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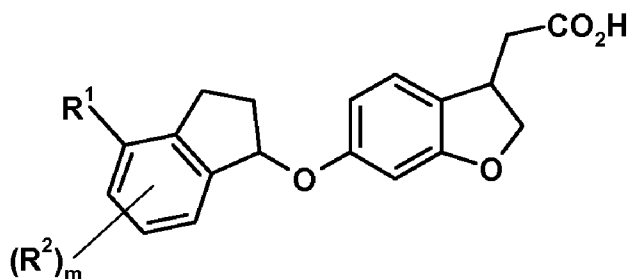
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(54) Title: NEW INDANYLOXYDIHYDROBENZOFURANYLACETIC ACID DERIVATIVES AND THEIR USE AS GPR40 RECEPTOR AGONISTS



(57) Abstract: The present invention relates to compounds of general formula (I), wherein the groups R¹, R² and m are defined as in claim 1, which have valuable pharmacological properties, in particular bind to the GPR40 receptor and modulate its activity. The compounds are suitable for treatment and prevention of diseases which can be influenced by this receptor, such as metabolic diseases, in particular diabetes type 2.

NEW INDANYLOXYDIHYDROBENZOFURANYLACETIC ACID DERIVATIVES AND THEIR
USE AS GPR40 RECEPTOR AGONISTS

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.

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

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

- 5 Persistent or inadequately controlled hyperglycemia is associated with a wide range of pathologies. Diabetes is a very disabling disease, because today's common anti-diabetic drugs do not control blood sugar levels well enough to completely prevent the occurrence of high and low blood sugar levels. Out of range blood sugar levels are toxic and cause long-term complications for example retinopathy, renopathy,
10 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
15 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
20 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).

- 25 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)
30 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 2,3-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.

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

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

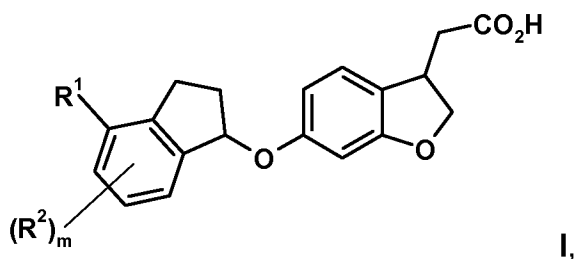
A further object of the present invention is to provide a combination of at least one
5 compound according to the invention with one or more additional therapeutic agents.

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

10 GPR40 modulators are known in the art, for example, the compounds disclosed in WO 2004041266 (EP 1559422), WO 2007033002 and WO 2009157418. 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
15 form stable salts.

Summary of the Invention

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



20

wherein

R^1 is selected from the group R^1 -G1 consisting of a phenyl ring, a tetrazolyl ring, and a 5- or 6-membered heteroaromatic ring which contains 1, 2, or 3 heteroatoms
25 independently of each other selected from =N-, -NH-, -O- and -S-;
wherein optionally a second ring is annulated to said phenyl or heteroaromatic ring,
wherein said second ring is 5- or 6-membered, unsaturated or aromatic and may contain 1, 2, or 3 heteroatoms independently of each other selected from =N-,

-NH-, -O- and -S- with the proviso that only up to two of the heteroatoms are O and S and no O-O, S-S, and S-O bond is formed, and wherein in said second ring independently of the presence of heteroatoms 1 or 2 CH₂ groups may be replaced by -C(=O)-, -S(=O)- or -S(=O)₂-, and

wherein said phenyl ring, tetrazolyl ring, heteroaromatic ring, annulated phenyl ring, and annulated heteroaromatic ring are substituted with one group R³; and

wherein each of the phenyl ring, tetrazolyl ring, heteroaromatic ring, annulated phenyl ring, and annulated heteroaromatic ring is optionally additionally substituted with 1 to 4 groups independently selected from R⁴; and

wherein in said heteroaromatic ring and/or said second ring the H-atom in one or more NH groups, if present, is replaced by R^N or R³;

R² is selected from the group R²-G1 consisting of F, Cl, Br, I, C₁₋₄-alkyl, C₃₋₆-cycloalkyl, NC-, H₂N-C(=O)-, C₁₋₄-alkyl-NR^N-C(=O)-, HO-C(=O)-, C₁₋₄-alkyl-O-C(=O)-, C₁₋₄-alkyloxy, and C₁₋₄-alkyl-S(=O)₂-,

wherein any alkyl and cycloalkyl group or sub-group within the groups mentioned is optionally substituted with one or more F atoms, and wherein multiple R² may be identical or different, if m is 2 or 3;

R³ is selected from the group R³-G1 consisting of

C₁₋₆-alkyl, C₂₋₆-alkenyl, C₂₋₆-alkinyl, C₃₋₆-cycloalkyl-, C₁₋₄-alkyl-NH-, (C₁₋₄-alkyl)₂N-, C₁₋₆-alkyl-O-, C₃₋₆-cycloalkyl-O-, C₁₋₄-alkyl-S-, C₁₋₄-alkyl-S(=O)-, and C₁₋₄-alkyl-S(=O)₂-,

wherein each alkyl and cycloalkyl group and each alkyl and cycloalkyl sub-group within the groups mentioned is substituted with 1 to 3 groups independently selected from R⁵ and optionally substituted with 1 or more F atoms;

or from C₁₋₄-alkyl-C(=O)-, heterocyclyl-C(=O)-, HNR^N-C(=O)-, C₁₋₄-alkyl-NR^N-C(=O)-, C₃₋₆-cycloalkyl-NR^N-C(=O)-, heterocyclyl-NR^N-C(=O)-, phenyl-NR^N-C(=O)-, heteroaryl-NR^N-C(=O)-, HO₂C-, C₁₋₄-alkyl-O-C(=O)-, C₃₋₆-cycloalkyl-O-C(=O)-, heterocyclyl-O-C(=O)-, -NHR^N, C₁₋₄-alkyl-C(=O)NR^N-, C₃₋₆-cycloalkyl-C(=O)NR^N-, heterocyclyl-C(=O)NR^N-, phenyl-C(=O)NR^N-, heteroaryl-C(=O)NR^N-, C₁₋₄-alkyl-S(=O)₂NR^N-, C₃₋₆-cycloalkyl-S(=O)₂NR^N-, heterocyclyl-S(=O)₂NR^N-,

phenyl-S(=O)₂NR^N-, heteroaryl-S(=O)₂NR^N-, heterocyclyl-O-, phenyl-O-, heteroaryl-O-, C₃₋₆-cycloalkyl-S-, heterocyclyl-S-, phenyl-S-, heteroaryl-S-, C₃₋₆-cycloalkyl-S(=O)-, heterocyclyl-S(=O)-, phenyl-S(=O)-, heteroaryl-S(=O)-, C₃₋₆-cycloalkyl-S(=O)₂-, heterocyclyl-S(=O)₂-, phenyl-S(=O)₂-, heteroaryl-S(=O)₂-,
 5 HNR^N-S(=O)₂-, C₁₋₄-alkyl-NR^N-S(=O)₂-, heterocyclyl, phenyl, and heteroaryl,

wherein each alkyl, cycloalkyl, and heterocyclyl group or sub-group within the groups mentioned is optionally substituted with 1 to 3 groups independently selected from R⁵ and optionally substituted with 1 or more F atoms; and

wherein each phenyl and heteroaryl group is optionally substituted with 1 to 5
 10 substituents independently selected from R⁶;

wherein heterocyclyl is selected from

a cyclobutyl group wherein 1 CH₂ group is replaced by -NH- or -O-,

a saturated or partially unsaturated C₅₋₇-cycloalkyl group wherein 1 CH₂ group is replaced by -C(=O)-, -NH-, -O-, -S(=O)- or -S(=O)₂- and/or 1 CH group by N;
 15

a saturated or partially unsaturated C₅₋₇-cycloalkyl group wherein 1 CH₂ group is replaced by -NH- or -O-, a second CH₂ group is replaced by -NH-, -C(=O)-, -S(=O)- or -S(=O)₂- and/or 1 CH group is replaced by N; and

a saturated or partially unsaturated C₅₋₇-cycloalkyl group wherein 2 CH₂ groups are replaced by -NH- or 1 CH₂ group by -NH- and the other by -O- and a third CH₂ group is replaced by -C(=O)-, -S(=O)- or -S(=O)₂- and/or 1 CH group by N;
 20

wherein heteroaryl is selected from

a tetrazolyl ring, and a 5- or 6-membered heteroaromatic ring which contains 1, 2, or 3 heteroatoms independently of each other selected from =N-, -NH-,
 25 -O-, and -S-, wherein in heteroaromatic groups containing a -HC=N- unit this group is optionally replaced by -NH-C(=O)-;

wherein in heteroaryl and heterocyclyl rings with one or more NH groups each of them is replaced by NR^N or NR⁵;

with the proviso that R³ in total cannot be C₁₋₄-alkyl-, C₁₋₄-alkyl-O-C₁₋₄-alkyl, HO-C₁₋₄-alkyl, C₃₋₄-alkenyl, C₃₋₄-alkinyl, H₂N-, C₁₋₄-alkyl-NH-, (C₁₋₄-alkyl)₂N-, C₁₋₄-alkyl-O-, C₁₋₄-alkyl-S-, C₁₋₄-alkyl-S(=O)-, and C₁₋₄-alkyl-S(=O)₂;

R^4 is selected from the group R^4 -G1 consisting of F, Cl, Br, I, CN, -OH, C_{1-4} -alkyl, C_{3-6} -cycloalkyl-, $HO-C_{1-4}$ -alkyl, C_{1-4} -alkyl-O- C_{1-4} -alkyl, $-NR^N H$, C_{1-4} -alkyl- NR^N -, C_{1-4} -alkyl-O-, C_{3-6} -cycloalkyl-O-, C_{1-4} -alkyl-O- C_{1-4} -alkyl-O-, C_{1-4} -alkyl-S-, C_{1-4} -alkyl-S(=O)-, and C_{1-4} -alkyl-S(=O)₂-,

5 wherein any alkyl and cycloalkyl group or sub-group within the groups mentioned is optionally substituted with 1 or more F atoms;

R^5 is selected from the group R^5 -G1 consisting of Cl, Br, I, C_{1-4} -alkyl-, CN, C_{3-6} -cycloalkyl-, heterocyclyl-C(=O)-, $H_2N-C(=O)-$, C_{1-4} -alkyl- NR^N -C(=O)-, C_{3-6} -cycloalkyl- NR^N -C(=O)-, heterocyclyl- NR^N -C(=O)-, phenyl- NR^N -C(=O)-, heteroaryl- NR^N -C(=O)-, $HO-C(=O)-$, C_{1-4} -alkyl-O-C(=O)-, $-NHR^N$, C_{1-4} -alkyl- NR^N -, C_{1-4} -alkyl-C(=O) NR^N -, C_{3-6} -cycloalkyl-C(=O) NR^N -, heterocyclyl-C(=O) NR^N -, phenyl-C(=O) NR^N -, heteroaryl-C(=O) NR^N -, C_{1-4} -alkyl-S(=O)₂ NR^N -, C_{3-6} -cycloalkyl-S(=O)₂ NR^N -, heterocyclyl-S(=O)₂ NR^N -, phenyl-S(=O)₂ NR^N -, heteroaryl-S(=O)₂ NR^N -, -OH, C_{1-4} -alkyl-O-, C_{1-4} -alkyl-O- C_{1-4} -alkyl-O-, C_{3-6} -cycloalkyl-O-, heterocyclyl-O-, phenyl-O-, heteroaryl-O-, C_{1-4} -alkyl-S-, C_{3-6} -cycloalkyl-S-, heterocyclyl-S-, phenyl-S-, heteroaryl-S-, C_{1-4} -alkyl-S(=O)-, C_{3-6} -cycloalkyl-S(=O)-, heterocyclyl-S(=O)-, phenyl-S(=O)-, heteroaryl-S(=O)-, C_{1-4} -alkyl-S(=O)₂-, C_{3-6} -cycloalkyl-S(=O)₂-, heterocyclyl-S(=O)₂-, phenyl-S(=O)₂-, heteroaryl-S(=O)₂-, $H_2N-S(=O)_2$ -, C_{1-4} -alkyl- NR^N -S(=O)₂-, heterocyclyl, phenyl, and heteroaryl,

