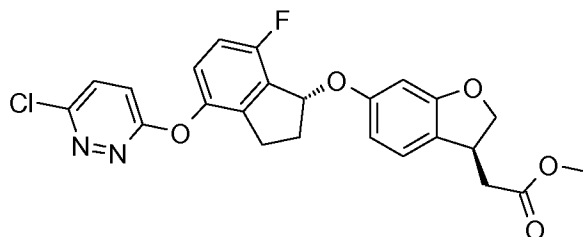
{(S)-6-[(R)-7-Fluoro-4-(5-trifluoromethyl-pyrid-2-yloxy)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester



The title compound is prepared from {(S)-6-[(R)-7-fluoro-4-hydroxy-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester and 2-fluoro-5-trifluoromethyl-pyridine following a procedure analogous to that described for Intermediate 12. LC (method 5): t_R = 1.22 min; Mass spectrum (ESI⁺): m/z = 504 [M+H]⁺.

Intermediate 20

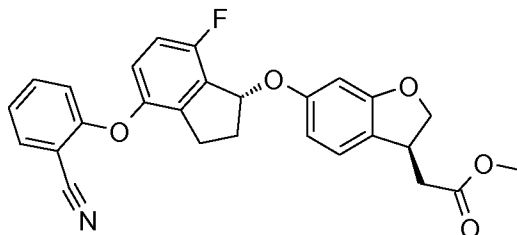
{(S)-6-[(R)-4-(6-Chloro-pyridazin-3-yloxy)-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester



The title compound is prepared from {(S)-6-[(R)-7-fluoro-4-hydroxy-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester and 3,6-dichloro-pyridazine following a procedure analogous to that described for Intermediate 12. LC (method 2): t_R = 1.11 min; Mass spectrum (ESI⁺): m/z = 471/473 (Cl) [M+H]⁺.

Intermediate 21

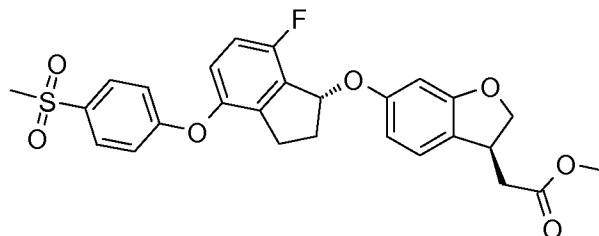
{{(S)-6-[(R)-4-(2-Cyano-phenoxy)-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester



The title compound is prepared from {{(S)-6-[(R)-7-fluoro-4-hydroxy-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester and 2-fluoro-benzonitrile following a procedure analogous to that described for Intermediate 12. LC (method 2): $t_R = 1.11$ min; Mass spectrum (ESI^+): $m/z = 460$ $[M+H]^+$.

Intermediate 22

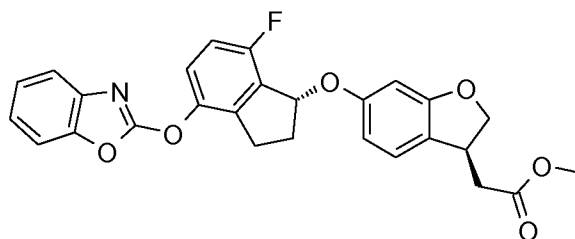
{{(S)-6-[(R)-7-Fluoro-4-(4-methylsulfonyl-phenoxy)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester



The title compound is prepared from {{(S)-6-[(R)-7-fluoro-4-hydroxy-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester and 1-fluoro-4-methylsulfonyl-benzene following a procedure analogous to that described for Intermediate 12. LC (method 2): $t_R = 1.11$ min; Mass spectrum (ESI^+): $m/z = 513$ $[M+H]^+$.

Intermediate 23

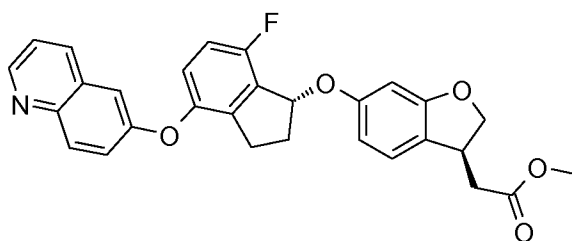
{{(S)-6-[(R)-4-Benzoxazol-2-yloxy-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester



The title compound is prepared from {(S)-6-[(R)-7-fluoro-4-hydroxy-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester and 2-chloro-benzoxazole following a procedure analogous to that described for Intermediate 12; K₂CO₃ and acetonitrile are used as base and solvent, respectively, at room temperature. LC (method 4): t_R = 0.83 min; Mass spectrum (ESI⁺): m/z = 476 [M+H]⁺.

Intermediate 24

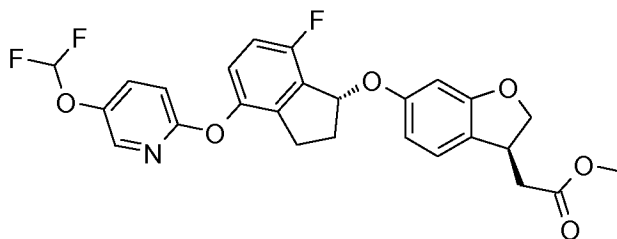
{(S)-6-[(R)-7-Fluoro-4-quinolin-6-yloxy-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester



The title compound is prepared from {(S)-6-[(R)-7-fluoro-4-hydroxy-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester and quinoline-6-boronic acid following a procedure analogous to that described for Intermediate 6. LC (method 4): t_R = 0.64 min; Mass spectrum (ESI⁺): m/z = 486 [M+H]⁺.

Intermediate 25

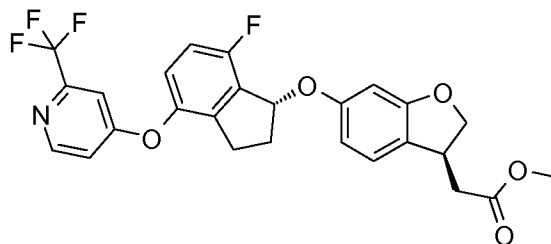
{(S)-6-[(R)-4-(5-Difluoromethoxy-pyrid-2-yloxy)-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester



The title compound is prepared from {(S)-6-[(R)-7-fluoro-4-hydroxy-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester and 5-difluoromethoxy-2-chloro-pyridine following a procedure analogous to that described for Intermediate 12. LC (method 2): t_R = 1.18 min; Mass spectrum (ESI⁺): m/z = 502 [M+H]⁺.

Intermediate 26

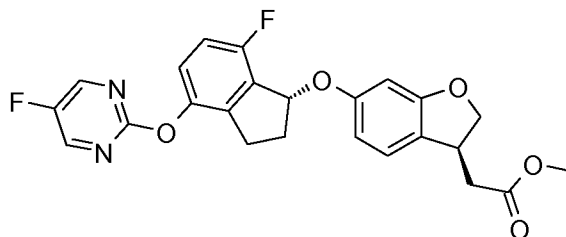
{{(S)-6-[(R)-7-Fluoro-4-(2-trifluoromethyl-pyrid-4-yloxy)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester



The title compound is prepared from {{(S)-6-[(R)-7-fluoro-4-hydroxy-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester and 4-fluoro-2-trifluoromethyl-pyridine following a procedure analogous to that described for Intermediate 12. LC (method 2): t_R = 1.10 min; Mass spectrum (ESI⁺): m/z = 504 [M+H]⁺.

Intermediate 27

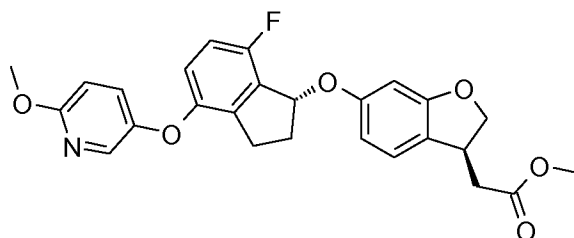
{{(S)-6-[(R)-7-Fluoro-4-(5-fluoro-pyrimid-2-yloxy)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester



The title compound is prepared from {{(S)-6-[(R)-7-fluoro-4-hydroxy-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester and 2-chloro-5-fluoro-pyrimidine following a procedure analogous to that described for Intermediate 12. LC (method 2): t_R = 1.03 min; Mass spectrum (ESI⁺): m/z = 455 [M+H]⁺.

Intermediate 28

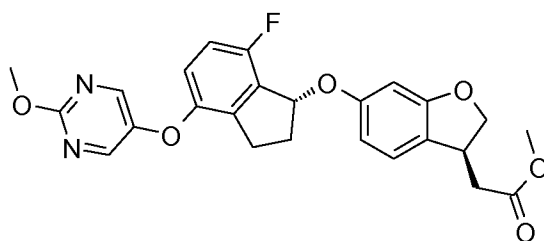
{{(S)-6-[(R)-7-Fluoro-4-(2-methoxy-pyrid-5-yloxy)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester



The title compound is prepared from {(S)-6-[(R)-7-fluoro-4-hydroxy-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester and 2-methoxy-5-pyridineboronic acid following a procedure analogous to that described for Intermediate 6. LC (method 2): t_R = 1.19 min; Mass spectrum (ESI⁺): m/z = 466 [M+H]⁺.

Intermediate 29

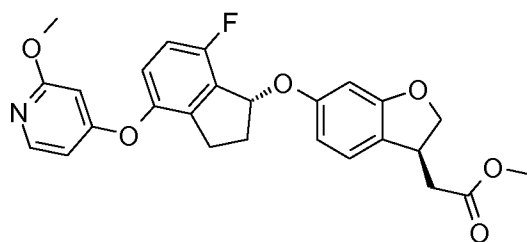
{(S)-6-[(R)-7-Fluoro-4-(2-methoxy-pyrimid-5-yloxy)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester



The title compound is prepared from {(S)-6-[(R)-7-fluoro-4-hydroxy-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester and 2-methoxy-5-pyrimidineboronic acid following a procedure analogous to that described for Intermediate 6. LC (method 2): t_R = 1.10 min; Mass spectrum (ESI⁺): m/z = 467 [M+H]⁺.

Intermediate 30

{(S)-6-[(R)-7-Fluoro-4-(2-methoxy-pyrid-4-yloxy)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester

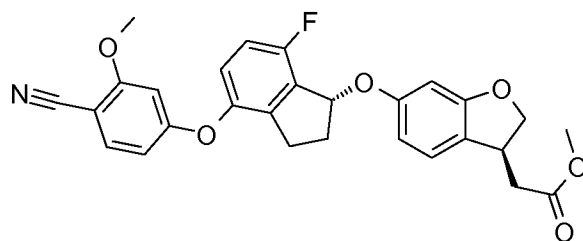


The title compound is prepared from {(S)-6-[(R)-7-fluoro-4-hydroxy-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester and 2-methoxy-4-pyridineboronic acid following a procedure analogous to that described for

Intermediate 6. LC (method 2): $t_R = 1.15$ min; Mass spectrum (ESI⁺): $m/z = 466$ [M+H]⁺.

Intermediate 31

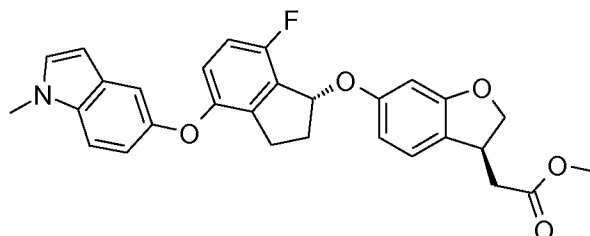
- 5 {{(S)-6-[(R)-4-(4-Cyano-3-methoxy-phenoxy)-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester



- The title compound is prepared from {{(S)-6-[(R)-7-fluoro-4-hydroxy-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester and 4-cyano-3-methoxy-phenylboronic acid following a procedure analogous to that described for Intermediate 6. LC (method 6): $t_R = 1.18$ min; Mass spectrum (ESI⁺): $m/z = 490$ [M+H]⁺.
- 10

Intermediate 32

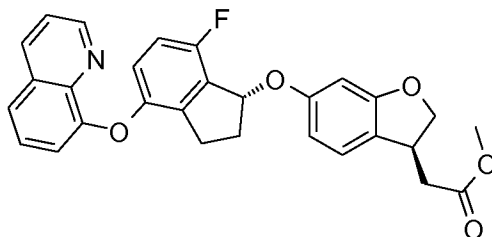
- 15 {{(S)-6-[(R)-7-Fluoro-4-(1-methyl-1H-indol-5-yloxy)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester



- The title compound is prepared from {{(S)-6-[(R)-7-fluoro-4-hydroxy-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester and N-methyl-indole-5-boronic acid following a procedure analogous to that described for Intermediate 6. LC (method 4): $t_R = 0.87$ min; Mass spectrum (ESI⁺): $m/z = 488$ [M+H]⁺.
- 20

Intermediate 33

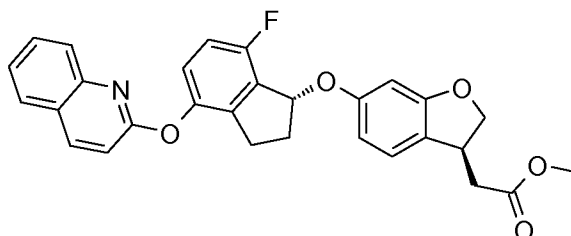
{{(S)-6-[(R)-7-Fluoro-4-(quinolin-8-yloxy)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester



The title compound is prepared from {{(S)-6-[(R)-7-fluoro-4-hydroxy-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester and quinoline-8-boronic acid following a procedure analogous to that described for Intermediate 6. LC (method 4): $t_R = 0.64$ min; Mass spectrum (ESI⁺): $m/z = 486$ [M+H]⁺.