15 wherein any alkyl, cycloalkyl and heterocyclyl group or sub-group within the groups mentioned is optionally substituted with 1 or more F atoms and optionally substituted with 1 or 2 groups independently selected from H_3C -, HO -, H_3C-O -, and -CN;

25 wherein heterocyclyl is selected from

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

a saturated or partially unsaturated C_{5-7} -cycloalkyl group wherein 1 CH_2 group is replaced by -C(=O)-, $-NR^N$ -, -O-, -S(=O)- or -S(=O)₂- and/or 1 CH group by N;

30 a saturated or partially unsaturated C_{5-7} -cycloalkyl group wherein 1 CH_2 group is replaced by $-NR^N$ - or -O-, a second CH_2 group is replaced by $-NR^N$ -, -C(=O)-, -S(=O)- or -S(=O)₂- and/or 1 CH group is replaced by N; and

a saturated or partially unsaturated C_{5-7} -cycloalkyl group wherein 2 CH_2 groups are replaced by $-NR^N$ - or 1 CH_2 group by $-NR^N$ - and the other by -O-,

and a third CH₂ group is replaced by -C(=O)-, -S(=O)- or -S(=O)₂- and/or 1 CH group by N;

and wherein heteroaryl is selected from

a tetrazolyl ring, and a 5- or 6-membered heteroaromatic ring which contains
5 1, 2, or 3 heteroatoms independently of each other selected from =N-, -NH-,
-O-, and -S-, wherein in heteroaromatic groups containing a -HC=N- unit this
group is optionally replaced by -NR^N-C(=O)-, and wherein in heteroaromatic
rings with one or more NH groups each of them is replaced by NR^N, and
each heteroaryl group is optionally substituted with 1 to 3 substituents
10 independently selected from F, Cl, -CH₃, -CN, and -O-CH₃;

R⁶ is selected from the group R⁶-G1 consisting of F, Cl, Br, I, CN, C₁₋₄-alkyl, C₃₋₆-
cycloalkyl-, HO-C₁₋₄-alkyl-, C₁₋₄-alkyl-O-C₁₋₄-alkyl-, R^NHN-, C₁₋₄-alkyl-O-, -S(=O)-
C₁₋₄-alkyl, and S(=O)₂-C₁₋₄-alkyl,

15 wherein any alkyl and cycloalkyl group or sub-group within the groups mentioned
is optionally substituted with one or more F atoms;

R^N is independently of each other selected from the group R^N-G1 consisting of H, C₁₋₄-
alkyl, C₁₋₄-alkyl-C(=O)-, C₁₋₄-alkyl-NH-C(=O)-, C₁₋₄-alkyl-N(C₁₋₄-alkyl)-C(=O)-,
20 C₁₋₄-alkyl-O-C(=O)-, and C₁₋₄-alkyl-S(=O)₂-; and

m is an integer selected from 0, 1, 2, and 3;

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

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

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

The extension -Gn used within the definitions is meant to identify genus n of the respective substituent. For example, R¹-G1 defines genus 1 of the substituent R¹.

- 5 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.
- 10 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.
- 15 According to another aspect of the invention, there is provided a method for treating a metabolic disease or disorder, such as diabetes, dyslipidemia and/or obesity, in a patient in need thereof characterized in that a therapeutically effective amount of a compound of general formula I or a pharmaceutically acceptable salt thereof is administered to the patient.
- 20 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.
- 25 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.
- 30 In a further aspect this invention relates to a method for treating a disease or condition mediated by the activation of the G-protein-coupled receptor GPR40 in a patient that includes the step of administering to the patient in need of such treatment a therapeutically effective amount of a compound of the general formula I or a

pharmaceutically acceptable salt thereof in combination with a therapeutically effective amount of one or more additional therapeutic agents.

5 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.

10 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.

15 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

20 Unless otherwise stated, the groups, residues, and substituents, particularly R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^N , and m are defined as above and hereinafter. If residues, substituents, or groups occur several times in a compound, as for example R^N , 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.

25 R^1 :

R^1 -G1:

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

R^1 -G2:

30 According to one embodiment the group R^1 is selected from the group R^1 -G2 consisting of a phenyl ring, a tetrazolyl ring, a 5-membered heteroaromatic ring which contains 2 or 3 heteroatoms independently of each other selected from =N-, -NH-, -O- and -S- with the proviso that not more than one heteroatom is -O- or -S-, and a 6-membered heteroaromatic ring which contains 1 or 2 =N- atoms;

wherein optionally a second ring is annulated to said phenyl ring and 5- and 6-membered heteroaromatic rings, wherein said second ring is 5- or 6-membered, unsaturated or aromatic and may contain 1 or 2 heteroatoms independently of each other selected from =N-, -NH-, -O- and -S- with the proviso that no O-O, S-S, and S-O bond is formed, and wherein in said second ring independently of the presence of heteroatoms 1 or 2 -CH₂- groups may be replaced by -C(=O)- or -S(=O)₂-, and wherein in said heteroaromatic ring and/or said second ring the H-atom in one or more NH groups, if present, is replaced by R^N or R³, and wherein each of said phenyl ring, tetrazolyl ring, heteroaromatic rings, annulated phenyl ring, and annulated heteroaromatic rings is substituted with one group R³ and optionally additionally substituted with 1 or 2 substituents independently selected from R⁴.

R¹-G2a:

According to one embodiment the group R¹ is selected from the group R¹-G2a consisting of a phenyl ring, a tetrazolyl ring, a 5-membered heteroaromatic ring which contains 2 or 3 heteroatoms independently of each other selected from =N-, -NH-, -O- and -S-, and a 6-membered heteroaromatic ring which contains 1 or 2 =N- atoms; wherein in said 5-membered heteroaromatic ring the H-atom in one or more NH groups is replaced with R^N or R³, and wherein each of said phenyl ring, tetrazolyl ring, and heteroaromatic rings is substituted with one group R³ and optionally additionally substituted with 1 or 2 substituents independently selected from R⁴.

R¹-G2b:

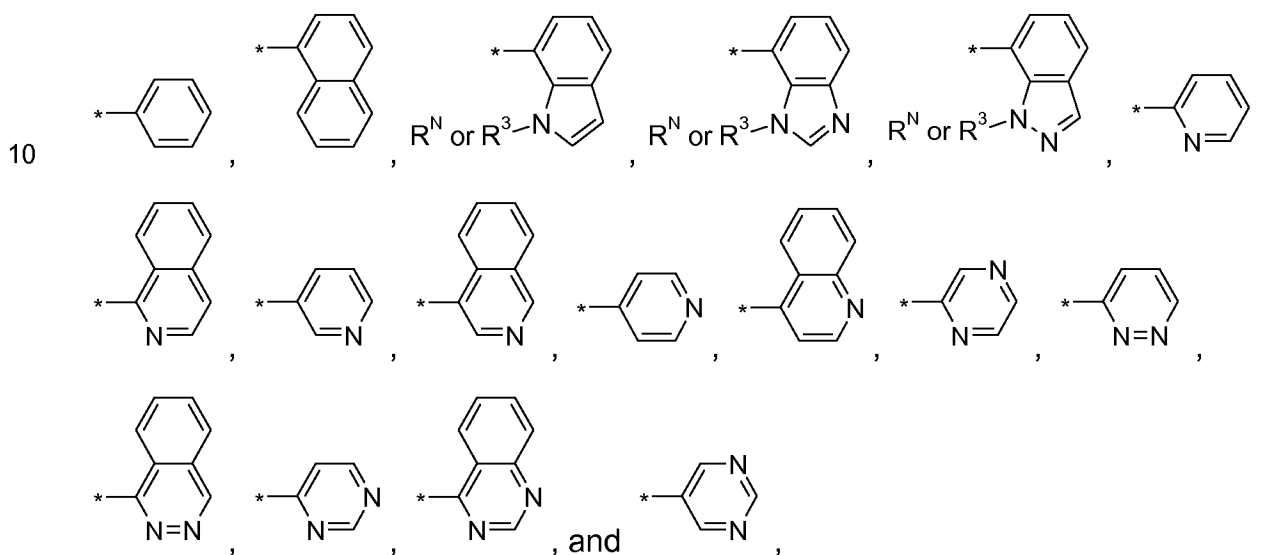
According to one embodiment the group R¹ is selected from the group R¹-G2b consisting of a phenyl ring, a 5-membered heteroaromatic ring which contains 2 or 3 heteroatoms independently of each other selected from =N-, -NH-, -O- and -S-, and a 6-membered heteroaromatic ring which contains 1 or 2 =N- atoms, wherein a second 5- or 6-membered, unsaturated or aromatic ring is annulated to said phenyl ring and 5- and 6-membered heteroaromatic rings, which may contain 1 or 2 heteroatoms independently of each other selected from =N-, -NH-, -O- and -S- with the proviso that no O-O, S-S, and S-O bond is formed, and wherein in said second ring 1 or 2 -CH₂- groups may be replaced by -C(=O)- or -S(=O)₂-, and

wherein in said heteroaromatic rings and said second rings the H-atom in one or more NH groups, if present, is replaced by R^N or R^3 , and

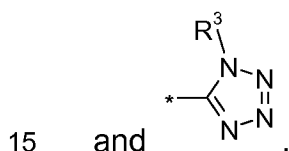
wherein each annulated phenyl ring and annulated heteroaromatic ring is substituted with one group R^3 and optionally additionally substituted with 1 or 2 substituents independently selected from R^4 .

R^1 -G3:

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

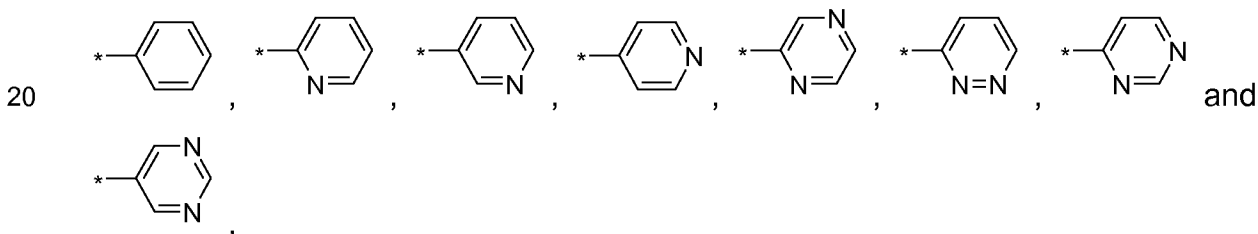


wherein each group is substituted with one group R^3 and optionally additionally substituted with 1 or 2 groups independently selected from R^4 ;



R^1 -G3a:

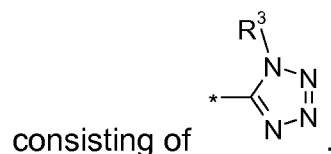
According to one embodiment the group R^1 is selected from the group R^1 -G3a consisting of



wherein each group is substituted with one group R^3 and optionally additionally substituted with 1 or 2 groups independently selected from R^4 .

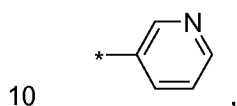
R^1 -G3b:

- 5 According to one embodiment the group R^1 is selected from the group R^1 -G3b



R^1 -G3c:

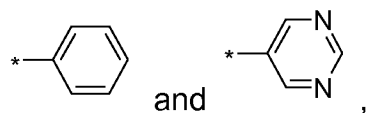
In another embodiment the group R^1 is selected from the group R^1 -G4 consisting of



which is substituted with one group R^3 and optionally additionally substituted with 1 or 2 groups independently selected from R^4 .

R^1 -G4:

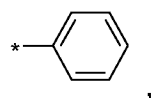
- 15 In another embodiment the group R^1 is selected from the group R^1 -G4 consisting of



wherein each group is substituted with one group R^3 and optionally additionally substituted with 1 or 2 groups independently selected from R^4 .

- 20 **R^1 -G4a:**

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

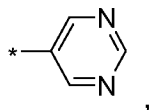


which is substituted with one group R^3 and optionally additionally substituted with 1 or 2 groups independently selected from R^4 .

25

R^1 -G4b:

In another embodiment the group R^1 is selected from the group R^1 -G4b consisting of

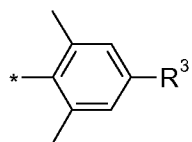


which is substituted with one group R^3 and optionally additionally substituted with 1 or 2 groups independently selected from R^4 .

5

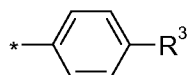
R^1 -G5:

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



10 R^1 -G5a:

In another embodiment the group R^1 is selected from the group R^1 -G5a consisting of



R^2 :

R^2 -G1:

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

R^2 -G2:

In another embodiment the group R^2 is selected from the group R^2 -G2 consisting of F, Cl, Br, H_3C- , H_2FC- , F_3C- , cyclopropyl, $NC-$, F_2HC-O- , F_3C-O- , and $H_3C-S(=O)_2-$.

20

R^2 -G3:

In another embodiment the group R^2 is selected from the group R^2 -G3 consisting of F, Cl, Br, H_2FC- , F_3C- , $NC-$, and F_3C-O- .

25 R^2 -G4:

In another embodiment the group R^2 is selected from the group R^2 -G4 consisting of F, Cl, and $NC-$.

R^2 -G4a:

In another embodiment the group R^2 is selected from the group R^2 -G4a consisting of F, Cl, F_3C- , and $NC-$.

R^2 -G4b:

- 5 In another embodiment the group R^2 is selected from the group R^2 -G4b consisting of F.

R^2 -G4c:

- 10 In another embodiment the group R^2 is selected from the group R^2 -G4c consisting of F_3C- .

R^3 :

R^3 -G1:

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

15

R^3 -G2:

In another embodiment the group R^3 is selected from the group R^3 -G2 consisting of C_{1-4} -alkyl, C_{3-6} -cycloalkyl-, C_{1-4} -alkyl-O-, C_{3-6} -cycloalkyl-O-, C_{1-4} -alkyl-S(=O)-, and C_{1-4} -alkyl-S(=O)₂-,

- 20 wherein each alkyl and cycloalkyl group and each alkyl and cycloalkyl sub-group within the groups mentioned is substituted with 1 to 3 groups independently selected from R^5 and optionally substituted with 1 or more F atoms;

- or from C_{1-4} -alkyl-C(=O)-, heterocyclyl-C(=O)-, HNR^N -C(=O)-, C_{1-4} -alkyl- NR^N -C(=O)-, C_{3-6} -cycloalkyl- NR^N -C(=O)-, heterocyclyl- NR^N -C(=O)-, phenyl- NR^N -C(=O)-, heteroaryl- NR^N -C(=O)-, C_{1-4} -alkyl-C(=O) NR^N -, C_{3-6} -cycloalkyl-C(=O) NR^N -, heterocyclyl-C(=O) NR^N -, phenyl-C(=O) NR^N -, heteroaryl-C(=O) NR^N -, C_{1-4} -alkyl-S(=O)₂ NR^N -, C_{3-6} -cycloalkyl-S(=O)₂ NR^N -, heterocyclyl-S(=O)₂ NR^N -, phenyl-S(=O)₂ NR^N -, heteroaryl-S(=O)₂ NR^N -, heterocyclyl-O-, phenyl-O-, heteroaryl-O-, C_{3-6} -cycloalkyl-S(=O)-, heterocyclyl-S(=O)-, phenyl-S(=O)-, heteroaryl-S(=O)-, C_{3-6} -cycloalkyl-S(=O)₂-, heterocyclyl-S(=O)₂-, phenyl-S(=O)₂-, heteroaryl-S(=O)₂-, HNR^N -S(=O)₂-, C_{1-4} -alkyl- NR^N -S(=O)₂-, heterocyclyl, phenyl, and heteroaryl,
- 25
30

wherein each alkyl, cycloalkyl, and heterocyclyl group or sub-group within the groups mentioned is optionally substituted with 1 to 3 groups independently selected from R^5 and optionally substituted with 1 or more F atoms; and

wherein each phenyl and heteroaryl group is optionally substituted with 1 to 3 substituents independently selected from R^6 ;

wherein heterocyclyl is selected from

a cyclobutyl group wherein 1 CH_2 group is replaced by -NH- or -O-,

a saturated or mono-unsaturated C_{5-6} -cycloalkyl group wherein 1 CH_2 group is replaced by -C(=O)-, -NH-, -O-, -S(=O)- or -S(=O)₂- and/or 1 CH group by N;

a saturated or mono-unsaturated C_{5-6} -cycloalkyl group wherein 1 CH_2 group is replaced by -NH- or -O-, a second CH_2 group is replaced by -NH-, -C(=O)-, -S(=O)- or -S(=O)₂- and/or 1 CH group is replaced by N; and

a saturated or mono-unsaturated C_{5-6} -cycloalkyl group wherein 2 CH_2 groups are replaced by -NH- or 1 CH_2 group by -NH- and the other by -O- and a third CH_2 group is replaced by -C(=O)-, -S(=O)- or -S(=O)₂- and/or 1 CH group by N;

wherein heteroaryl is selected from

a tetrazolyl ring, a pyridin-2-onyl ring, a 5-membered heteroaromatic ring which contains 1, 2, or 3 heteroatoms independently of each other selected from =N-, -NH-, O, and S, and a 6-membered heteroaromatic ring which contains 1 or 2 =N- atom,

and wherein in heteroaryl and heterocyclyl rings with one or more NH groups each of them is replaced by NR^N or NR^5 ,

with the proviso that R^3 in total cannot be C_{1-4} -alkyl-, C_{1-4} -alkyl-O- C_{1-4} -alkyl, HO- C_{1-4} -alkyl, C_{1-4} -alkyl-O-, C_{1-4} -alkyl-S(=O)-, and C_{1-4} -alkyl-S(=O)₂.

R^3 -G2a:

In another embodiment the group R^3 is selected from the group R^3 -G2a consisting of C_{1-4} -alkyl, C_{3-6} -cycloalkyl-, C_{1-4} -alkyl-O-, C_{3-6} -cycloalkyl-O-, C_{1-4} -alkyl-S(=O)-, and C_{1-4} -alkyl-S(=O)₂-,

wherein each alkyl and cycloalkyl group and each alkyl and cycloalkyl sub-group within the groups mentioned is substituted with 1 to 3 groups independently selected from R^5 and optionally substituted with 1 or more F atoms;

or from

C₁₋₄-alkyl-C(=O)-, heterocyclyl-C(=O)-, HNR^N-C(=O)-, C₁₋₄-alkyl-NR^N-C(=O)-, C₃₋₆-
 cycloalkyl-NR^N-C(=O)-, heterocyclyl-NR^N-C(=O)-, phenyl-NR^N-C(=O)-, heteroaryl-
 NR^N-C(=O)-, C₁₋₄-alkyl-C(=O)NR^N-, C₃₋₆-cycloalkyl-C(=O)NR^N-, heterocyclyl-
 5 C(=O)NR^N-, phenyl-C(=O)NR^N-, heteroaryl-C(=O)NR^N-, C₁₋₄-alkyl-S(=O)₂NR^N-, C₃₋₆-
 cycloalkyl-S(=O)₂NR^N-, heterocyclyl-S(=O)₂NR^N-, phenyl-S(=O)₂NR^N-, heteroaryl-
 S(=O)₂NR^N-, heterocyclyl-O-, phenyl-O-, heteroaryl-O-, C₃₋₆-cycloalkyl-S(=O)-,
 heterocyclyl-S(=O)-, phenyl-S(=O)-, heteroaryl-S(=O)-, C₃₋₆-cycloalkyl-S(=O)₂-,
 heterocyclyl-S(=O)₂-, phenyl-S(=O)₂-, heteroaryl-S(=O)₂-, HNR^N-S(=O)₂-, C₁₋₄-alkyl-
 10 NR^N-S(=O)₂-, heterocyclyl, phenyl, and heteroaryl,

wherein each alkyl, cycloalkyl, and heterocyclyl group or sub-group within the groups
 mentioned is optionally substituted with 1 to 3 groups independently selected
 from R⁵ and optionally substituted with 1 or more F atoms; and

wherein each phenyl and heteroaryl group is optionally substituted with 1 to 3
 15 substituents independently selected from R⁶;

wherein heterocyclyl is selected from

a cyclobutyl group wherein 1 CH₂ group is replaced by -NH- or -O-,
 a saturated or mono-unsaturated C₅₋₇-cycloalkyl group wherein 1 CH₂ group is
 replaced by -C(=O)-, -NH-, -O-, -S(=O)- or -S(=O)₂- and/or 1 CH group by N;
 20 a saturated or mono-unsaturated C₅₋₆-cycloalkyl group wherein 1 CH₂ group is
 replaced by -NH- or -O-, a second CH₂ group is replaced by -NH-, -C(=O)-,
 -S(=O)- or -S(=O)₂- and/or 1 CH group is replaced by N; and
 a saturated or mono-unsaturated C₅₋₆-cycloalkyl group wherein 2 CH₂ groups are
 replaced by -NH- or 1 CH₂ group by -NH- and the other by -O- and a third CH₂
 25 group is replaced by -C(=O)-, -S(=O)- or -S(=O)₂- and/or 1 CH group by N;

wherein heteroaryl is selected from

a tetrazolyl ring, a 5-membered heteroaromatic ring which contains 1, 2, or 3
 heteroatoms independently of each other selected from =N-, -NH-, O, and S, and
 a 6-membered heteroaromatic ring which contains 1 or 2 =N- atom and wherein
 30 a -HC=N- unit is optionally replaced by -NH-C(=O)-; and

wherein in heteroaryl and heterocyclyl rings with one or more NH groups each of
 them is replaced by NR^N or NR⁵,

with the proviso that R^3 in total cannot be C_{1-4} -alkyl-, C_{1-4} -alkyl-O- C_{1-4} -alkyl, HO- C_{1-4} -alkyl, C_{1-4} -alkyl-O-, C_{1-4} -alkyl-S(=O)-, and C_{1-4} -alkyl-S(=O)₂.

R^3 -G3:

- 5 In another embodiment the group R^3 is selected from the group R^3 -G3 consisting of C_{1-4} -alkyl, C_{3-6} -cycloalkyl-, C_{1-4} -alkyl-O-, and C_{3-6} -cycloalkyl-O-, wherein each alkyl and cycloalkyl group and each alkyl and cycloalkyl sub-group within the groups mentioned is substituted with 1 to 3 groups independently selected from R^5 and optionally substituted with 1 or more F atoms;
- 10 or from $H_3C-C(=O)-$, heterocyclyl- $C(=O)-$, $H_2N-C(=O)-$, C_{1-3} -alkyl- $NR^N-C(=O)-$, C_{1-4} -alkyl- $C(=O)NR^N-$, C_{3-6} -cycloalkyl- $C(=O)NR^N-$, heterocyclyl- $C(=O)NR^N-$, C_{1-4} -alkyl-S(=O)₂ NR^N- , heterocyclyl-O-, phenyl-O-, heteroaryl-O-, heterocyclyl-S(=O)₂-, $H_2N-S(=O)_2-$, heterocyclyl, phenyl, and heteroaryl,
- 15 wherein each alkyl, cycloalkyl, and heterocyclyl group or sub-group within the groups mentioned is optionally substituted with 1 or 2 groups independently selected from R^5 and optionally substituted with 1 or more F atoms; and wherein each phenyl and heteroaryl group is optionally substituted with 1 to 3 substituents independently selected from R^6 ;
- 20 wherein heterocyclyl is selected from
- a cyclobutyl group wherein 1 CH_2 group is replaced by -NH- or -O-,
 - a saturated or mono-unsaturated C_{5-6} -cycloalkyl group wherein 1 CH_2 group is replaced by -C(=O)-, -NH-, -O- or -S(=O)₂- and/or 1 CH group by N;
 - a saturated or mono-unsaturated C_{5-6} -cycloalkyl group wherein 1 CH_2 group is replaced by -NH- or -O-, a second CH_2 group is replaced by -C(=O)- or -S(=O)₂- and/or 1 CH group is replaced by N; and
- 25 wherein heteroaryl is selected from
- a pyridin-2-onyl ring, a 5-membered heteroaromatic ring which contains 1, 2, or 3 heteroatoms independently of each other selected from =N-, -NH-, O, and S, and
 - 30 a 6-membered heteroaromatic ring which contains 1 or 2 =N- atoms,
- and wherein in heteroaryl and heterocyclyl rings with one or more NH groups each of them is replaced by NR^N or NR^5 ;

with the proviso that R^3 in total cannot be C_{1-4} -alkyl-, C_{1-4} -alkyl-O- C_{1-4} -alkyl, HO- C_{1-4} -alkyl, and C_{1-4} -alkyl-O-.