Intermediate 34

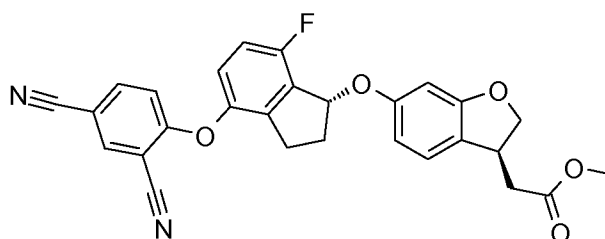
{{(S)-6-[(R)-7-Fluoro-4-(quinolin-2-yloxy)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester



The title compound is prepared from {{(S)-6-[(R)-7-fluoro-4-hydroxy-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester and quinoline-2-boronic acid following a procedure analogous to that described for Intermediate 6. LC (method 4): $t_R = 0.86$ min; Mass spectrum (ESI⁺): $m/z = 486$ [M+H]⁺.

Intermediate 35

{{(S)-6-[(R)-4-(2,4-Dicyano-phenoxy)-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester

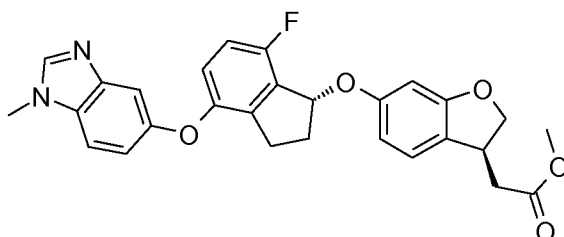


The title compound is prepared from {(S)-6-[(R)-7-fluoro-4-hydroxy-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester and 4-fluoro-isophthalonitrile following a procedure analogous to that described for Intermediate 12. LC (method 6): t_R = 1.14 min; Mass spectrum (ESI⁺): m/z = 485 [M+H]⁺.

5

Intermediate 36

{(S)-6-[(R)-7-fluoro-4-(1-methyl-1H-benzimidazol-5-yloxy)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester

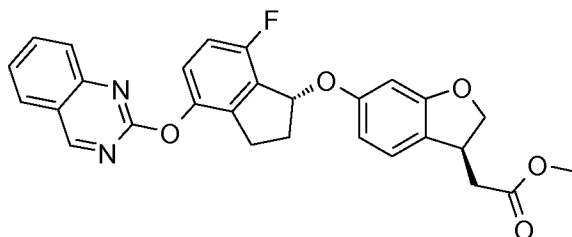


10 The title compound is prepared from {(S)-6-[(R)-7-fluoro-4-hydroxy-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester and (1-methyl-1H-benzimidazol-5-yl)boronic acid following a procedure analogous to that described for Intermediate 6. LC (method 7): t_R = 0.36 min; Mass spectrum (ESI⁺): m/z = 489 [M+H]⁺.

15

Intermediate 37

{(S)-6-[(R)-7-Fluoro-4-(quinazolin-2-yloxy)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester

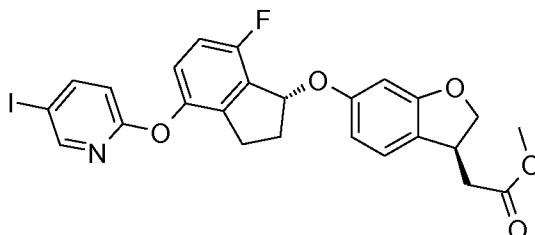


20 The title compound is prepared from {(S)-6-[(R)-7-fluoro-4-hydroxy-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester and 2-chloro-quinazoline following a procedure analogous to that described for Intermediate 12; K₂CO₃ and acetonitrile are used as base and solvent, respectively, at 50 °C. LC (method 3): t_R = 0.53 min; Mass spectrum (ESI⁺): m/z = 487 [M+H]⁺.

25

Intermediate 38

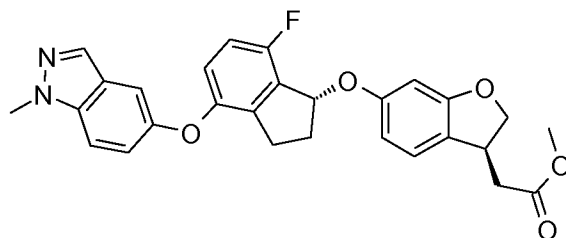
{{(S)-6-[(R)-7-fluoro-4-(5-iodo-pyrid-2-yloxy)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester



- 5 The title compound is prepared from {{(S)-6-[(R)-7-fluoro-4-hydroxy-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester and 2-fluoro-5-iodo-pyridine following a procedure analogous to that described for Intermediate 12. LC (method 6): $t_R = 1.24$ min; Mass spectrum (ESI^+): $m/z = 562$ $[M+H]^+$.

Intermediate 39

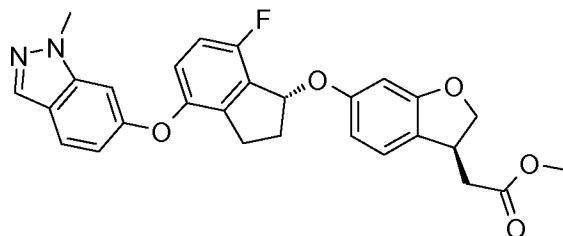
{{(S)-6-[(R)-7-Fluoro-4-(1-methyl-1H-indazol-5-yloxy)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester



- 15 The title compound is prepared from {{(S)-6-[(R)-7-fluoro-4-hydroxy-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester and 1-methyl-indazole-5-boronic acid following a procedure analogous to that described for Intermediate 6. LC (method 3): $t_R = 0.65$ min; Mass spectrum (ESI^+): $m/z = 489$ $[M+H]^+$.

Intermediate 40

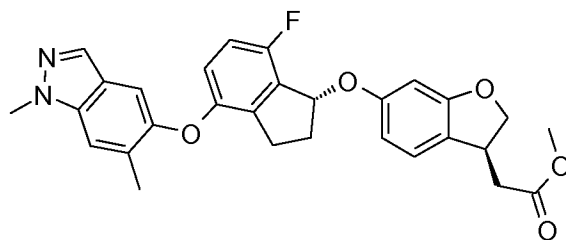
- 20 {{(S)-6-[(R)-7-Fluoro-4-(1-methyl-1H-indazol-6-yloxy)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester



The title compound is prepared from {(S)-6-[(R)-7-fluoro-4-hydroxy-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester and 1-methyl-indazole-6-boronic acid following a procedure analogous to that described for Intermediate 6. LC (method 3): $t_R = 0.65$ min; Mass spectrum (ESI⁺): $m/z = 489$ [M+H]⁺.

Intermediate 41

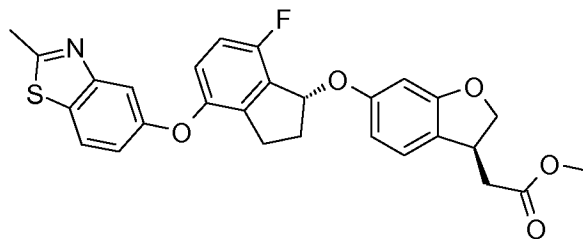
{(S)-6-[(R)-7-Fluoro-4-(1,6-dimethyl-1H-indazol-5-yloxy)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester



The title compound is prepared from {(S)-6-[(R)-7-fluoro-4-hydroxy-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester and 1,6-dimethyl-indazole-5-boronic acid following a procedure analogous to that described for Intermediate 6. LC (method 10): $t_R = 0.89$ min; Mass spectrum (ESI⁺): $m/z = 503$ [M+H]⁺.

Intermediate 42

{(S)-6-[(R)-7-Fluoro-4-(2-methyl-benzothiazol-5-yloxy)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester

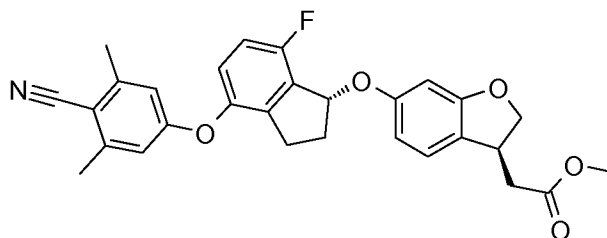


The title compound is prepared from {(S)-6-[(R)-7-fluoro-4-hydroxy-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester and 2-methyl-benzothiazole-5-

boronic acid following a procedure analogous to that described for Intermediate 6. LC (method 10): $t_R = 0.91$ min; Mass spectrum (ESI⁺): $m/z = 506$ [M+H]⁺.

Intermediate 43

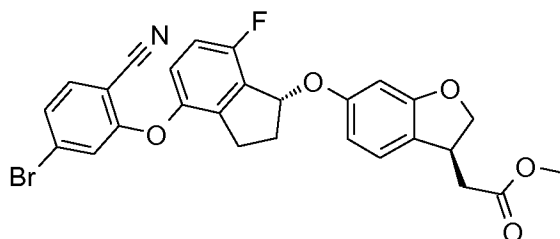
- 5 {{(S)-6-[(R)-4-(4-Cyano-3,5-dimethyl-phenoxy)-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester



- The title compound is prepared from {{(S)-6-[(R)-7-fluoro-4-hydroxy-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester and 2,6-dimethyl-4-fluorobenzonitrile following a procedure analogous to that described for Intermediate 12. LC (method 6): $t_R = 1.24$ min; Mass spectrum (ESI⁺): $m/z = 488$ [M+H]⁺.

Intermediate 44

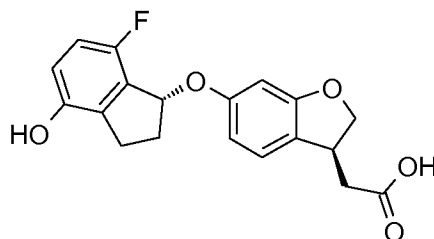
- 15 {{(S)-6-[(R)-4-(5-Bromo-2-cyano-phenoxy)-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester



- The title compound is prepared from {{(S)-6-[(R)-7-fluoro-4-hydroxy-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester and 4-bromo-2-fluorobenzonitrile following a procedure analogous to that described for Intermediate 12. LC (method 11): $t_R = 0.87$ min; Mass spectrum (ESI⁺): $m/z = 538/540$ (Br) [M+H]⁺.

Intermediate 45

{{(S)-6-[(R)-7-Fluoro-4-hydroxy-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid

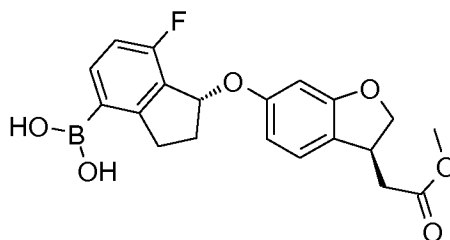


The title compound is prepared from {(S)-6-[(R)-7-fluoro-4-hydroxy-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester following a procedure analogous to that described for Example 1.