R^3 -G3a:

- 5 In another embodiment the group R^3 is selected from the group R^3 -G3a consisting of C_{1-4} -alkyl, C_{3-6} -cycloalkyl-, C_{1-4} -alkyl-O-, and C_{3-6} -cycloalkyl-O-, wherein each alkyl and cycloalkyl group and each alkyl and cycloalkyl sub-group within the groups mentioned is substituted with 1 to 3 groups independently selected from R^5 and optionally substituted with 1 to 3 F atoms;
- 10 or from
 C_3 -alkyl-S(=O)₂- substituted with 1 HO- or H₃C-O- group;
H₃C-C(=O)-, heterocyclyl-C(=O)-, H₂N-C(=O)-, tetrahydropyran-4-yl-NH-C(=O)-, C_{1-3} -alkyl-NR^N-C(=O)-, C_{1-4} -alkyl-C(=O)NR^N-, C_{3-6} -cycloalkyl-C(=O)NR^N-, heterocyclyl-
15 C(=O)NR^N-, C_{1-4} -alkyl-S(=O)₂NR^N-, heterocyclyl-O-, phenyl-O-, heteroaryl-O-, heterocyclyl-S(=O)₂-, H₂N-S(=O)₂-, heterocyclyl, phenyl and heteroaryl, wherein each alkyl, cycloalkyl, and heterocyclyl group or sub-group within the groups mentioned is optionally substituted with 1 or 2 groups independently selected from R^5 and optionally substituted with 1 to 3 F atoms; and
- 20 wherein each phenyl and heteroaryl group is optionally substituted with 1 to 3 substituents independently selected from R^6 ;
- wherein heterocyclyl is selected from
a cyclobutyl group wherein 1 CH₂ group is replaced by -NH- or -O-;
a saturated or mono-unsaturated C_{5-7} -cycloalkyl group wherein 1 CH₂ group is
25 replaced by -C(=O)-, -NH-, -O- or -S(=O)₂- and/or 1 CH group by N;
a saturated or mono-unsaturated C_{5-6} -cycloalkyl group wherein 1 CH₂ group is replaced by -NH- or -O-, a second CH₂ group is replaced by -C(=O)- or -S(=O)₂- and/or 1 CH group is replaced by N; and
- wherein heteroaryl is selected from
30 tetrazolyl, a 5-membered heteroaromatic ring which contains 1, 2 or 3 heteroatoms independently of each other selected from =N-, -NH-, O, and S, and a 6-membered heteroaromatic ring which contains 1 or 2 =N- atoms and wherein a -HC=N- unit is optionally replaced by -NH-C(=O)-; and

wherein in heteroaryl and heterocyclyl rings with one ore more NH groups each of them is replaced by NR^{N} or NR^5 ;

with the proviso that R^3 in total cannot be C_{1-4} -alkyl-, C_{1-4} -alkyl-O- C_{1-4} -alkyl, HO- C_{1-4} -alkyl, and C_{1-4} -alkyl-O-.

R^3 -G4:

In another embodiment the group R^3 is selected from the group R^3 -G4 consisting of C_{1-4} -alkyl, C_{3-6} -cycloalkyl-, C_{1-4} -alkyl-O-, and C_{3-6} -cycloalkyl-O-,

wherein each alkyl and cycloalkyl group and each alkyl and cycloalkyl sub-group within the groups mentioned is substituted with 1 group selected from R^5 and optionally substituted with 1 or 2 H_3C - group;

or from $\text{H}_3\text{C-C(=O)-}$, heterocyclyl-C(=O)-, $\text{H}_2\text{N-C(=O)-}$, $\text{H}_3\text{C-NR}^{\text{N}}\text{-C(=O)-}$, heterocyclyl-O-, heteroaryl-O-, $\text{H}_2\text{N-S(=O)}_2\text{-}$, heterocyclyl, phenyl, and heteroaryl,

wherein each heterocyclyl group or sub-group within the groups mentioned is optionally substituted with 1 or 2 groups independently selected from R^5 and optionally substituted with 1 or more F atoms; and

wherein each phenyl and heteroaryl group is optionally substituted with 1 or 2 substituents independently selected from R^6 ;

wherein heterocyclyl is selected from

a cyclobutyl group wherein 1 CH_2 group is replaced by -NH- or -O-;

a saturated or mono-unsaturated C_{5-6} -cycloalkyl group wherein 1 CH_2 group is replaced by -C(=O)-, -NH-, -O- or -S(=O)₂- and/or 1 CH group by N;

a saturated or mono-unsaturated C_{5-6} -cycloalkyl group wherein 1 CH_2 group is replaced by -NH- or -O-, a second CH_2 group is replaced by -NH-, -C(=O)- or -S(=O)₂- and/or 1 CH group is replaced by N; and

wherein heteroaryl is selected from

a 5-membered heteroaromatic ring which contains 1 or 2 heteroatoms independently of each other selected from =N-, -NH-, -O-, and -S-, and a 6-

membered heteroaromatic ring which contains 1 or 2 =N- atoms, and wherein in heteroaryl and heterocyclyl rings with one ore more NH groups each of them is replaced by NR^{N} or NR^5 ;

with the proviso that R^3 in total cannot be C_{1-4} -alkyl-, C_{1-4} -alkyl-O- C_{1-4} -alkyl, HO- C_{1-4} -alkyl, and C_{1-4} -alkyl-O-.

R^3 -G4a:

- 5 In another embodiment the group R^3 is selected from the group R^3 -G4a consisting of C_{1-4} -alkyl, C_{3-6} -cycloalkyl-, C_{1-4} -alkyl-O-, and C_{3-6} -cycloalkyl-O-, wherein each alkyl and cycloalkyl group and each alkyl and cycloalkyl sub-group within the groups mentioned is substituted with 1 group selected from R^5 and optionally substituted with 1 or 2 H_3C - groups;

10

or from

C_5 -alkyl-O- substituted with 2 HO- groups;

C_3 -alkyl-S(=O)₂- substituted with 1 HO- or H_3C -O- group; and

H_3C -C(=O)-, heterocyclyl-C(=O)-, H_2N -C(=O)-, HO-(H_3C)₂C-CH₂-NH-C(=O)-,

- 15 tetrahydropyran-4-yl-NH-C(=O)-, H_3C -NR^N-C(=O)-, H_3C -S(=O)₂-NH-, heterocyclyl-O-, phenyl-O-, heteroaryl-O-, H_2N -S(=O)₂-, heterocyclyl, phenyl and heteroaryl,

wherein each heterocyclyl group or sub-group within the groups mentioned is optionally substituted with 1 or 2 groups independently selected from R^5 and optionally substituted with 1 or more F atoms; and

- 20 wherein each phenyl and heteroaryl group is optionally substituted with 1 or 2 substituents independently selected from R^6 ;

wherein heterocyclyl is selected from

a cyclobutyl group wherein 1 CH_2 group is replaced by -NH- or -O-;

- 25 a saturated or mono-unsaturated C_{5-7} -cycloalkyl group wherein 1 CH_2 group is replaced by -C(=O)-, -NH-, -O- or -S(=O)₂- and/or 1 CH group by N;

a saturated or mono-unsaturated C_{5-6} -cycloalkyl group wherein 1 CH_2 group is replaced by -NH- or -O-, a second CH_2 group is replaced by -NH-, -C(=O)- or -S(=O)₂- and/or 1 CH group is replaced by N; and

wherein heteroaryl is selected from

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

wherein in heteroaryl and heterocyclyl rings with one or more NH groups each of them is replaced by NR^{N} or NR^5 ;

with the proviso that R^3 in total cannot be C_{1-4} -alkyl-, C_{1-4} -alkyl-O- C_{1-4} -alkyl, HO- C_{1-4} -alkyl, and C_{1-4} -alkyl-O-.

R^3 -G5:

According to another embodiment the group R^3 is selected from the group R^3 -G5 consisting of

- 10 cyclopropyl substituted with 1 NC- group;
 C_{1-4} -alkyl-O- optionally substituted with 1 or 2 H_3C - groups but necessarily substituted with 1 group selected from cyclopropyl, NC-, heterocyclyl-C(=O)-, H_2N -C(=O)-, H_3CNH -C(=O)-, $(\text{H}_3\text{C})_2\text{N}$ -C(=O)-, $(\text{H}_3\text{C})_2\text{N}$ -, HO-, C_{1-2} -alkyl-O-, C_{1-2} -alkyl-O- C_2 -alkyl-O-, H_3C -S(=O)-, H_3C -S(=O) $_2$ -, heterocyclyl, and heteroaryl;
- 15 wherein each heterocyclyl group and subgroup is selected from the group consisting of azetidiny, oxetanyl, pyrrolidiny, pyrrolidin-2-onyl, tetrahydrofuranyl, sulfolanyl, piperidiny, tetrahydropyranyl, 1,1-dioxo-tetrahydrothiopyranyl, morpholinyl, and oxazolidin-2-onyl, each of which optionally substituted with 1 H_3C - group and wherein a NH group, if present, optionally is replaced by C_{1-3} -alkyl-S(=O) $_2$ -N; and
- 20 wherein heteroaryl is selected from the group consisting of imidazolyl, pyrazolyl, oxazolyl, and pyridin-2-onyl, wherein a NH group, if present, optionally is replaced by N- CH_3 and each of which is optionally substituted with 1 H_3C - group;
 C_{4-5} -cycloalkyl-O- substituted with -N(CH_3)S(=O) $_2$ CH_3 or -OH;
 H_3C -C(=O)-, H_2N -C(=O)-, H_3C -NH-C(=O)-, $(\text{H}_3\text{C})_2\text{N}$ -C(=O)-, morpholin-4-yl-C(=O)-,
 25 3,6-dihydropyranyl, 1-methanesulfonyl-1,2,3,6-tetrahydropyridinyl, pyrrolidin-2-onyl;
 azetidinyloxy and pyrrolidinyloxy, wherein in each of both the NH group is replaced by NR^{N} ;
 tetrahydrofuranyloxy, tetrahydropyranyloxy, 1,1-dioxo-tetrahydrothiopyranyloxy, H_2N -S(=O) $_2$ -; and
- 30 phenyl, pyrazolyl, oxazolyl, isoxazolyl, and pyrimidinyl, wherein a NH group, if present, optionally is replaced by N- CH_3 .

R^3 -G5a:

According to another embodiment the group R^3 is selected from the group R^3 -G5a consisting of

C₅-alkyl substituted with 1 HO- group;

C₂₋₃-alkyl substituted with 1 group selected from H₃C-C(=O)-NH-, H₃C-S(=O)₂-NH- and H₃C-S(=O)₂-;

cyclopropyl substituted with 1 NC- group;

(H₃C)₃C-CH₂-O-; C₅-alkyl-O- substituted with 2 HO- groups;

cyclopropyl-CH₂-O- and cyclohexyl-CH₂-O-, each of both cycloalkyl groups is substituted with 1 HO- group and optionally substituted with 1 or 2 F atoms;

C₁₋₄-alkyl-O- optionally substituted with 1 or 2 H₃C- groups and necessarily substituted with 1 group selected from cyclopropyl, NC-, heterocyclyl-C(=O)-, H₂N-C(=O)-, H₃CNH-C(=O)-, (H₃C)₂N-C(=O)-, (H₃C)₂N-, H₃C-C(=O)-NH-, (H₃C)₃C-O-C(=O)-NH-, H₃C-S(=O)₂-NH-, HO-, C₁₋₂-alkyl-O-, C₁₋₂-alkyl-O-C₂-alkyl-O-, H₃C-S(=O)-, H₃C-S(=O)₂-, heterocyclyl, phenyl and heteroaryl;

wherein each heterocyclyl group and subgroup is selected from the group consisting of azetidiny, oxetanyl, pyrrolidiny, pyrrolidin-2-onyl, tetrahydrofuranyl, sulfolanyl, 1,1-dioxo-isothiazolidiny, piperidiny, tetrahydropyranyl, 1,1-dioxo-tetrahydrothiopyranyl, morpholin-4-yl and oxazolidin-2-on-3-yl, each of which is optionally substituted with 1 group selected from H₃C- and HO- group, and wherein a NH group, if present, optionally is replaced by C₁₋₃-alkyl-S(=O)₂-N; and wherein heteroaryl is selected from the group consisting of imidazolyl, pyrazolyl, oxazolyl, pyridinyl and pyridin-2-onyl, wherein a NH group, if present, optionally is replaced by N-CH₃ and each heteroaryl is optionally substituted with 1 H₃C- or 1 H₃C-O- group;

C₄₋₅-cycloalkyl-O- substituted with 1 H₃C-S(=O)₂-N(CH₃)- or 1 HO- group and optionally substituted with 1 H₃C- group;

azetidinyloxy, pyrrolidinyloxy, pyrrolidin-2-onyloxy, piperidinyloxy and 1,1-dioxo-[1,2]thiazinanyloxy, in each of which the NH group is optionally replaced by N-CH₃ or N-S(=O)₂-CH₃;

tetrahydrofuranyloxy, tetrahydropyranyloxy, 1,1-dioxo-tetrahydrothiopyranyloxy and phenyloxy;

H₃C-C(=O)-, H₂N-C(=O)-, H₃C-NH-C(=O)-, HO-(H₃C)₂C-CH₂-NH-C(=O)-, (H₃C)₂N-C(=O)-, tetrahydropyran-4-yl-NH-C(=O)-, morpholin-4-yl-C(=O)-, pyrrolidiny, tetrahydrofuranyl, piperidiny, morpholin-4-yl, [1,4]oxazepan-4-yl, tetrahydropyranyl,

3,6-dihydropyranyl, 1-methanesulfonyl-1,2,3,6-tetrahydropyridinyl, pyrrolidin-2-onyl, 6-oxo-3,6-dihydro-pyran-4-yl;

$\text{H}_3\text{C-S(=O)}_2\text{-NH-}$, $\text{H}_2\text{N-S(=O)}_2\text{-}$;

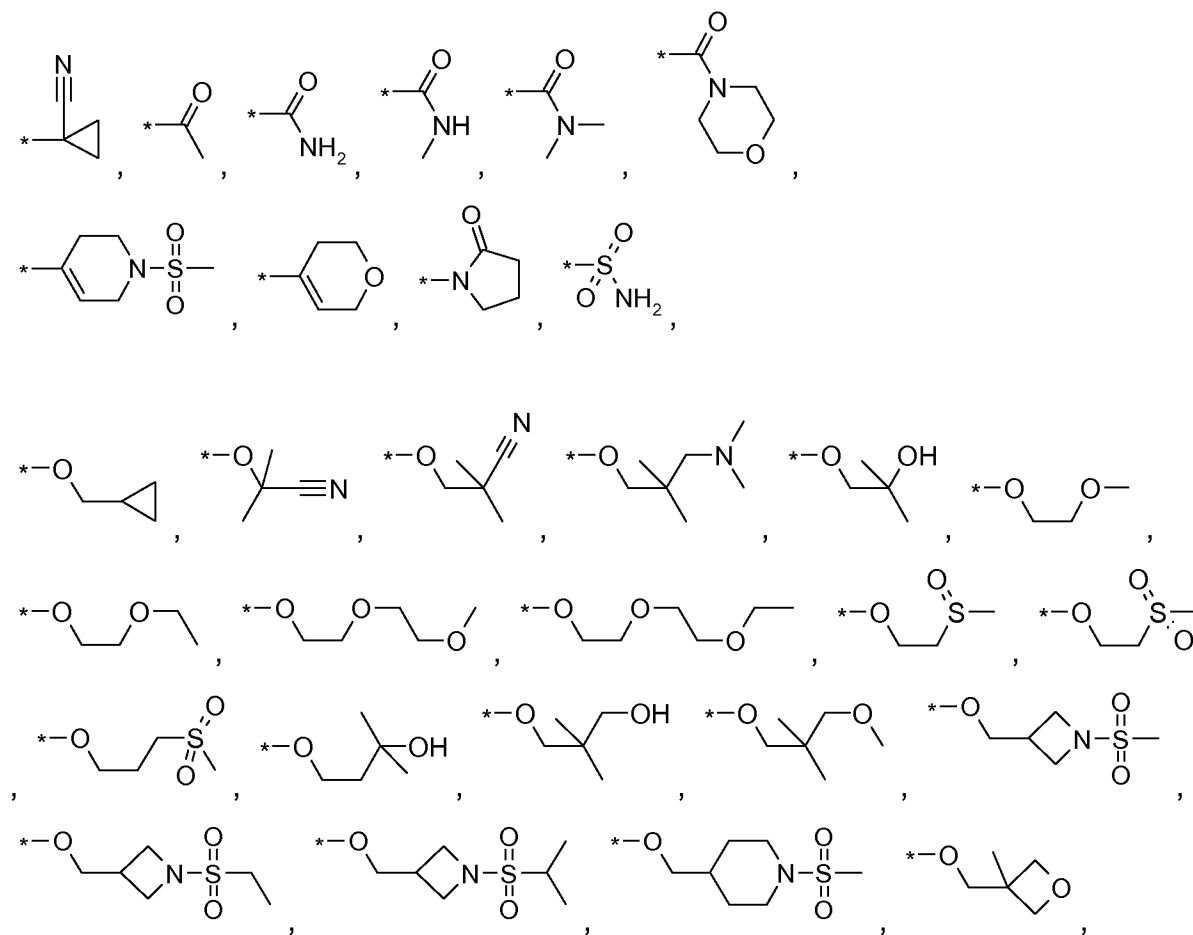
$\text{C}_3\text{-alkyl-S(=O)}_2\text{-}$ substituted with 1 HO- or $\text{H}_3\text{C-O-}$ group; and

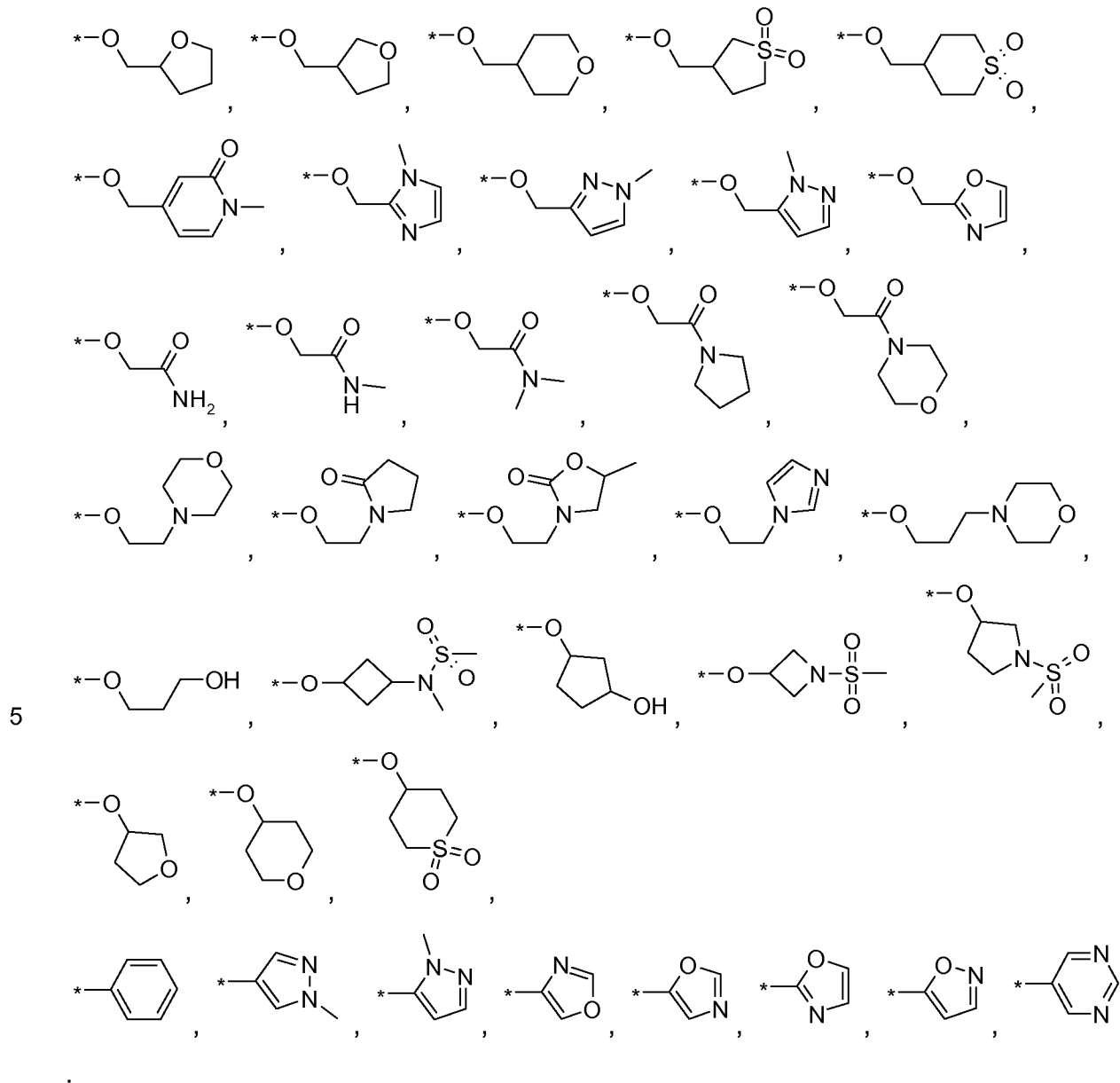
- 5 phenyl, furanyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, triazolyl, oxadiazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, pyridin-2-onyl, pyrimidin-2-onyl, pyrimidin-4-onyl and pyridazin-3-onyl, wherein a NH group, if present, optionally is replaced by N-CH₃, N-CH₂-C(CH₃)₂-OH or N-C(CH₃)₂-CH₂-OH, and which are optionally substituted with 1 H₃C- group and optionally substituted with
- 10 1 group selected from -CH₃, -CH₂-CH₃, -CH(CH₃)₂, cyclopropyl, -CF₃, -C(CH₃)₂-OH, -O-CH₃ and -CH₂-C(CH₃)₂-OH.