5

Intermediate 46

(R)-7-Fluoro-1-[(S)-3-methoxycarbonylmethyl-2,3-dihydrobenzofuran-6-yloxy]-2,3-dihydro-1H-inden-4-ylboronic acid



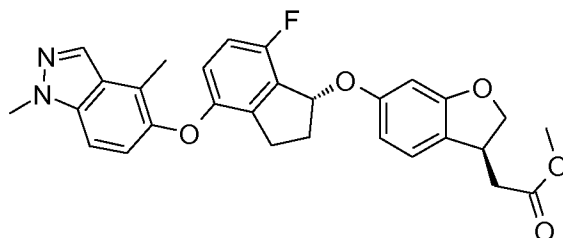
- 10 A microwave vial charged with a stir bar, {(S)-6-[(R)-4-bromo-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester (7.00 g), bis(pinacolato)-diboron (5.60 g), potassium acetate (4.20 g) and 1,4-dioxane (100 mL) is purged with argon for 10 min. [1,1'-Bis(diphenylphosphino)-ferrocene]-dichloropalladium(II) (0.60 g) is added, the vial is sealed, and the mixture is stirred at 100 °C for 4 h. After
- 15 cooling to room temperature, saturated aqueous NH₄Cl solution is added and the resulting mixture is extracted with diethyl ether. The combined extracts are dried (MgSO₄) and concentrated. The residue is chromatographed on silica gel (cyclohexane/ethyl acetate 99:1→70:30) to give {(S)-6-[(R)-7-fluoro-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester.
- 20

{(S)-6-[(R)-7-fluoro-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester (3.00 g) is dissolved in acetone (20 mL) and water (10 mL). NaIO₄ (5.90 g) and NH₄O₂CCH₃ (2.85 g) are added. The mixture is stirred at room temperature for 36 h. Water is added and the resulting

mixture is extracted with ethyl acetate. The combined extract is dried (Na_2SO_4) and concentrated to give the title compound LC (method 12): $t_R = 1.02$ min; Mass spectrum (ESI^+): $m/z = 387$ $[\text{M}+\text{H}]^+$.

5 Intermediate 47

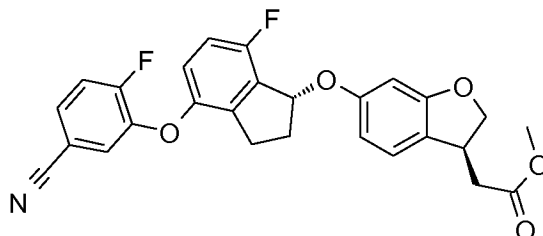
{{(S)-6-[(R)-7-Fluoro-4-(1,4-dimethyl-1H-indazol-5-yloxy)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester



The title compound is prepared from {{(S)-6-[(R)-7-fluoro-4-hydroxy-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester and 1,4-dimethyl-indazole-5-boronic acid following a procedure analogous to that described for Intermediate 6. LC (method 10): $t_R = 0.88$ min; Mass spectrum (ESI^+): $m/z = 503$ $[\text{M}+\text{H}]^+$.

Intermediate 48

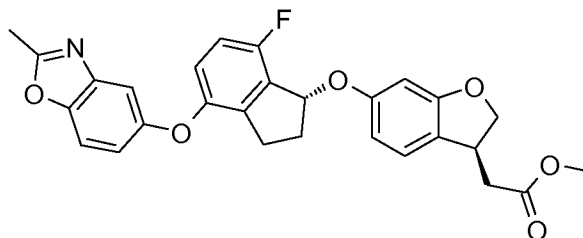
15 {{(S)-6-[(R)-4-(5-Cyano-2-fluoro-phenoxy)-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester



The title compound is prepared from {{(S)-6-[(R)-7-fluoro-4-hydroxy-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester and 5-cyano-2-fluorophenylboronic acid following a procedure analogous to that described for Intermediate 6. LC (method 10): $t_R = 0.84$ min; Mass spectrum (ESI^+): $m/z = 478$ $[\text{M}+\text{H}]^+$.

Intermediate 49

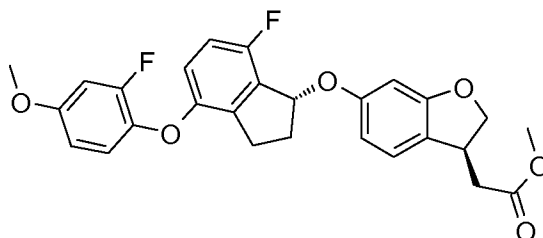
{{(S)-6-[(R)-7-Fluoro-4-(2-methyl-benzoxazol-5-yloxy)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester



The title compound is prepared from (R)-7-fluoro-1-[(S)-3-methoxycarbonylmethyl-
 5 2,3-dihydrobenzofuran-6-yloxy]-2,3-dihydro-1H-inden-4-ylboronic acid and 5-hydroxy-2-methyl-benzoxazole following a procedure analogous to that described for Intermediate 6. LC (method 10): t_R = 0.85 min; Mass spectrum (ESI⁺): m/z = 490 [M+H]⁺.

10 Intermediate 50

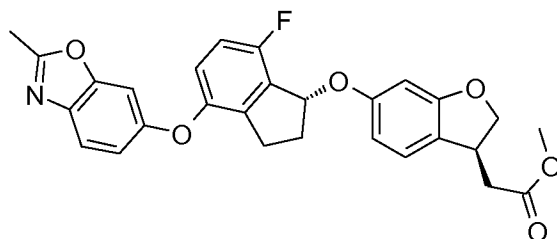
{{(S)-6-[(R)-4-(2-Fluoro-4-methoxy-phenoxy)-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester



The title compound is prepared from {{(S)-6-[(R)-7-fluoro-4-hydroxy-indan-1-yloxy]-
 15 2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester and 2-fluoro-4-methoxy-phenylboronic acid following a procedure analogous to that described for Intermediate 6. LC (method 10): t_R = 0.92 min; Mass spectrum (ESI⁺): m/z = 505 [M+Na]⁺.

20 Intermediate 51

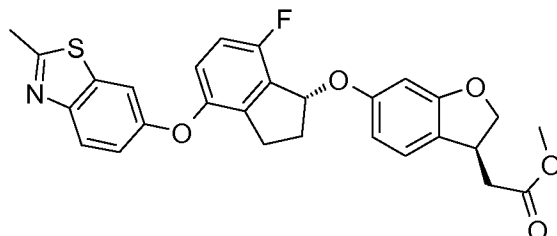
{{(S)-6-[(R)-7-Fluoro-4-(2-methyl-benzoxazol-6-yloxy)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester



The title compound is prepared from {(S)-6-[(R)-7-fluoro-4-hydroxy-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester and 2-methyl-benzoxazol-6-boronic acid (prepared from 6-bromo-2-methyl-benzoxazole in analogy to the
 5 procedure described for Intermediate 46) following a procedure analogous to that described for Intermediate 6. LC (method 3): t_R = 0.65 min; Mass spectrum (ESI⁺): m/z = 490 [M+H]⁺.

Intermediate 52

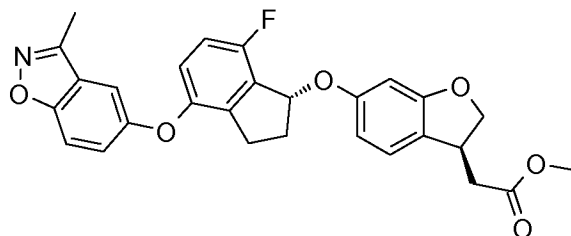
10 {(S)-6-[(R)-7-Fluoro-4-(2-methyl-benzothiazol-6-yloxy)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester



The title compound is prepared from {(S)-6-[(R)-7-fluoro-4-hydroxy-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester and 2-methyl-benzothiazol-6-boronic acid (prepared from 2-methyl-benzothiazole-6-ylboronic acid pinacol ester
 15 using NaIO₄ and NH₄O₂CCH₃ in acetone and water) following a procedure analogous to that described for Intermediate 6. LC (method 3): t_R = 0.74 min; Mass spectrum (ESI⁺): m/z = 506 [M+H]⁺.

Intermediate 53

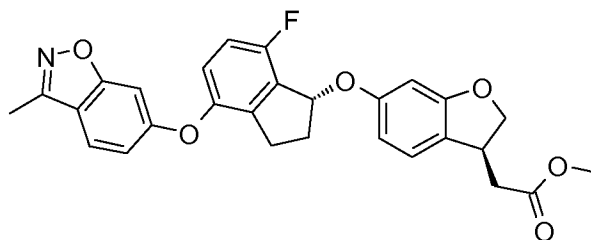
20 {(S)-6-[(R)-7-Fluoro-4-(3-methyl-benzo[d]isoxazol-5-yloxy)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester



The title compound is prepared from (*R*)-7-fluoro-1-[(*S*)-3-methoxycarbonylmethyl-2,3-dihydrobenzofuran-6-yloxy]-2,3-dihydro-1*H*-inden-4-ylboronic acid and 3-methyl-benzo[d]isoxazol-5-ol following a procedure analogous to that described for
 5 Intermediate 6. LC (method 3): t_R = 0.68 min; Mass spectrum (ESI⁺): m/z = 490 [M+H]⁺.

Intermediate 54

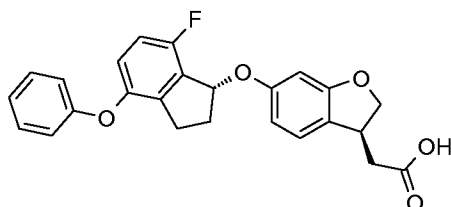
{(S)-6-[(R)-7-Fluoro-4-(3-methyl-benzo[d]isoxazol-6-yloxy)-indan-1-yloxy]-2,3-
 10 dihydro-benzofuran-3-yl}-acetic acid methyl ester



The title compound is prepared from (*R*)-7-fluoro-1-[(*S*)-3-methoxycarbonylmethyl-2,3-dihydrobenzofuran-6-yloxy]-2,3-dihydro-1*H*-inden-4-ylboronic acid and 3-methyl-benzo[d]isoxazol-6-ol following a procedure analogous to that described for
 15 Intermediate 6. LC (method 3): t_R = 0.66 min; Mass spectrum (ESI⁺): m/z = 490 [M+H]⁺.

Example 1

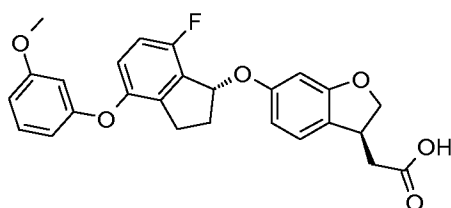
{(S)-6-[(R)-7-Fluoro-4-phenoxy-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic
 20 acid



1 M aqueous NaOH solution (3.0 mL) is added to a solution of {(S)-6-[(R)-7-fluoro-4-phenoxy-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester (0.18 g) in methanol (6 mL) and tetrahydrofuran (6 mL) at room temperature. The mixture is stirred at room temperature for 4 h. The organic solvent is evaporated, water (2 mL) is added, and the resulting solution is neutralized with 1 M aqueous HCl solution (3 mL). The solution is stirred at room temperature for 1 h. The precipitate is separated by filtration, washed with water and dried to give the title compound (if the compound does not precipitate, the solution is concentrated and the residue is purified by HPLC on reversed phase using acetonitrile, water and ammonia as eluent). LC (method 3): $t_R = 1.14$ min; Mass spectrum (ESI^-): $m/z = 419$ $[M-H]^-$.

Example 2

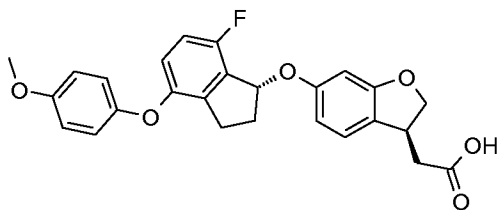
{(S)-6-[(R)-7-Fluoro-4-(3-methoxy-phenoxy)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid



The title compound is prepared from {(S)-6-[(R)-7-fluoro-4-(3-methoxy-phenoxy)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester following a procedure analogous to that described for Example 1. LC (method 3): $t_R = 0.55$ min; Mass spectrum (ESI^-): $m/z = 449$ $[M-H]^-$.

Example 3

{(S)-6-[(R)-7-Fluoro-4-(4-methoxy-phenoxy)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid

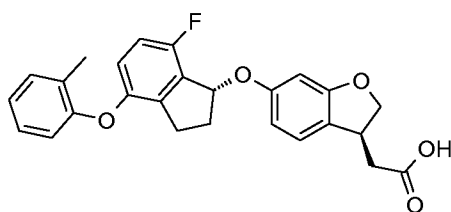


The title compound is prepared from {(S)-6-[(R)-7-fluoro-4-(4-methoxy-phenoxy)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester following a

procedure analogous to that described for Example 1. LC (method 3): $t_R = 0.50$ min; Mass spectrum (ESI⁻): $m/z = 449$ [M-H]⁻.

Example 4

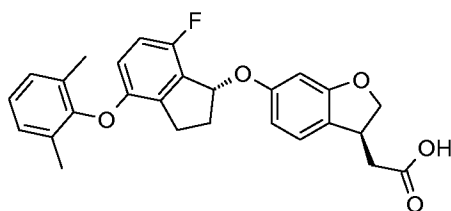
5 {{(S)-6-[(R)-7-Fluoro-4-(2-methyl-phenoxy)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid



The title compound is prepared from {(S)-6-[(R)-7-fluoro-4-(2 methyl-phenoxy)-indan-1-yloxy]-2,3-dihydro-benzofuran-1-yloxy}-acetic acid methyl ester following a procedure
10 analogous to that described for Example 1. LC (method 3): $t_R = 0.68$ min; Mass spectrum (ESI⁻): $m/z = 433$ [M-H]⁻.

Example 5

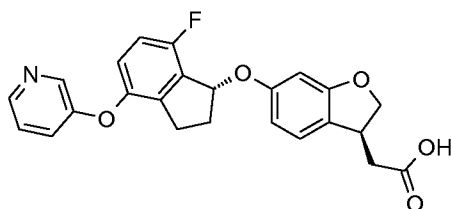
15 {{(S)-6-[(R)-7-Fluoro-4-(2,6-dimethyl-phenoxy)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid



The title compound is prepared from {(S)-6-[(R)-7-fluoro-4-(2,6-dimethyl-phenoxy)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester following a procedure analogous to that described for Example 1. LC (method 3): $t_R = 0.77$ min;
20 Mass spectrum (ESI⁻): $m/z = 447$ [M-H]⁻.

Example 6

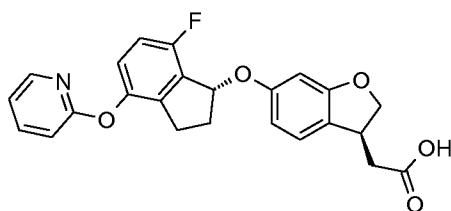
{{(S)-6-[(R)-7-Fluoro-4-pyrid-3-yloxy-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid



The title compound is prepared from {(S)-6-[(R)-7-fluoro-4-pyrid-3-yloxy-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester following a procedure analogous to that described for Example 1. LC (method 2): $t_R = 0.97$ min; Mass spectrum (ESI⁻): $m/z = 420$ [M-H]⁻.

Example 7

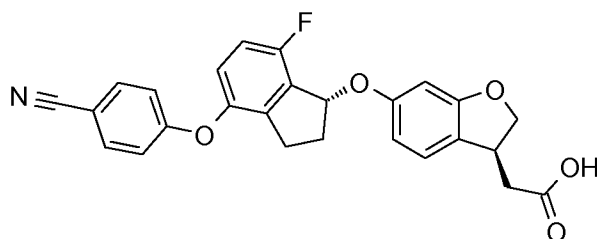
{(S)-6-[(R)-7-Fluoro-4-pyrid-2-yloxy-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid



The title compound is prepared from {(S)-6-[(R)-7-fluoro-4-pyrid-2-yloxy-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester following a procedure analogous to that described for Example 1. LC (method 2): $t_R = 1.05$ min; Mass spectrum (ESI⁻): $m/z = 420$ [M-H]⁻.

Example 8

{(S)-6-[(R)-4-(4-Cyano-phenoxy)-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid

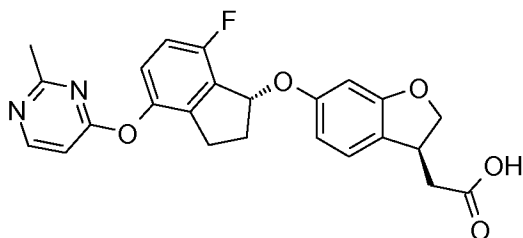


The title compound is prepared from {(S)-6-[(R)-4-(4-cyano-phenoxy)-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester following a procedure

analogous to that described for Example 1. LC (method 2): $t_R = 1.09$ min; Mass spectrum (ESI⁻): $m/z = 444$ [M-H]⁻.

Example 9

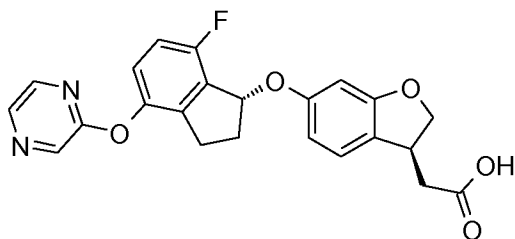
5 {{(S)-6-[(R)-7-Fluoro-4-(2-methyl-pyrimid-4-yloxy)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid



The title compound is prepared from {{(S)-6-[(R)-7-fluoro-4-(2-methyl-pyrimid-4-yloxy)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester following a procedure analogous to that described for Example 1. LC (method 2): $t_R = 0.96$ min; Mass spectrum (ESI⁻): $m/z = 435$ [M-H]⁻.

Example 10

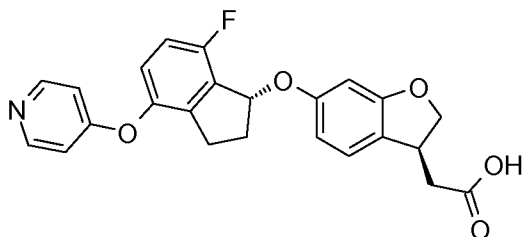
15 {{(S)-6-[(R)-7-Fluoro-4-pyrazin-2-yloxy-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid



The title compound is prepared from {{(S)-6-[(R)-7-fluoro-4-pyrazin-2-yloxy-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester following a procedure analogous to that described for Example 1. LC (method 2): $t_R = 1.01$ min; Mass spectrum (ESI⁻): $m/z = 421$ [M-H]⁻.

Example 11

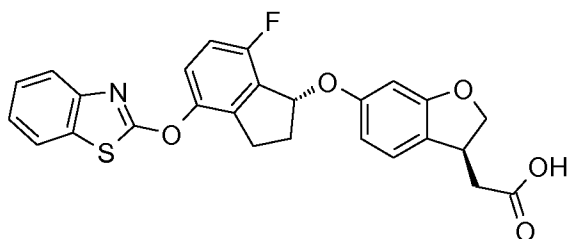
{{(S)-6-[(R)-7-Fluoro-4-pyrid-4-yloxy-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid



The title compound is prepared from {(S)-6-[(R)-7-fluoro-4-pyrid-4-yloxy-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester following a procedure analogous to that described for Example 1. LC (method 2): $t_R = 0.82$ min; Mass spectrum (ESI⁺): $m/z = 422$ [M+H]⁺.

Example 12

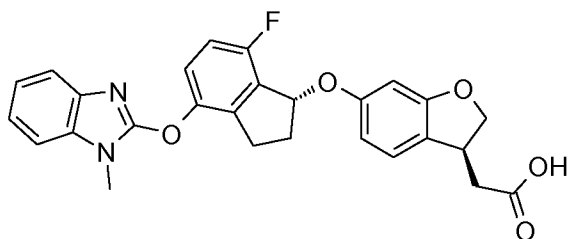
{(S)-6-[(R)-4-Benzothiazol-2-yloxy-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid



The title compound is prepared from {(S)-6-[(R)-4-benzothiazol-2-yloxy-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester following a procedure analogous to that described for Example 1. LC (method 2): $t_R = 1.15$ min; Mass spectrum (ESI⁻): $m/z = 476$ [M-H]⁻.

Example 13

{(S)-6-[(R)-7-Fluoro-4-(1-methyl-1H-benzoimidazol-2-yloxy)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid

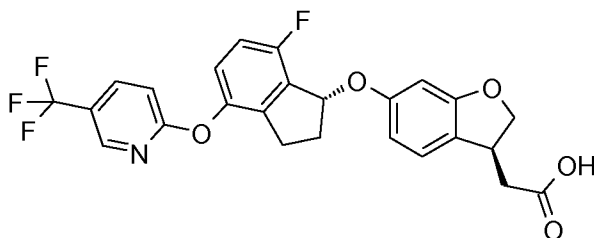


The title compound is prepared from {(S)-6-[(R)-7-fluoro-4-(1-methyl-1H-benzoimidazol-2-yloxy)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid

methyl ester following a procedure analogous to that described for Example 1. LC (method 4): $t_R = 0.59$ min; Mass spectrum (ESI⁻): $m/z = 473$ [M-H]⁻.

Example 14

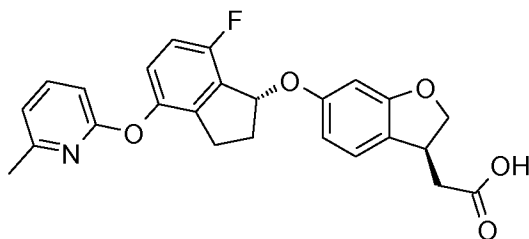
- 5 {{(S)-6-[(R)-7-Fluoro-4-(5-trifluoromethyl-pyrid-2-yloxy)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid



- 10 The title compound is prepared from {{(S)-6-[(R)-7-fluoro-4-(5-trifluoromethyl-pyrid-2-yloxy)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester following a procedure analogous to that described for Example 1. LC (method 5): $t_R = 0.83$ min; Mass spectrum (ESI⁻): $m/z = 488$ [M-H]⁻.

Example 15

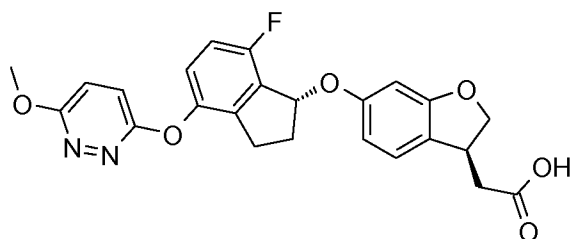
- 15 {{(S)-6-[(R)-7-Fluoro-4-(6-methyl-pyrid-2-yloxy)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid



- 20 The title compound is prepared from {{(S)-6-[(R)-7-fluoro-4-(hydroxy-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester and 2-fluoro-6-methyl-pyridine following a procedure analogous to that described for Intermediate 12; the reaction is conducted at 150 °C in a microwave oven, the ester is cleaved, too. LC (method 2): $t_R = 1.10$ min; Mass spectrum (ESI⁺): $m/z = 436$ [M+H]⁺.

Example 16

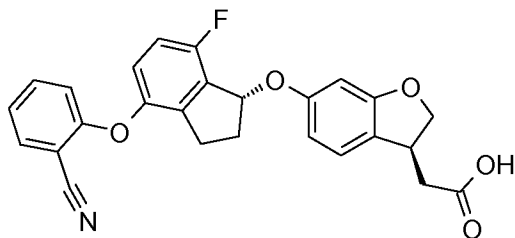
- 25 {{(S)-6-[(R)-7-Fluoro-4-(6-methoxy-pyridazin-3-yloxy)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid



NaOCH₃ (0.5 mol/L in methanol; 1.3 mL) is added to a solution of {(S)-6-[(R)-4-(6-chloro-pyridazin-3-yloxy)-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester in tetrahydrofuran (3 mL) and methanol (0.1 mL) at room temperature. The solution is stirred at room temperature for 1 h, and then 4 M aqueous NaOH solution (0.21 mL) is added. The solution is stirred for 1 h and is then concentrated. The residue is purified by HPLC (acetonitrile/water/ammonia) to give the title compound. LC (method 2): t_R = 1.02 min; Mass spectrum (ESI⁻): m/z = 451 [M-H]⁻.

Example 17

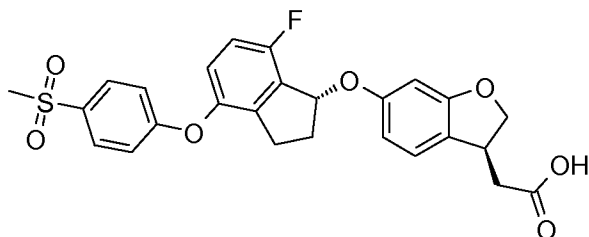
{(S)-6-[(R)-4-(2-Cyano-phenoxy)-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid



The title compound is prepared from {(S)-6-[(R)-4-(2-cyano-phenoxy)-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester following a procedure analogous to that described for Example 1. LC (method 2): t_R = 1.08 min; Mass spectrum (ESI⁻): m/z = 444 [M-H]⁻.

Example 18

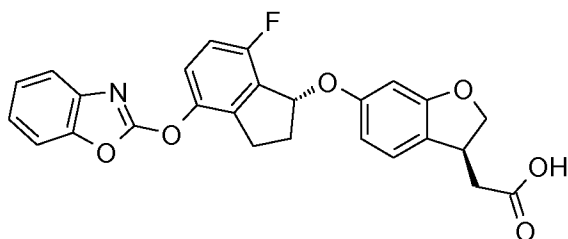
{(S)-6-[(R)-7-Fluoro-4-(4-methylsulfonyl-phenoxy)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid



The title compound is prepared from {(S)-6-[(R)-7-fluoro-4-(4-methylsulfonylphenoxy)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester following a procedure analogous to that described for Example 1. LC (method 2): $t_R =$
 5 1.08 min; Mass spectrum (ESI⁺): $m/z = 499$ [M+H]⁺.