R³-G6:

According to another embodiment the group R³ is selected from the group R³-G6

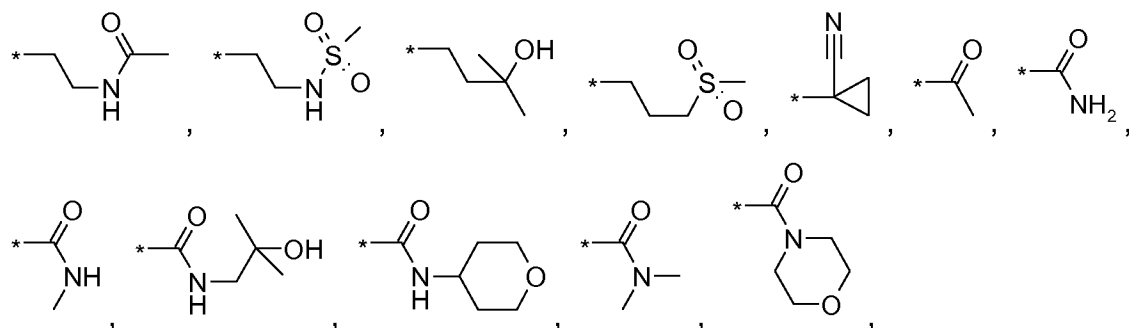
15 consisting of

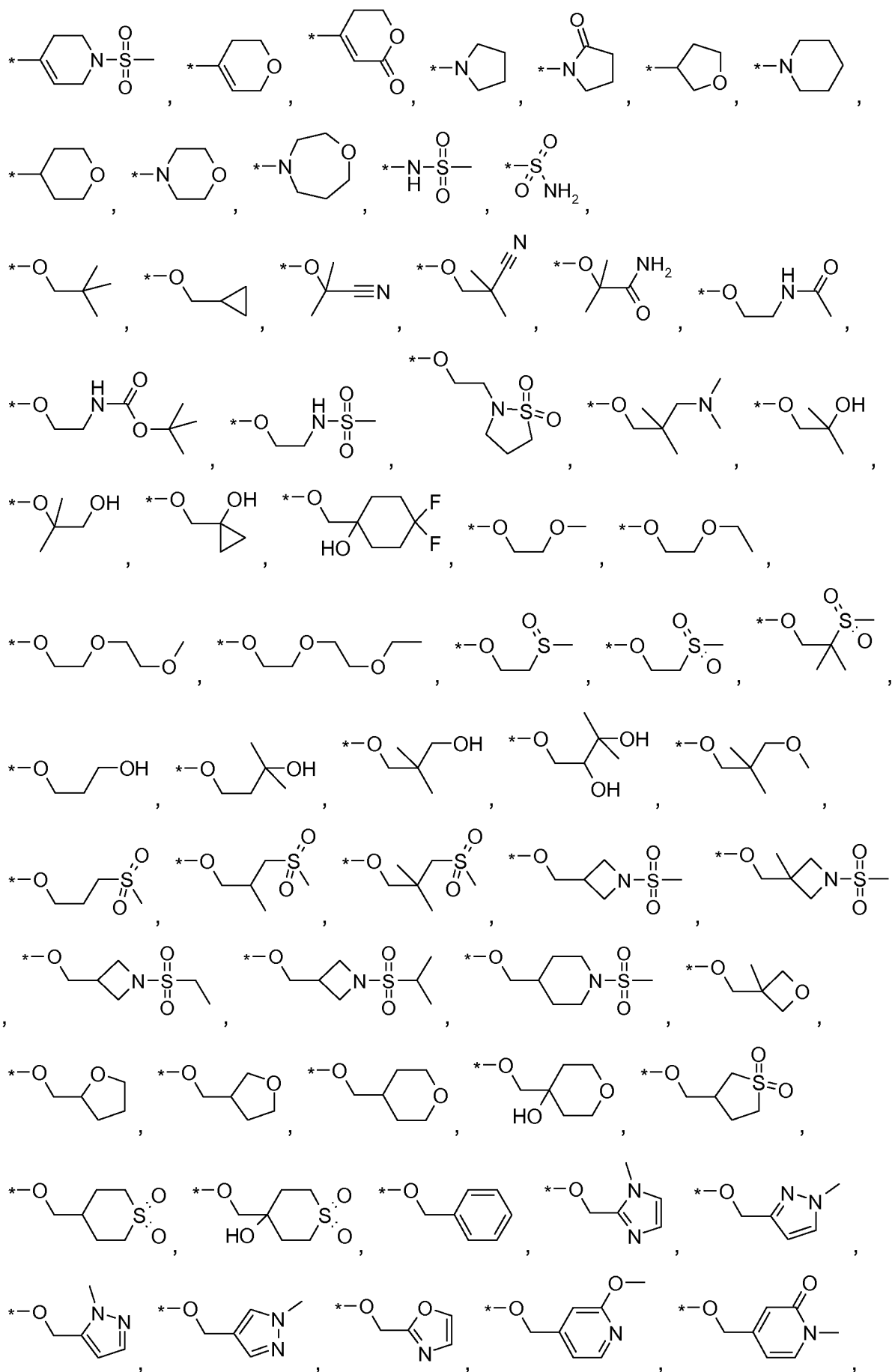


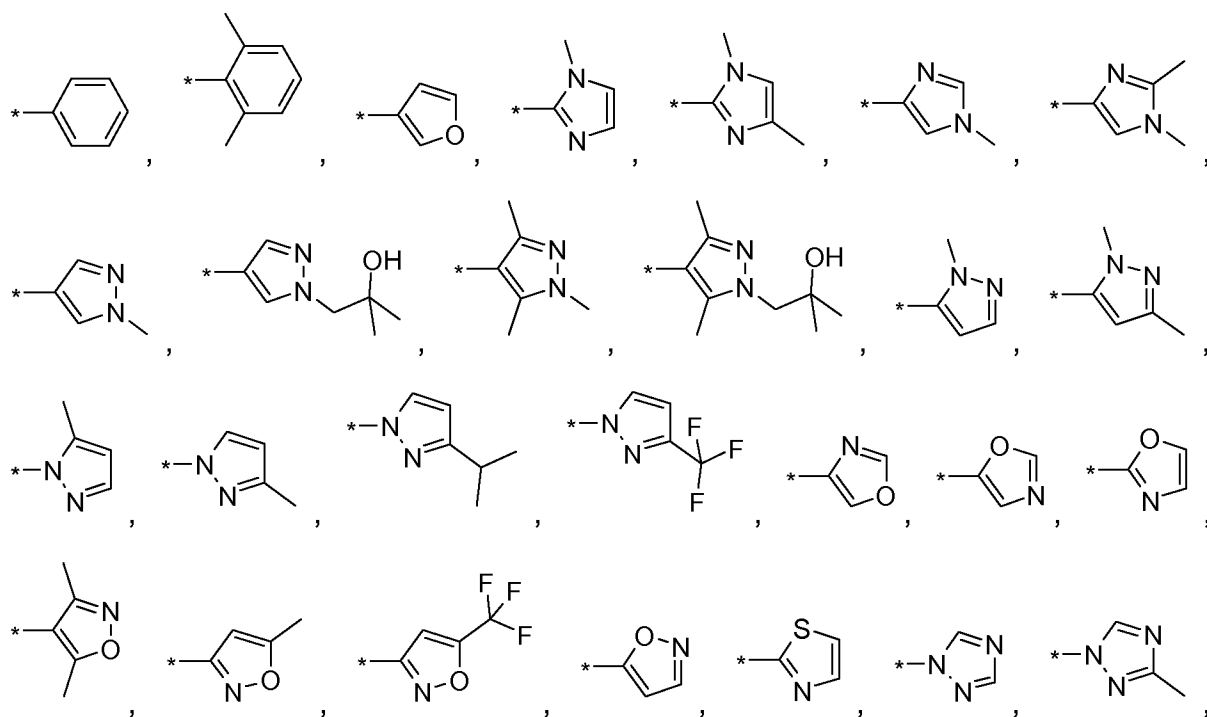
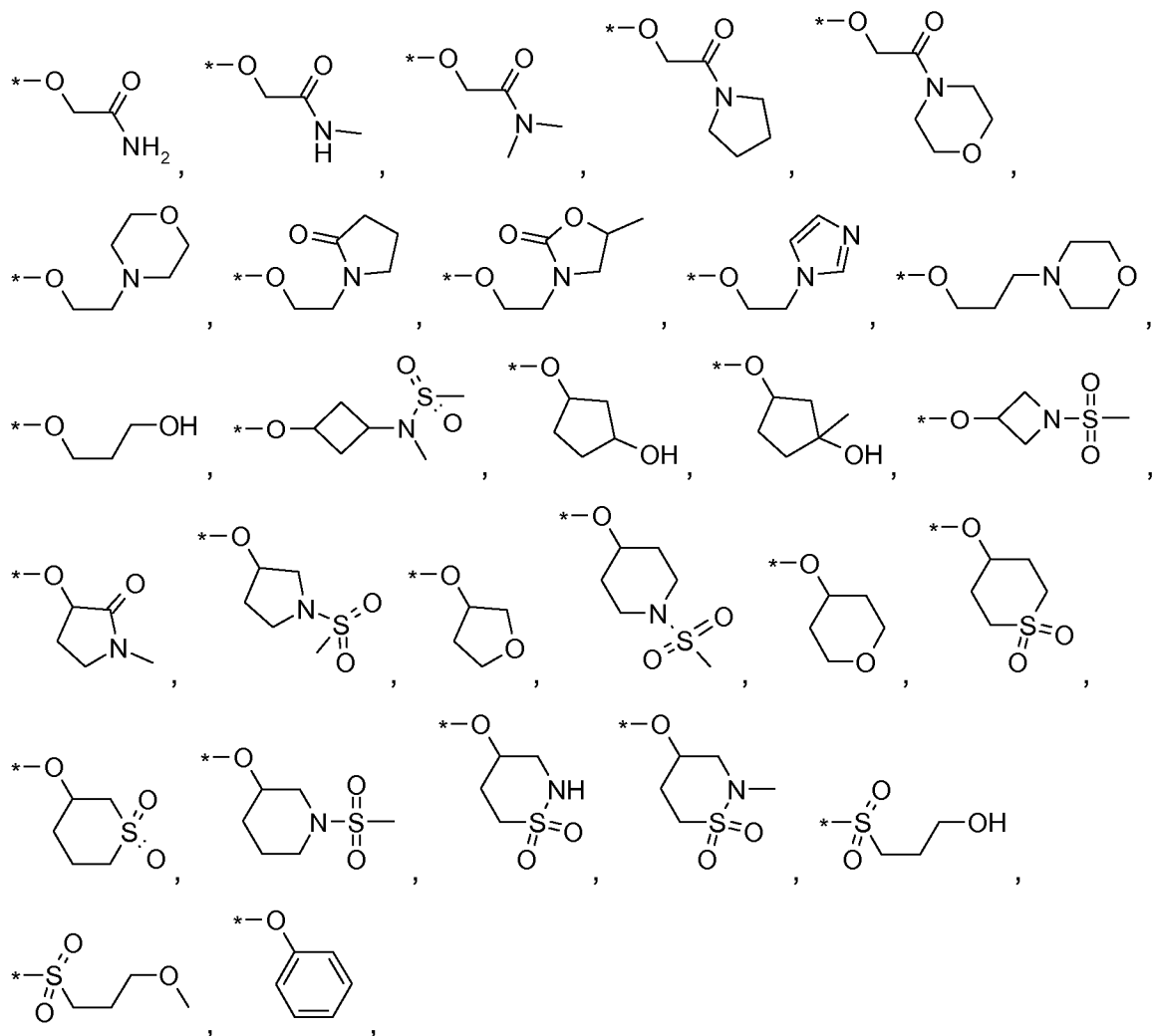


10 **R³-G6a:**

According to another embodiment the group R^3 is selected from the group R^3 -G6a consisting of







R⁴

R⁴-G1:

The group R⁴ is preferably selected from the group R⁴-G1 as defined hereinbefore.

R⁴-G2:

- 5 In another embodiment the group R⁴ is selected from the group R⁴-G2 consisting of F, Cl, Br, CN, C₁₋₃-alkyl, C₃₋₄-cycloalkyl-, HO-C₁₋₃-alkyl, C₁₋₃-alkyl-O-C₁₋₃-alkyl, -NR^NH, C₁₋₄-alkyl-O-, C₃₋₅-cycloalkyl-O-, H₃C-S(=O)-, H₃C-S(=O)₂-, wherein any alkyl and cycloalkyl group is optionally substituted with 1 or more F atoms.