Example 19

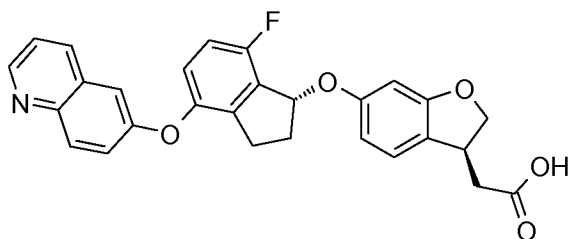
{(S)-6-[(R)-4-Benzoxazol-2-yloxy-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid



The title compound is prepared from {(S)-6-[(R)-4-benzoxazol-2-yloxy-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester following a procedure analogous to that described for Example 1. LC (method 4): $t_R = 0.68$ min; Mass spectrum (ESI⁻): $m/z = 460$ [M-H]⁻.

Example 20

{(S)-6-[(R)-7-Fluoro-4-quinolin-6-yloxy-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid

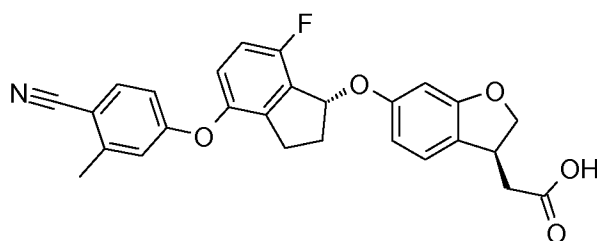


The title compound is prepared from {(S)-6-[(R)-7-fluoro-4-quinolin-6-yloxy-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester following a procedure

analogous to that described for Example 1. LC (method 4): $t_R = 0.47$ min; Mass spectrum (ESI⁻): $m/z = 470$ [M-H]⁻.

Example 21

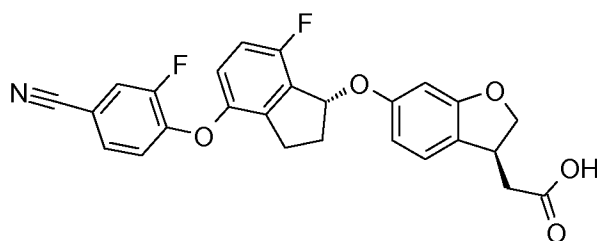
5 {{(S)-6-[(R)-4-(4-Cyano-3-methyl-phenoxy)-7-fluoro-4-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid



The methyl ester of the title compound is prepared from {(S)-6-[(R)-7-fluoro-4-hydroxy-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester and 4-fluoro-2-methyl-benzonitrile following a procedure analogous to that described for
10 Intermediate 12. The title compound is obtained after saponification of the methyl ester as described for Example 1. LC (method 2): $t_R = 1.13$ min; Mass spectrum (ESI⁺): $m/z = 460$ [M+H]⁺.

15 Example 22

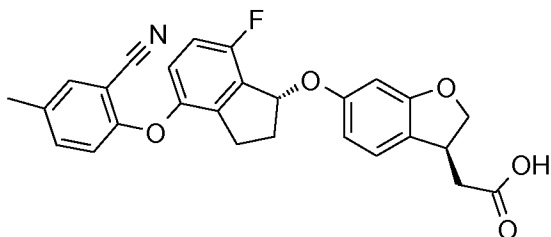
{{(S)-6-[(R)-4-(4-Cyano-2-fluoro-phenoxy)-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid



The methyl ester of the title compound is prepared from {(S)-6-[(R)-7-fluoro-4-hydroxy-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester and 3,4-difluoro-benzonitrile following a procedure analogous to that described for
20 Intermediate 12. The title compound is obtained after saponification of the methyl ester as described for Example 1. LC (method 2): $t_R = 1.11$ min; Mass spectrum (ESI⁺): $m/z = 464$ [M+H]⁺.

Example 23

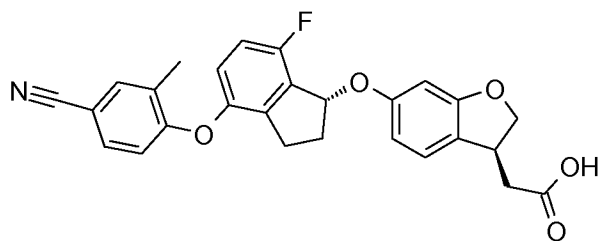
{{(S)-6-[(R)-4-(2-Cyano-4-methyl-phenoxy)-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid



- 5 The methyl ester of the title compound is prepared from {(S)-6-[(R)-7-fluoro-4-hydroxy-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester and 2-fluoro-5-methyl-benzonitrile following a procedure analogous to that described for Intermediate 12. The title compound is obtained after saponification of the methyl ester as described for Example 1. LC (method 2): $t_R = 1.12$ min; Mass spectrum (ESI⁺): $m/z = 460$ [M+H]⁺.
- 10

Example 24

{{(S)-6-[(R)-4-(4-Cyano-2-methyl-phenoxy)-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid

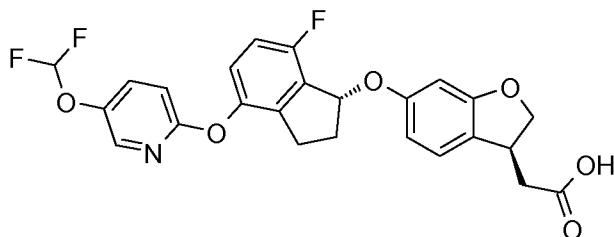


- 15 The methyl ester of the title compound is prepared from {(S)-6-[(R)-7-fluoro-4-hydroxy-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester and 4-fluoro-3-methyl-benzonitrile following a procedure analogous to that described for Intermediate 12. The title compound is obtained after saponification of the methyl ester as described for Example 1. LC (method 2): $t_R = 1.14$ min; Mass spectrum (ESI⁺): $m/z = 460$ [M+H]⁺.
- 20

Example 25

{{(S)-6-[(R)-4-(5-Difluoromethoxy-pyrid-2-yloxy)-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid

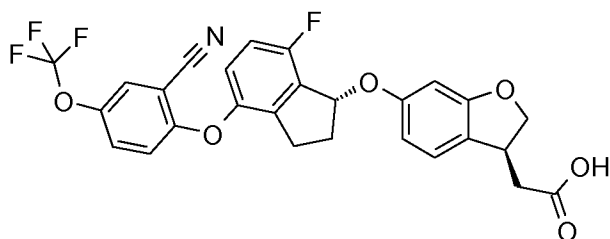
- 25



The title compound is prepared from {(S)-6-[(R)-4-(5-difluoromethoxy-pyrid-2-yloxy)-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester following a procedure analogous to that described for Example 1. LC (method 8): t_R = 0.64 min; Mass spectrum (ESI⁻): m/z = 488 [M-H]⁻.

Example 26

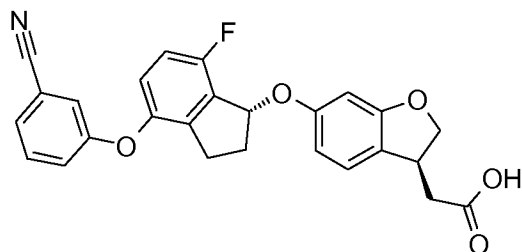
{(S)-6-[(R)-4-(2-Cyano-4-trifluoromethoxy-phenoxy)-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid



The methyl ester of the title compound is prepared from {(S)-6-[(R)-7-fluoro-4-hydroxy-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester and 2-fluoro-5-trifluoromethoxy-benzonitrile following a procedure analogous to that described for Intermediate 12. The title compound is obtained after saponification of the methyl ester as described for Example 1. LC (method 2): t_R = 1.16 min; Mass spectrum (ESI⁺): m/z = 530 [M+H]⁺.

Example 27

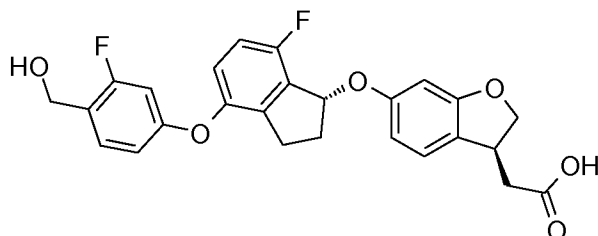
{(S)-6-[(R)-4-(3-Cyano-phenoxy)-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid



The methyl ester of the title compound is prepared from {(S)-6-[(R)-7-fluoro-4-hydroxy-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester and 3-cyano-phenylboronic acid following a procedure analogous to that described for
 5 Intermediate 6. The title compound is obtained after saponification of the methyl ester as described for Example 1. LC (method 2): $t_R = 1.10$ min; Mass spectrum (ESI⁺): $m/z = 446$ [M+H]⁺.

Example 28

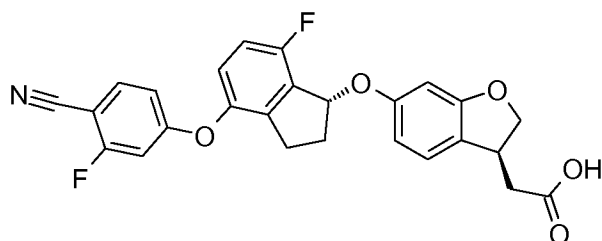
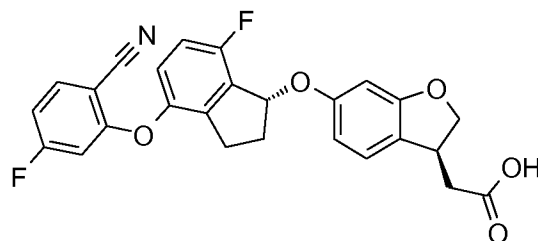
10 {(S)-6-[(R)-7-Fluoro-4-(3-fluoro-4-hydroxymethyl-phenoxy)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid



The methyl ester of the title compound is prepared from {(S)-6-[(R)-7-fluoro-4-hydroxy-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester and 3-fluoro-4-hydroxymethyl-phenylboronic acid following a procedure analogous to that
 15 described for Intermediate 6. The title compound is obtained after saponification of the methyl ester as described for Example 1. LC (method 6): $t_R = 1.02$ min; Mass spectrum (ESI⁻): $m/z = 467$ [M-H]⁻.

20 Example 29 and Example 30

{(S)-6-[(R)-4-(4-Cyano-3-fluoro-phenoxy)-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid (Example 29) and {(S)-6-[(R)-4-(2-Cyano-5-fluoro-phenoxy)-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid (Example
 30)

**Example 29****Example 30**

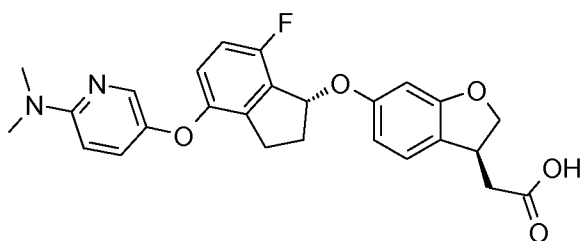
A mixture of the methyl esters of the title compounds are prepared from {(S)-6-[(R)-7-fluoro-4-hydroxy-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester and 2,4-difluoro-benzonitrile following a procedure analogous to that described for Intermediate 12. The title compounds are obtained in separated fractions after saponification of the methyl esters as described for Example 1 and subsequent HPLC purification (acetonitrile/water/trifluoroacetic acid).

Example 29: LC (method 2): t_R = 1.10 min; Mass spectrum (ESI^-): m/z = 462 $[M-H]^-$.

Example 30: LC (method 2): t_R = 1.08 min; Mass spectrum (ESI^-): m/z = 462 $[M-H]^-$.

Example 31

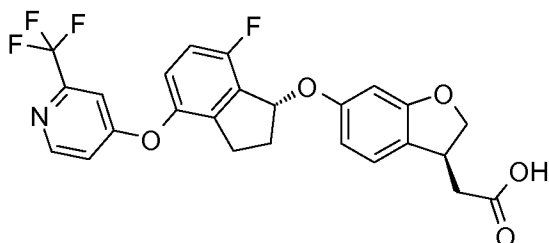
{(S)-6-[(R)-4-(2-dimethylamino-pyrid-5-yloxy)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid



The methyl ester of the title compound is prepared from {(S)-6-[(R)-7-fluoro-4-hydroxy-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester and 2-dimethylamino-pyridineboronic acid following a procedure analogous to that described for Intermediate 6. The title compound is obtained after saponification of the methyl ester as described for Example 1. LC (method 2): t_R = 0.91 min; Mass spectrum (ESI^+): m/z = 465 $[M+H]^+$.

Example 32

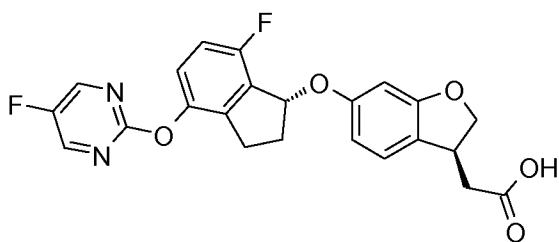
{(S)-6-[(R)-7-Fluoro-4-(2-trifluoromethyl-pyrid-4-yloxy)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid



The title compound is prepared from {(S)-6-[(R)-7-fluoro-4-(2-trifluoromethyl-pyrid-4-yloxy)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester following a procedure analogous to that described for Example 1. LC (method 2): t_R = 1.09 min; Mass spectrum (ESI⁺): m/z = 490 [M+H]⁺.

Example 33

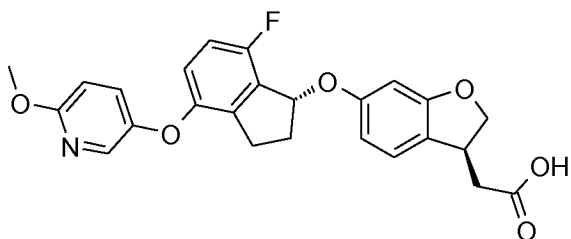
{(S)-6-[(R)-7-Fluoro-4-(5-fluoro-pyrimid-2-yloxy)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid



The title compound is prepared from {(S)-6-[(R)-7-fluoro-4-(5-fluoro-pyrimid-2-yloxy)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester following a procedure analogous to that described for Example 1. LC (method 2): t_R = 1.02 min; Mass spectrum (ESI⁻): m/z = 439 [M-H]⁻.

Example 34

{(S)-6-[(R)-7-Fluoro-4-(2-methoxy-pyrid-5-yloxy)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid

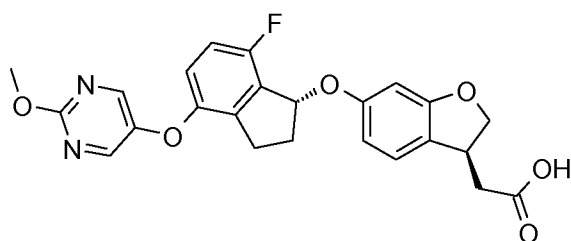


The title compound is prepared from {(S)-6-[(R)-7-fluoro-4-(2-methoxy-pyrid-5-yloxy)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester following a

procedure analogous to that described for Example 1. LC (method 2): $t_R = 1.08$ min; Mass spectrum (ESI⁺): $m/z = 452$ [M+H]⁺.

Example 35

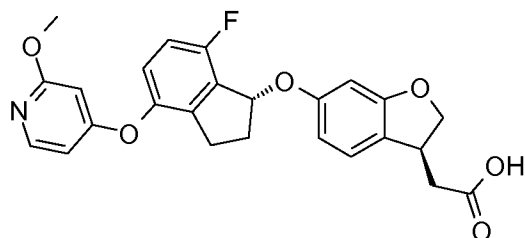
5 {{(S)-6-[(R)-7-Fluoro-4-(2-methoxy-pyrimid-5-yloxy)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid



The title compound is prepared from {(S)-6-[(R)-7-fluoro-4-(2-methoxy-pyrimid-5-yloxy)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester following a procedure analogous to that described for Example 1. LC (method 2): $t_R = 1.00$ min; Mass spectrum (ESI⁺): $m/z = 453$ [M+H]⁺.

Example 36

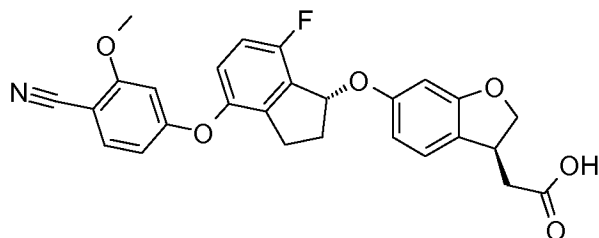
15 {{(S)-6-[(R)-7-Fluoro-4-(2-methoxy-pyrid-4-yloxy)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid



The title compound is prepared from {(S)-6-[(R)-7-fluoro-4-(2-methoxy-pyrid-4-yloxy)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester following a procedure analogous to that described for Example 1. LC (method 2): $t_R = 1.06$ min; Mass spectrum (ESI⁺): $m/z = 452$ [M+H]⁺.

Example 37

{{(S)-6-[(R)-4-(4-Cyano-3-methoxy-phenoxy)-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid

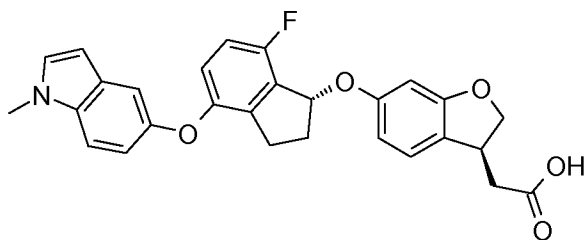


The title compound is prepared from {(S)-6-[(R)-4-(4-cyano-3-methoxy-phenoxy)-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester following a procedure analogous to that described for Example 1. LC (method 6): $t_R = 1.10$ min;

5 Mass spectrum (ESI⁻): $m/z = 474$ [M-H]⁻.

Example 38

{(S)-6-[(R)-7-Fluoro-4-(1-methyl-1H-indol-5-yloxy)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid



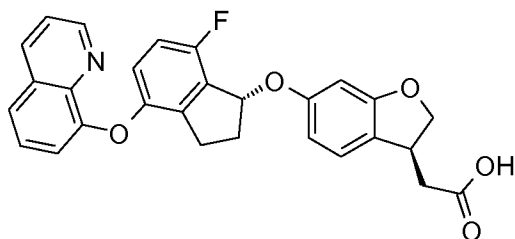
10

The title compound is prepared from {(S)-6-[(R)-7-fluoro-4-(1-methyl-1H-indol-5-yloxy)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester following a procedure analogous to that described for Example 1. LC (method 9): $t_R = 1.19$ min; Mass spectrum (ESI⁻): $m/z = 472$ [M-H]⁻.

15

Example 39

{(S)-6-[(R)-7-Fluoro-4-(quinolin-8-yloxy)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid

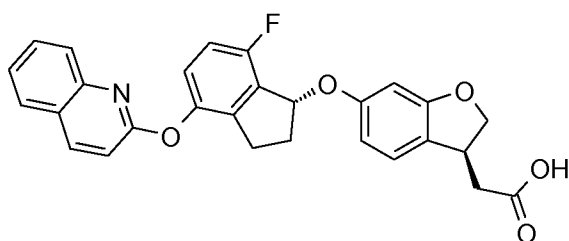


20 The title compound is prepared from {(S)-6-[(R)-7-fluoro-4-(quinolin-8-yloxy)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester following a procedure

analogous to that described for Example 1. LC (method 9): $t_R = 1.04$ min; Mass spectrum (ESI⁻): $m/z = 470$ [M-H]⁻.

Example 40

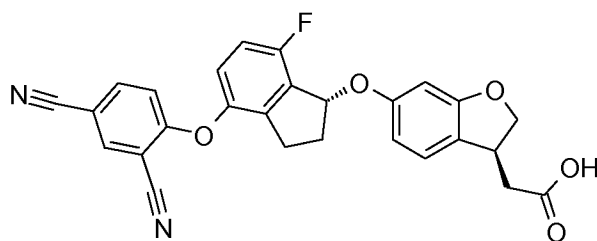
5 {{(S)-6-[(R)-7-Fluoro-4-(quinolin-2-yloxy)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid



The title compound is prepared from {{(S)-6-[(R)-7-fluoro-4-(quinolin-2-yloxy)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester following a procedure
10 analogous to that described for Example 1. LC (method 9): $t_R = 1.18$ min; Mass spectrum (ESI⁻): $m/z = 470$ [M-H]⁻.

Example 41

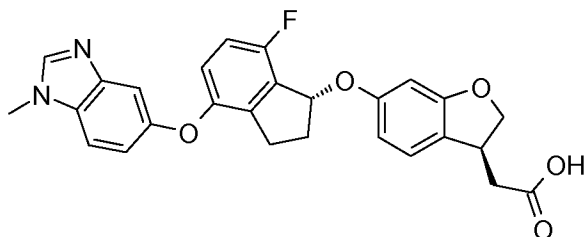
15 {{(S)-6-[(R)-4-(2,4-Dicyano-phenoxy)-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid



The title compound is prepared from {{(S)-6-[(R)-4-(2,4-dicyano-phenoxy)-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester following a procedure analogous to that described for Example 1. LC (method 6): $t_R = 1.05$ min;
20 Mass spectrum (ESI⁻): $m/z = 469$ [M-H]⁻.

Example 42

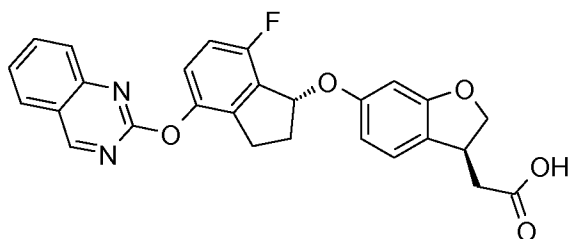
{{(S)-6-[(R)-7-Fluoro-4-(1-methyl-1H-benzoimidazol-5-yloxy)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid



The title compound is prepared from {(S)-6-[(R)-7-fluoro-4-(1-methyl-1H-benzimidazol-5-yloxy)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester following a procedure analogous to that described for Example 1. LC (method 5): $t_R = 0.75$ min; Mass spectrum (ESI⁺): $m/z = 475$ [M+H]⁺.

Example 43

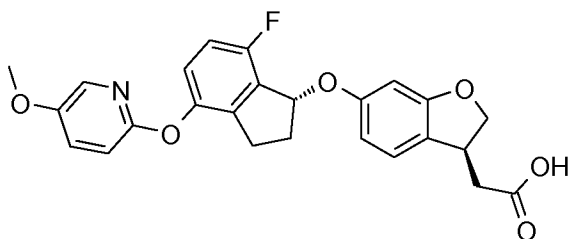
{(S)-6-[(R)-7-Fluoro-4-(quinazolin-2-yloxy)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid



The title compound is prepared from {(S)-6-[(R)-7-fluoro-4-(quinazolin-2-yloxy)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester following a procedure analogous to that described for Example 1. LC (method 6): $t_R = 1.05$ min; Mass spectrum (ESI⁻): $m/z = 471$ [M-H]⁻.

Example 44

{(S)-6-[(R)-7-Fluoro-4-(5-methoxy-pyrid-2-yloxy)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid

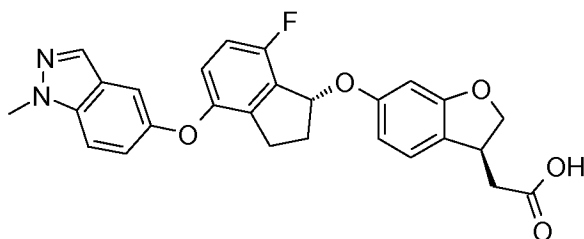


Methanol (24 μ L) is added to a flask charged with a stir bar, {(S)-6-[(R)-7-fluoro-4-(5-iodo-pyrid-2-yloxy)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl

ester (60 mg), CuI (1 mg), Cs₂CO₃ (52 mg), 2,3,7,8-tetramethyl-1,10-phenanthroline (2.5 mg) and toluene (2 mL) under Ar atmosphere at room temperature. The flask is sealed and heated to 120 °C, and the mixture is stirred at this temperature overnight. After cooling to room temperature, 4 M aqueous NaOH solution (50 µL) is added and the mixture is stirred for 4 h. Water is added, and the resulting mixture is extracted with ethyl acetate. The combined extract is washed with brine, dried (Na₂SO₄) and concentrated. The residue is purified by HPLC (water/acetonitrile/trifluoroacetic acid) to give the title compound. LC (method 6): t_R = 1.06 min; Mass spectrum (ESI⁺): m/z = 452 [M+H]⁺.

Example 45

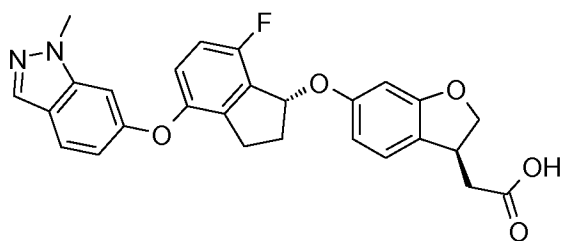
{{(S)-6-[(R)-7-Fluoro-4-(1-methyl-1H-indazol-5-yloxy)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid



The title compound is prepared from {(S)-6-[(R)-7-fluoro-4-(1-methyl-1H-indazol-5-yloxy)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester following a procedure analogous to that described for Example 1. LC (method 3): t_R = 0.33 min; Mass spectrum (ESI⁻): m/z = 473 [M-H]⁻.