10 **R⁴-G3:**

In another embodiment the group R⁴ is selected from the group R⁴-G3 consisting of F, Cl, CN, -CH₃, -CF₃, isopropyl, cyclopropyl, H₃C-O-CH₂-, H₃C-O-, and F₃C-O-.

R⁴-G4:

- 15 In another embodiment the group R⁴ is selected from the group R⁴-G4 consisting of CH₃.

R⁴-G4a:

- 20 In another embodiment the group R⁴ is selected from the group R⁴-G4a consisting of F and CH₃.

R⁵**R⁵-G1:**

The group R⁵ is preferably selected from the group R⁵-G1 as defined hereinbefore.

25

R⁵-G2:

- In one embodiment the group R⁵ is selected from the group R⁵-G2 consisting of Cl, C₁₋₄-alkyl-, -CN, C₃₋₆-cycloalkyl-, heterocyclyl-C(=O)-, H₂N-C(=O)-, C₁₋₄-alkyl-NR^N-C(=O)-, C₃₋₆-cycloalkyl-NR^N-C(=O)-, heterocyclyl-NR^N-C(=O)-, heteroaryl-NR^N-C(=O)-, -NH₂, C₁₋₄-alkyl-NR^N-, C₁₋₄-alkyl-C(=O)NR^N-, C₃₋₆-cycloalkyl-C(=O)NR^N-, heterocyclyl-C(=O)NR^N-, heteroaryl-C(=O)NR^N-, C₁₋₄-alkyl-S(=O)₂NR^N-, -OH, C₁₋₄-alkyl-O-, C₁₋₄-alkyl-O-C₁₋₄-alkyl-O-, C₃₋₆-cycloalkyl-O-, heterocyclyl-O-, phenyl-O-, heteroaryl-O-, C₁₋₄-alkyl-S(=O)-, C₃₋₆-cycloalkyl-S(=O)-, C₁₋₄-alkyl-S(=O)₂-, C₃₋₆-cycloalkyl-S(=O)₂-, heterocyclyl, and heteroaryl,
- 30

wherein any alkyl, cycloalkyl, and heterocyclyl group or sub-group within the groups mentioned is optionally substituted with 1 or more F atoms and optionally substituted with 1 or 2 groups independently selected from H₃C-, HO-, H₃C-O-, and -CN,

5 wherein heterocyclyl is selected from

a cyclobutyl group wherein 1 CH₂ group is replaced by -NR^N- or -O-;

a saturated or partially unsaturated C₅₋₆-cycloalkyl group wherein 1 CH₂ group is replaced by -C(=O)-, -NR^N-, -O-, -S(=O)- or -S(=O)₂- and/or 1 CH group by N;

10 a saturated or partially unsaturated C₅₋₆-cycloalkyl group wherein 1 CH₂ group is replaced by -NR^N- or -O-, a second CH₂ group is replaced by -NR^N-, -C(=O)-, -S(=O)- or -S(=O)₂- and/or 1 CH group is replaced by N; and

a saturated or partially unsaturated C₅₋₆-cycloalkyl group wherein 2 CH₂ group are replaced by -NR^N- or 1 CH₂ group by -NR^N- and the other by -O-, and a third CH₂ group is replaced by -C(=O)-, -S(=O)- or -S(=O)₂- and/or 1 CH group by N;

15 and wherein heteroaryl is selected from a tetrazolyl ring, a pyridin-2-onyl ring, a 5-membered heteroaromatic ring which contains 1, 2, or 3 heteroatoms independently of each other selected from =N-, -NH-, -O-, and -S-, and a 6-membered heteroaromatic ring which contains 1 or 2 =N- atoms, and wherein in heteroaromatic rings with one ore more NH groups each of them is replaced by
20 NR^N, and each heteroaryl group is optionally substituted with 1 to 3 substituents independently selected from F, Cl, -CH₃, -CN, and -O-CH₃.

R⁵-G2a:

In one embodiment the group R⁵ is selected from the group R⁵-G2a consisting of Cl,
25 C₁₋₄-alkyl-, -CN, C₃₋₆-cycloalkyl-, heterocyclyl-C(=O)-, H₂N-C(=O)-, C₁₋₄-alkyl-NR^N-C(=O)-, C₃₋₆-cycloalkyl-NR^N-C(=O)-, heterocyclyl-NR^N-C(=O)-, heteroaryl-NR^N-C(=O)-, -NH₂, C₁₋₄-alkyl-NR^N-, -NHC(=O)-O-C(CH₃)₃, C₁₋₄-alkyl-C(=O)NR^N-, C₃₋₆-cycloalkyl-C(=O)NR^N-, heterocyclyl-C(=O)NR^N-, heteroaryl-C(=O)NR^N-, C₁₋₄-alkyl-S(=O)₂NR^N-, -OH, C₁₋₄-alkyl-O-, C₁₋₄-alkyl-O-C₁₋₄-alkyl-O-, C₃₋₆-cycloalkyl-O-,
30 heterocyclyl-O-, phenyl-O-, heteroaryl-O-, C₁₋₄-alkyl-S(=O)-, C₃₋₆-cycloalkyl-S(=O)-, C₁₋₄-alkyl-S(=O)₂-, C₃₋₆-cycloalkyl-S(=O)₂-, heterocyclyl, phenyl and heteroaryl,
wherein any alkyl, cycloalkyl, and heterocyclyl group or sub-group within the groups mentioned is optionally substituted with 1 or more F atoms and optionally

substituted with 1 or 2 groups independently selected from H₃C-, HO-, H₃C-O-, and -CN,

wherein heterocyclyl is selected from

a cyclobutyl group wherein 1 CH₂ group is replaced by -NR^N- or -O-;

5 a saturated or partially unsaturated C₅₋₆-cycloalkyl group wherein 1 CH₂ group is replaced by -C(=O)-, -NR^N-, -O-, -S(=O)- or -S(=O)₂- and/or 1 CH group by N;

a saturated or partially unsaturated C₅₋₆-cycloalkyl group wherein 1 CH₂ group is replaced by -NR^N- or -O-, a second CH₂ group is replaced by -NR^N-, -C(=O)-, -S(=O)- or -S(=O)₂- and/or 1 CH group is replaced by N; and

10 a saturated or partially unsaturated C₅₋₆-cycloalkyl group wherein 2 CH₂ group are replaced by -NR^N- or 1 CH₂ group by -NR^N- and the other by -O-, and a third CH₂ group is replaced by -C(=O)-, -S(=O)- or -S(=O)₂- and/or 1 CH group by N;

and wherein heteroaryl is selected from a tetrazolyl ring, a pyridin-2-onyl ring, a 5-membered heteroaromatic ring which contains 1, 2, or 3 heteroatoms independently of each other selected from =N-, -NH-, -O-, and -S-, and a 6-membered heteroaromatic ring which contains 1 or 2 =N- atoms, and wherein in heteroaromatic rings with one or more NH groups each of them is replaced by NR^N, and each heteroaryl group is optionally substituted with 1 to 3 substituents independently selected from F, Cl, -CH₃, -CN, and -O-CH₃.

20

R⁵-G3:

In another embodiment the group R⁵ is selected from the group R⁵-G3 consisting of C₁₋₄-alkyl-, -CN, C₃₋₆-cycloalkyl-, heterocyclyl-C(=O)-, H₂N-C(=O)-, C₁₋₄-alkyl-NR^N-C(=O)-, C₁₋₄-alkyl-NR^N-, C₁₋₄-alkyl-C(=O)NR^N-, C₁₋₄-alkyl-S(=O)₂NR^N-, -OH, C₁₋₄-alkyl-O-, C₁₋₄-alkyl-O-C₁₋₄-alkyl-O-, C₃₋₆-cycloalkyl-O-, heterocyclyl-O-, C₁₋₄-alkyl-S(=O)-, C₁₋₄-alkyl-S(=O)₂-, heterocyclyl, and heteroaryl,

25

wherein any alkyl, cycloalkyl, and heterocyclyl group or sub-group within the groups mentioned is optionally substituted with 1 or more F atoms and optionally substituted with 1 or 2 groups independently selected from H₃C-, H₃C-O-, and -CN,

30

wherein heterocyclyl is selected from

a cyclobutyl group wherein 1 CH₂ group is replaced by -NR^N- or -O-, ,

a saturated or partially unsaturated C₅₋₆-cycloalkyl group wherein 1 CH₂ group is replaced by -C(=O)-, -NR^N-, -O-, -S(=O)- or -S(=O)₂- and/or 1 CH group by N;

a saturated or partially unsaturated C₅₋₆-cycloalkyl group wherein 1 CH₂ group is replaced by -NR^N- or -O-, a second CH₂ group is replaced by -NR^N-, -C(=O)-, -S(=O)- or -S(=O)₂- and/or 1 CH group is replaced by N; and

a saturated or partially unsaturated C₅₋₆-cycloalkyl group wherein 2 CH₂ groups are replaced by -NR^N- or 1 CH₂ group by -NR^N- and the other by -O-, and a third CH₂ group is replaced by -C(=O)-, -S(=O)- or -S(=O)₂- and/or 1 CH group by N;

and wherein heteroaryl is selected from

a pyridin-2-onyl ring, a 5-membered heteroaromatic ring which contains 1 or 2 heteroatoms independently of each other selected from =N-, -NH-, -O-, and -S-, and a 6-membered heteroaromatic ring which contains 1 or 2 =N- atoms, and wherein in heteroaromatic rings with one or more NH groups each of them is replaced by NR^N, and each heteroaryl group is optionally substituted with 1 or 2 substituents independently selected from F, Cl, -CH₃, -CN, and -O-CH₃.

R⁵-G3a:

In another embodiment the group R⁵ is selected from the group R⁵-G3a consisting of C₁₋₄-alkyl-, -CN, C₃₋₆-cycloalkyl-, heterocyclyl-C(=O)-, H₂N-C(=O)-, C₁₋₄-alkyl-NR^N-C(=O)-, -NHC(=O)-O-C(CH₃)₃, C₁₋₄-alkyl-NR^N-, C₁₋₄-alkyl-C(=O)NR^N-, C₁₋₄-alkyl-S(=O)₂NR^N-, -OH, C₁₋₄-alkyl-O-, C₁₋₄-alkyl-O-C₁₋₄-alkyl-O-, C₃₋₆-cycloalkyl-O-, heterocyclyl-O-, C₁₋₄-alkyl-S(=O)-, C₁₋₄-alkyl-S(=O)₂-, heterocyclyl, phenyl and heteroaryl,

wherein any alkyl, cycloalkyl, and heterocyclyl group or sub-group within the groups mentioned is optionally substituted with 1 or more F atoms and optionally substituted with 1 or 2 groups independently selected from H₃C-, HO-, H₃C-O- and -CN,

wherein heterocyclyl is selected from

a cyclobutyl group wherein 1 CH₂ group is replaced by -NR^N- or -O-,

a saturated or partially unsaturated C₅₋₆-cycloalkyl group wherein 1 CH₂ group is replaced by -C(=O)-, -NR^N-, -O-, -S(=O)- or -S(=O)₂- and/or 1 CH group by N;

a saturated or partially unsaturated C₅₋₆-cycloalkyl group wherein 1 CH₂ group is replaced by -NR^N- or -O-, a second CH₂ group is replaced by -NR^N-, -C(=O)-, -S(=O)- or -S(=O)₂- and/or 1 CH group is replaced by N; and

a saturated or partially unsaturated C₅₋₆-cycloalkyl group wherein 2 CH₂ groups are replaced by -NR^N- or 1 CH₂ group by -NR^N- and the other by -O-, and a third CH₂ group is replaced by -C(=O)-, -S(=O)- or -S(=O)₂- and/or 1 CH group by N; and wherein heteroaryl is selected from

- 5 a pyridin-2-onyl ring, a 5-membered heteroaromatic ring which contains 1 or 2 heteroatoms independently of each other selected from =N-, -NH-, -O-, and -S-, and a 6-membered heteroaromatic ring which contains 1 or 2 =N- atoms, and wherein in heteroaromatic rings with one ore more NH groups each of them is replaced by NR^N, and each heteroaryl group is optionally substituted with 1 or 2
10 substituents independently selected from F, Cl, -CH₃, -CN, and -O-CH₃.