Example 46

{{(S)-6-[(R)-7-Fluoro-4-(1-methyl-1H-indazol-6-yloxy)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid

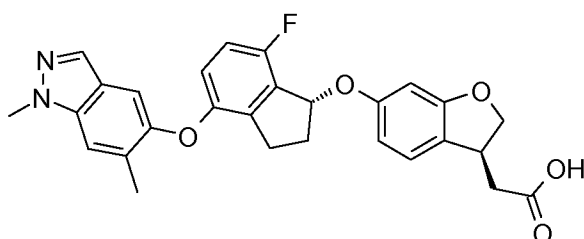


The title compound is prepared from {(S)-6-[(R)-7-fluoro-4-(1-methyl-1H-indazol-6-yloxy)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester following a procedure analogous to that described for Example 1. LC (method 3): t_R = 0.33 min; Mass spectrum (ESI⁻): m/z = 473 [M-H]⁻.

5

Example 47

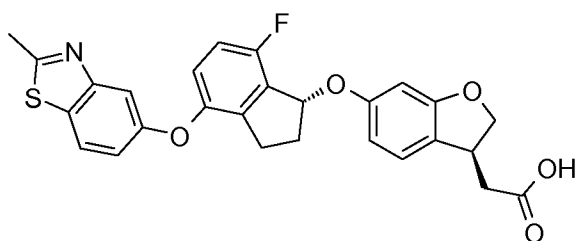
{(S)-6-[(R)-7-Fluoro-4-(1,6-dimethyl-1H-indazol-5-yloxy)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid



10 The title compound is prepared from {(S)-6-[(R)-7-fluoro-4-(1,6-dimethyl-1H-indazol-5-yloxy)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester following a procedure analogous to that described for Example 1. LC (method 10): t_R = 0.71 min; Mass spectrum (ESI⁻): m/z = 487 [M-H]⁻.

15 **Example 48**

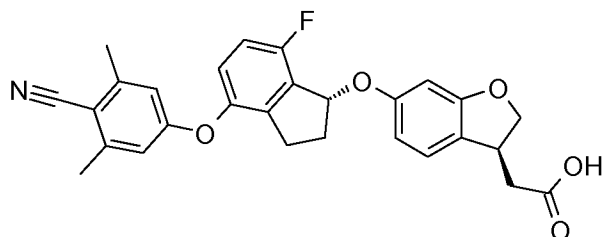
{(S)-6-[(R)-7-Fluoro-4-(2-methyl-benzothiazol-5-yloxy)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid



20 The title compound is prepared from {(S)-6-[(R)-7-fluoro-4-(2-methyl-benzothiazol-5-yloxy)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester following a procedure analogous to that described for Example 1. LC (method 10): t_R = 0.75 min; Mass spectrum (ESI⁻): m/z = 490 [M-H]⁻.

Example 49

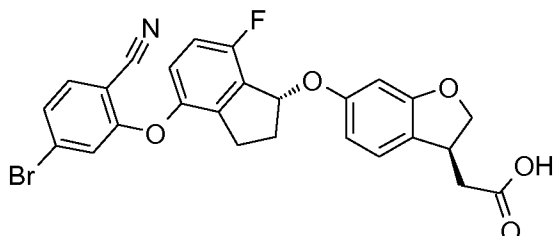
{{(S)-6-[(R)-4-(4-Cyano-3,5-dimethyl-phenoxy)-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid



The title compound is prepared from {{(S)-6-[(R)-4-(4-cyano-3,5-dimethyl-phenoxy)-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester following a procedure analogous to that described for Example 1. LC (method 5): t_R = 0.87 min; Mass spectrum (ESI⁻): m/z = 472 [M-H]⁻.

Example 50

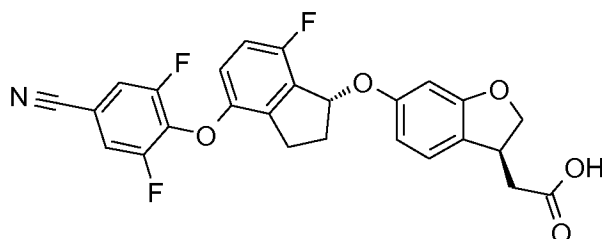
{{(S)-6-[(R)-4-(5-Bromo-2-cyano-phenoxy)-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid



The title compound is prepared from {{(S)-6-[(R)-4-(5-bromo-2-cyano-phenoxy)-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester following a procedure analogous to that described for Example 1. LC (method 11): t_R = 0.63 min; Mass spectrum (ESI⁻): m/z = 522/524 (Br) [M-H]⁻.

Example 51

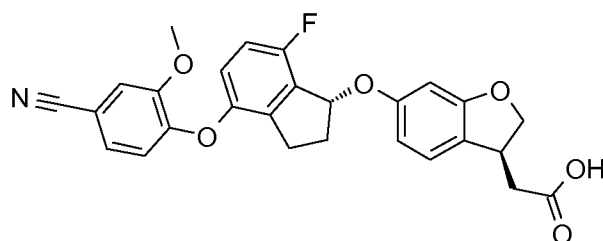
{{(S)-6-[(R)-4-(4-cyano-2,6-difluoro-phenoxy)-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid



The title compound is prepared from 3,4,5-trifluoro-benzonitrile and {(S)-6-[(R)-7-fluoro-4-hydroxy-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid (prepared from {(S)-6-[(R)-7-fluoro-4-hydroxy-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester using the procedure described for Example 1) following a procedure analogous to that described for Intermediate 12. LC (method 4): $t_R = 1.11$ min; Mass spectrum (ESI⁻): $m/z = 480$ [M-H]⁻.

Example 52

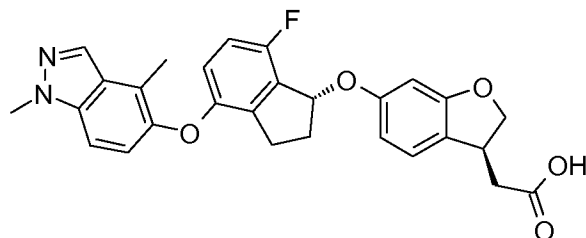
{(S)-6-[(R)-4-(4-Cyano-2-methoxy-phenoxy)-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid



The title compound is prepared from {(S)-6-[(R)-4-(4-cyano-2-methoxy-phenoxy)-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester following a procedure analogous to that described for Example 1. {(S)-6-[(R)-4-(4-Cyano-2-methoxy-phenoxy)-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester is obtained from (R)-7-fluoro-1-[(S)-3-methoxycarbonylmethyl-2,3-dihydrobenzofuran-6-yloxy]-2,3-dihydro-1H-inden-4-ylboronic acid and 4-cyano-2-methoxy-phenol following a procedure analogous to that described for Intermediate 6. LC (method 2): $t_R = 1.07$ min; Mass spectrum (ESI⁻): $m/z = 474$ [M-H]⁻.

Example 53

{(S)-6-[(R)-7-Fluoro-4-(1,4-dimethyl-1H-indazol-5-yloxy)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid

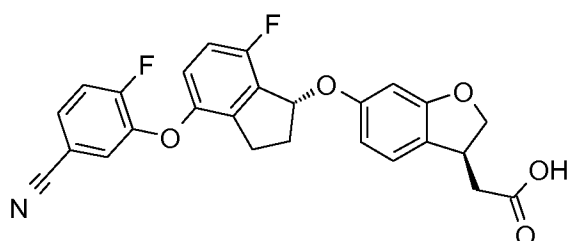


The title compound is prepared from {(S)-6-[(R)-7-fluoro-4-(1,4-dimethyl-1H-indazol-5-yloxy)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester following a procedure analogous to that described for Example 1. LC (method 10): t_R = 0.71 min; Mass spectrum (ESI⁻): m/z = 487 [M-H]⁻.

5

Example 54

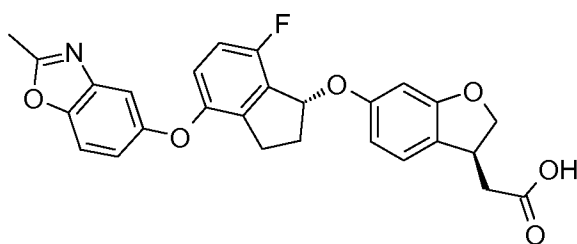
{(S)-6-[(R)-4-(5-Cyano-2-fluoro-phenoxy)-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid



- 10 The title compound is prepared from {(S)-6-[(R)-4-(5-cyano-2-fluoro-phenoxy)-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester following a procedure analogous to that described for Example 1. LC (method 10): t_R = 0.68 min; Mass spectrum (ESI⁻): m/z = 462 [M-H]⁻.

15 **Example 55**

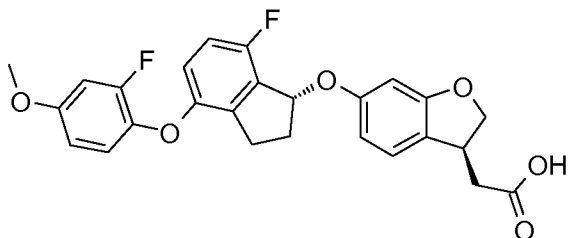
{(S)-6-[(R)-7-Fluoro-4-(2-methyl-benzoxazol-5-yloxy)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid



- 20 The title compound is prepared from {(S)-6-[(R)-7-fluoro-4-(2-methyl-benzoxazol-5-yloxy)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester following a procedure analogous to that described for Example 1. LC (method 10): t_R = 0.70 min; Mass spectrum (ESI⁻): m/z = 474 [M-H]⁻.

Example 56

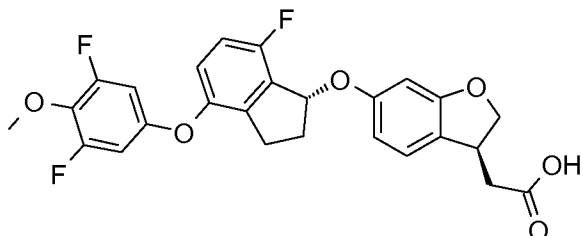
{{(S)-6-[(R)-4-(2-Fluoro-4-methoxy-phenoxy)-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid



The title compound is prepared from {(S)-6-[(R)-4-(2-fluoro-4-methoxy-phenoxy)-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester following a procedure analogous to that described for Example 1. LC (method 10): $t_R = 0.77$ min; Mass spectrum (ESI⁻): $m/z = 467$ [M-H]⁻.

Example 57

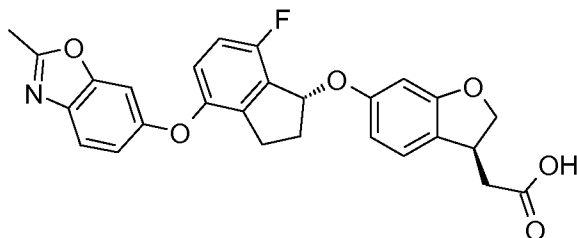
{{(S)-6-[(R)-4-(3,5-Difluoro-4-methoxy-phenoxy)-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid



The title compound is prepared from {(S)-6-[(R)-4-(3,5-difluoro-4-methoxy-phenoxy)-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester following a procedure analogous to that described for Example 1. {(S)-6-[(R)-4-(3,5-Difluoro-4-methoxy-phenoxy)-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester is obtained from (R)-7-fluoro-1-[(S)-3-methoxycarbonylmethyl-2,3-dihydrobenzofuran-6-yloxy]-2,3-dihydro-1H-inden-4-ylboronic acid and 3,5-difluoro-4-methoxy-phenol following a procedure analogous to that described for Intermediate 6. LC (method 2): $t_R = 1.09$ min; Mass spectrum (ESI⁻): $m/z = 485$ [M-H]⁻.

Example 58

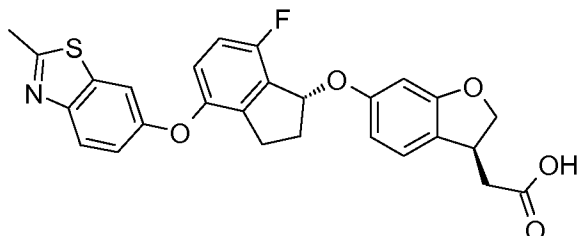
{{(S)-6-[(R)-7-Fluoro-4-(2-methyl-benzoxazol-6-yloxy)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid



The title compound is prepared from {(S)-6-[(R)-7-fluoro-4-(2-methyl-benzoxazol-6-yloxy)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester following a procedure analogous to that described for Example 1. LC (method 3): t_R = 0.38 min; Mass spectrum (ESI⁻): m/z = 474 [M-H]⁻.

Example 59

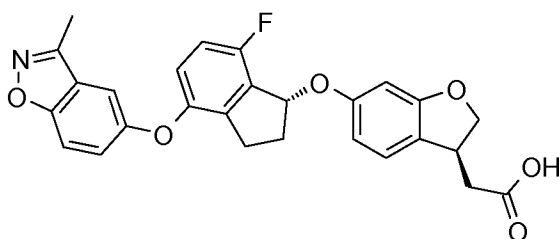
{{(S)-6-[(R)-7-Fluoro-4-(2-methyl-benzothiazol-6-yloxy)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid



The title compound is prepared from {(S)-6-[(R)-7-fluoro-4-(2-methyl-benzothiazol-6-yloxy)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester following a procedure analogous to that described for Example 1. LC (method 3): t_R = 0.46 min; Mass spectrum (ESI⁻): m/z = 490 [M-H]⁻.

Example 60

{{(S)-6-[(R)-7-Fluoro-4-(3-methyl-benzo[d]isoxazol-5-yloxy)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid

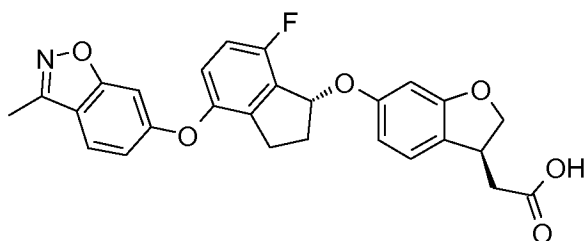


The title compound is prepared from {(S)-6-[(R)-7-fluoro-4-(3-methyl-benzo[d]isoxazol-5-yloxy)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester following a procedure analogous to that described for Example 1. LC (method 3): $t_R = 0.37$ min; Mass spectrum (ESI⁻): $m/z = 474$ [M-H]⁻.

5

Example 61

{(S)-6-[(R)-7-Fluoro-4-(3-methyl-benzo[d]isoxazol-6-yloxy)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid

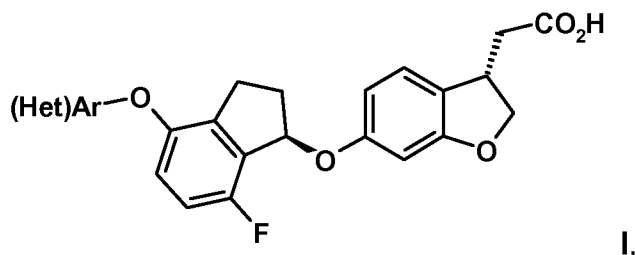


10 The title compound is prepared from {(S)-6-[(R)-7-fluoro-4-(3-methyl-benzo[d]isoxazol-6-yloxy)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester following a procedure analogous to that described for Example 1. LC (method 3): $t_R = 0.33$ min; Mass spectrum (ESI⁻): $m/z = 474$ [M-H]⁻.

15

Claims

1. A compound of formula I



5 wherein

(Het)Ar is linked via a carbon atom and is selected from the group (Het)Ar-G1 consisting of phenyl, naphthyl and a mono- or bicyclic heteroaromatic group having 5 to 10 ring member atoms of which 2 to 9 ring members are carbon atoms and either

one ring member is an unsubstituted or substituted heteroatom selected from N, NH, NR^N, O, S, S(=O) and S(=O)₂, or

one ring member is N and a second ring member is selected from N, NH, NR^N, O, S, S(=O) and S(=O)₂, or

two ring members are N and a third ring member is selected from N, NH, NR^N, O, S, S(=O) and S(=O)₂,

wherein in naphthyl the ring not attached to the indanyl-O atom of formula I may be partially saturated,

wherein in bicyclic heteroaromatic groups the ring not attached to the indanyl-O atom of formula I may be partially saturated, while at least one aromatic ring includes a heteroatom, and optionally

one ring member in the partially or fully saturated bridge is replaced by N, NH, NR^N, O, S, S(=O) or S(=O)₂, or

one ring member in the partially or fully saturated bridge is replaced by N, NH or NR^N and second ring member is replaced by NH, NR^N, O, S, C(=O), S(=O) or S(=O)₂, or

5 two not vicinal ring members in a fully saturated bridge are replaced by O atoms,

wherein any of these groups is optionally and independently substituted with 1 to 5 R¹ groups;

10 R¹ is selected from the group consisting of F, Cl, Br, I, CN, NO₂, NH₂, C₁₋₄-alkyl-NH-, (C₁₋₄-alkyl)₂N-, C₁₋₄-alkyl-, C₂₋₄-alkenyl-, C₂₋₄-alkinyl-, OH, HO-C₁₋₄-alkyl, C₁₋₄-alkyl-O-, C₁₋₄-alkyl-O-C₁₋₄-alkyl, C₁₋₄-alkyl-S-, C₁₋₄-alkyl-S(=O)-, C₁₋₄-alkyl-S(=O)₂-, C₃₋₆-cycloalkyl-, C₃₋₆-cycloalkyl-O-, wherein any alkyl and cycloalkyl group or submoiety is optionally substituted with 1 to 5 F atoms; and

15 R^N is selected from the group R^N-G1 consisting of C₁₋₄-alkyl, C₃₋₄-alkenyl, HO-C₁₋₄-alkyl, C₁₋₄-alkyl-O-C₁₋₄-alkyl, C₁₋₄-alkyl-C(=O)-, C₁₋₄-alkyl-S(=O)₂-, and C₃₋₆-cycloalkyl-, wherein any alkyl and cycloalkyl group or submoiety is optionally substituted with 1 to 5 F atoms;

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

or a salt thereof.

25

2. A compound according to claim 1, wherein

(Het)Ar is selected from the group consisting of phenyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, quinolinyl, isoquinolinyl, quinazolinyl, indolinyl, 30 benzoimidazolyl, indazolyl, benzoxazolyl, benzoisoxazolyl and benzothiazolyl, wherein each of these groups is optionally substituted with 1 to 3 groups

independently selected from R¹ and wherein independently a NH group optionally is replaced by a NR^N group;

or a salt thereof.

5

3. A compound according to claim 1, wherein R¹ is selected from the group consisting of F, Cl, Br, C₁₋₄-alkyl, C₂₋₄-alkinyl, HO-C₁₋₄-alkyl, C₁₋₄-alkyl-O-C₁₋₄-alkyl, CN, NH₂, C₁₋₄-alkyl-NH-, (C₁₋₄-alkyl)₂N-, OH, C₁₋₄-alkyl-O-, C₁₋₄-alkyl-S(=O)-, C₁₋₄-alkyl-S(=O)₂-, C₃₋₆-cycloalkyl and C₃₋₆-cycloalkyl-O-, wherein any alkyl and cycloalkyl
10 group or submoiety is optionally substituted with 1 to 3 F atoms;

or a salt thereof.

4. A compound according to claim 1, wherein R¹ is selected from the group
15 consisting of F, Cl, Br, C₁₋₄-alkyl, F₂HC-, F₃C-, HO-C₁₋₄-alkyl, H₃C-O-C₁₋₄-alkyl, H₃C-NH-, (H₃C)₂N-, CN, OH, C₁₋₄-alkyl-O-, F₂HC-O-, F₃C-O-, H₃C-S(=O)-, H₃C-S(=O)₂-, C₃₋₅-cycloalkyl and C₅₋₆-cycloalkyl-O-;

or a salt thereof.

20

5. A compound according to claim 1, wherein

(Het)Ar is selected from the group consisting of phenyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, quinolinyl, isoquinolinyl, quinazolinyl, indolinyl, benzimidazolyl, indazolyl, benzoxazolyl, benzoisoxazolyl and benzothiazolyl, wherein each of these
25 groups is optionally substituted with 1 to 3 groups independently selected from R¹;
and

R¹ is selected from the group consisting of F, Cl, Br, C₁₋₄-alkyl, C₂₋₄-alkinyl, HO-C₁₋₄-alkyl, C₁₋₄-alkyl-O-C₁₋₄-alkyl, CN, NH₂, C₁₋₄-alkyl-NH-, (C₁₋₄-alkyl)₂N-, OH, C₁₋₄-alkyl-O-, C₁₋₄-alkyl-S(=O)-, C₁₋₄-alkyl-S(=O)₂-, C₃₋₆-cycloalkyl and C₃₋₆-cycloalkyl-O-,
30

wherein any alkyl and cycloalkyl group or submoiety is optionally substituted with 1 to 3 F atoms; and

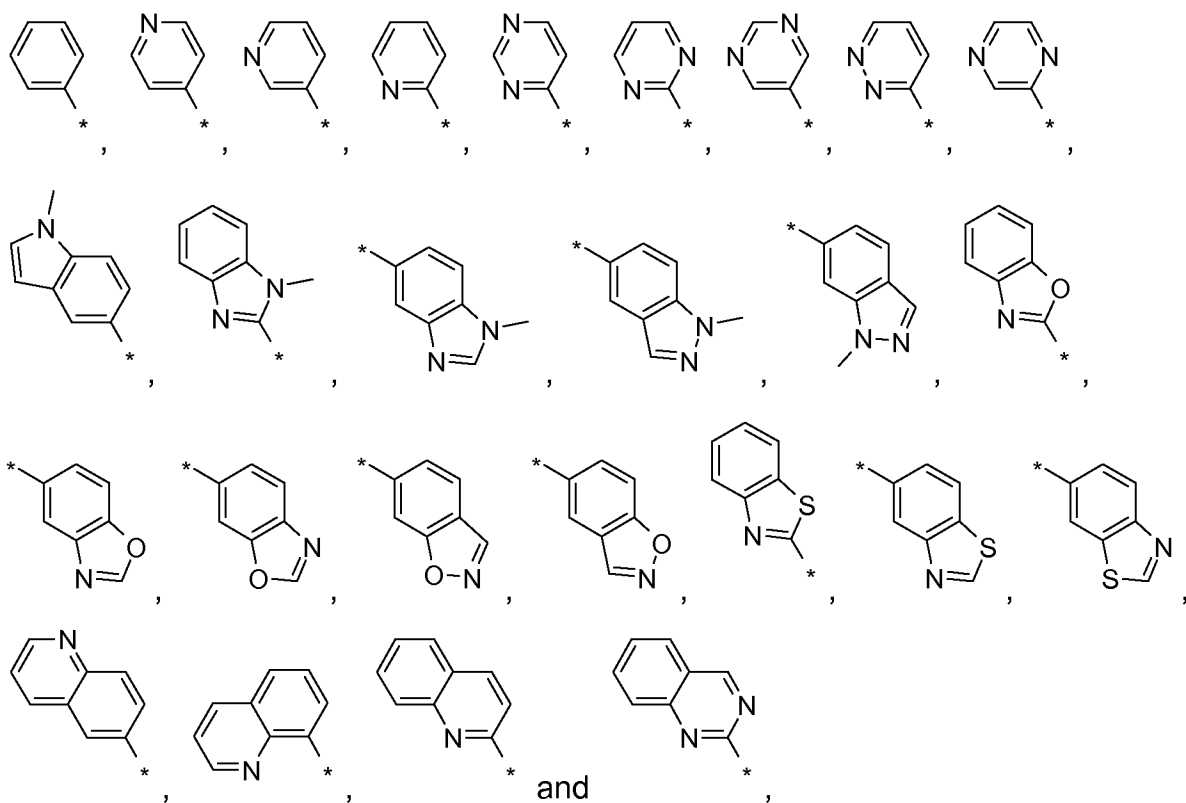
R^N is selected from the group consisting of C_{1-3} -alkyl, $HO-C_{1-4}$ -alkyl, H_3C-O-C_{1-4} -alkyl,
 5 $H_3C-S(=O)_2-$, and $H_3C-C(=O)-$;

or a salt thereof.

6. A compound according to claim 1, wherein,

10

(Het)Ar is selected from the group consisting of



wherein each of these groups is optionally substituted with 1 to 3 substituents independently selected from R^1 ; and

R^1 is selected from the group consisting of F, Cl, Br, C_{1-4} -alkyl, F_2HC- , F_3C- , $HO-C_{1-4}$ -alkyl,
 20 alkyl, H_3C-O-C_{1-4} -alkyl, H_3C-NH- , $(H_3C)_2N-$, CN, OH, C_{1-4} -alkyl-O-, F_2HC-O- , F_3C-O- ,
 $H_3C-S(=O)-$, $H_3C-S(=O)_2-$, C_{3-5} -cycloalkyl and C_{5-6} -cycloalkyl-O-;

or a salt thereof.

7. A pharmaceutically acceptable salt of a compound according to one or more of
5 the claims 1 to 6.

8. A pharmaceutical composition comprising one or more compounds according
to one or more of the claims 1 to 6 or one or more pharmaceutically acceptable salts
thereof, optionally together with one or more inert carriers and/or diluents.

10
9. A method for treating diseases or conditions which can be influenced by the
modulation of the function of GPR40 receptor, 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,
15 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 6 or a
pharmaceutically acceptable salt thereof is administered to the patient.

10. A compound according to one or more of the claims 1 to 6 or a
20 pharmaceutically acceptable salt thereof for use as a medicament.

11. A compound according to one or more of the claims 1 to 6 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
25 receptor, 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.

30 12. A pharmaceutical composition comprising one or more compounds according
to one or more of the claims 1 to 6 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.

13. A pharmaceutical composition according to claim 12 wherein the additional
5 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