R⁵-G4:

In another embodiment the group R⁵ is selected from the group R⁵-G4 consisting of C₁₋₂-alkyl-, -CN, C₃₋₅-cycloalkyl-, heterocyclyl-C(=O)-, H₂N-C(=O)-, -C(=O)NHCH₃,
15 -C(=O)N(CH₃)₂, -N(CH₃)₂, H₃C-C(=O)NH-, H₃C-C(=O)NCH₃-, H₃C-S(=O)₂NH-, H₃C-S(=O)₂NCH₃-, -O H, C₁₋₃-alkyl-O-, C₁₋₂-alkyl-O-C₂-alkyl-O-, C₃₋₅-cycloalkyl-O-, heterocyclyl-O-, H₃C-S(=O)-, H₃C-S(=O)₂-, heterocyclyl, and heteroaryl, wherein heterocyclyl is selected from

- an azetidiny, oxetanyl, a pyrrolidinyl, pyrrolidin-2-onyl, tetrahydrofuranyl,
20 sulfolanyl, piperidinyl, tetrahydropyranyl, 1,1-dioxo-tetrahydrothiopyranyl, morpholinyl, and an oxazolidin-2-onyl ring, wherein each of these rings optionally is substituted with 1 CH₃ group and wherein an NH group, if present, optionally is replaced with NS(=O)₂-C₁₋₃-alkyl;

and wherein heteroaryl is selected from

- 25 a pyridin-2-onyl, imidazolyl, pyrazolyl, and oxazolyl ring, wherein in a heteroaryl group with a NH group this unit optionally is replaced by a N-CH₃ group.

R⁵-G4a:

In another embodiment the group R⁵ is selected from the group R⁵-G4a consisting of C₁₋₂-alkyl-, -CN, 2-hydroxy-isobutyl, C₃₋₅-cycloalkyl, 1-hydroxy-cyclopropyl, 4,4-difluoro-1-hydroxy-cyclohex-1-yl, heterocyclyl-C(=O)-, H₂N-C(=O)-, -C(=O)NHCH₃,
30 -C(=O)N(CH₃)₂, -N(CH₃)₂, H₃C-C(=O)NH-, H₃C-C(=O)NCH₃-, H₃C-S(=O)₂NH-, H₃C-S(=O)₂NCH₃-, -NHC(=O)-O-C(CH₃)₃, -OH, C₁₋₃-alkyl-O-, C₁₋₂-alkyl-O-C₂-alkyl-O-, C₃₋

5-cycloalkyl-O-, heterocyclyl-O-, $\text{H}_3\text{C-S(=O)-}$, $\text{H}_3\text{C-S(=O)}_2\text{-}$, heterocyclyl, phenyl, and heteroaryl,

wherein heterocyclyl is selected from

an azetidiny, oxetanyl, a pyrrolidiny, pyrrolidin-2-onyl, tetrahydrofuranyl, sulfolanyl, piperidiny, tetrahydropyranyl, 1,1-dioxo-tetrahydrothiopyranyl, morpholiny, 1,1-dioxo-isothiazolidin-2-yl and an oxazolidin-2-onyl ring, wherein each of these rings optionally is substituted with 1 CH_3 or 1 OH group and wherein an NH group, if present, optionally is replaced with $\text{NS(=O)}_2\text{-C}_{1-3}\text{-alkyl}$;

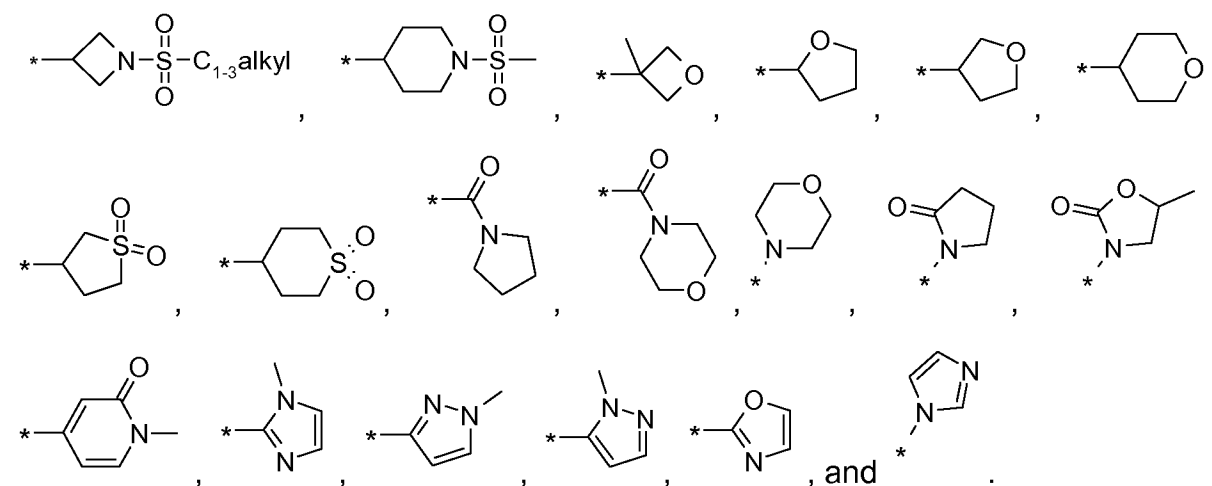
and wherein heteroaryl is selected from

pyridin-2-onyl, pyridiny, imidazolyl, pyrazolyl, and oxazolyl ring, each of which is optionally substituted with a $\text{H}_3\text{C-O-}$ group and wherein a heteroaryl group with a NH group this unit optionally is replaced by a N-CH_3 group.

R⁵-G5:

According to another embodiment the group R⁵ is selected from the group R⁵-G5 consisting of

$-\text{CH}_3$, cyclopropyl, $-\text{CN}$, $-\text{C(=O)NH}_2$, $-\text{C(=O)NHCH}_3$, $-\text{C(=O)N(CH}_3)_2$, $-\text{N(CH}_3)_2$, $-\text{N(CH}_3)\text{S(=O)}_2\text{CH}_3$, $-\text{OH}$, $-\text{O-CH}_3$, $-\text{O-CH}_2\text{CH}_3$, $-\text{O-CH}_2\text{CH}_2\text{-O-CH}_3$, $-\text{O-CH}_2\text{CH}_2\text{-O-CH}_2\text{CH}_3$, $-\text{S(=O)CH}_3$, $-\text{S(=O)}_2\text{CH}_3$,

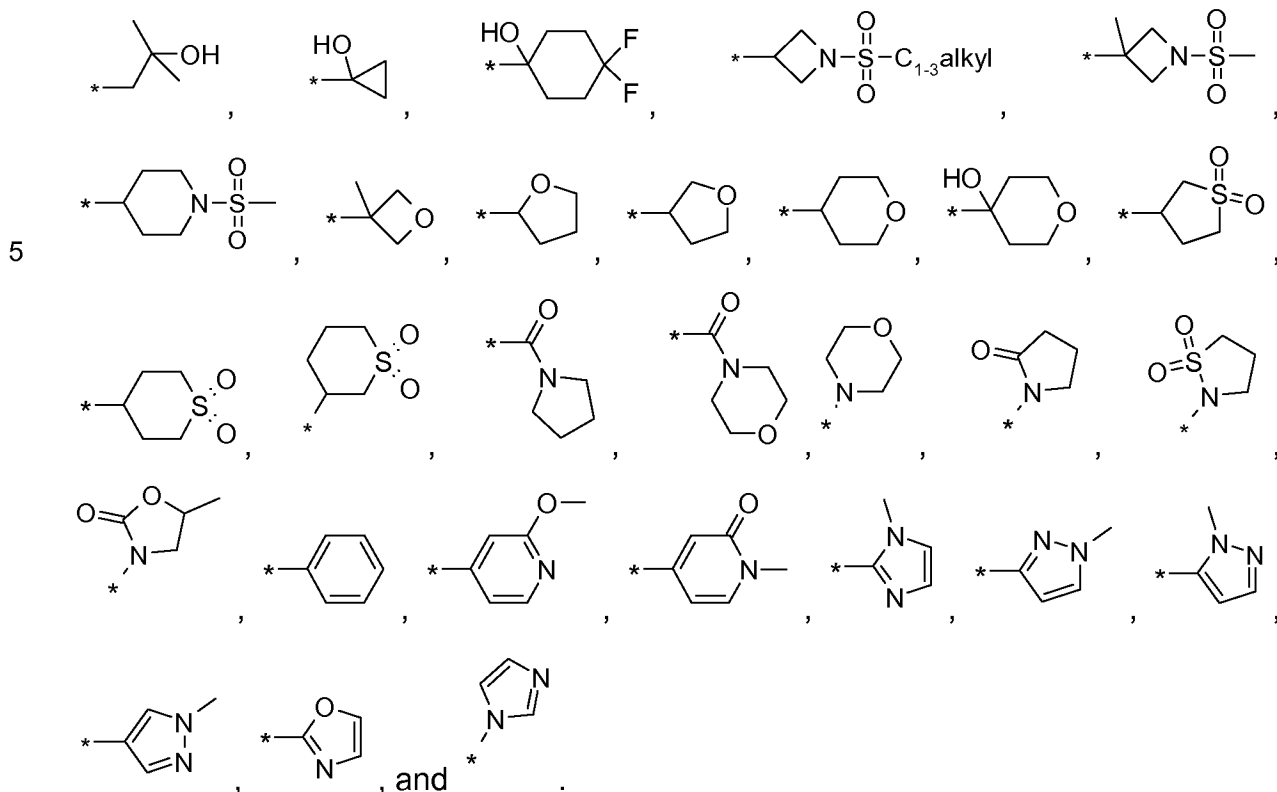


R⁵-G5a:

According to another embodiment the group R⁵ is selected from the group R⁵-G5a consisting of

$-\text{CH}_3$, cyclopropyl, $-\text{CN}$, $-\text{C(=O)NH}_2$, $-\text{C(=O)NHCH}_3$, $-\text{C(=O)N(CH}_3)_2$, $-\text{N(CH}_3)_2$,

-NHC(=O)CH₃, -NHS(=O)₂CH₃, N(CH₃)S(=O)₂CH₃, NHC(=O)-O-C(CH₃)₃, -OH, -O-CH₃, -O-CH₂CH₃, -O-CH₂CH₂-O-CH₃, -O-CH₂CH₂-O-CH₂CH₃, -S(=O)CH₃, -S(=O)₂CH₃,



10 **R⁶**

R⁶-G1:

The group R⁶ is preferably selected from the group R⁶-G1 as defined hereinbefore.

R⁶-G2:

15 In one embodiment the group R⁶ is selected from the group R⁶-G2 consisting of F, Cl, -CN, C₁₋₃-alkyl, cyclopropyl, HO-C₁₋₃-alkyl-, H₃C-O-C₁₋₃-alkyl-, H₃C-O-, -S(=O)CH₃, and -S(=O)₂-CH₃, wherein any alkyl and cycloalkyl group or sub-group within the groups mentioned is optionally substituted with one or more F atoms.

20 **R⁶-G2a:**

In one embodiment the group R⁶ is selected from the group R⁶-G2a consisting of F, Cl, -CN, C₁₋₃-alkyl, cyclopropyl, HO-C₁₋₄-alkyl-, H₃C-O-C₁₋₄-alkyl-, H₃C-O-, -S(=O)CH₃, and -S(=O)₂-CH₃, wherein any alkyl and cycloalkyl group or sub-group within the groups mentioned is optionally substituted with one or more F atoms.

R⁶-G3:

In another embodiment the group R⁶ is selected from the group R⁶-G3 consisting of F, Cl, -CN, -CH₃, -CF₃, -OCH₃, -OCF₃, -S(=O)CH₃, and -S(=O)₂-CH₃.

5

R⁶-G3a:

In another embodiment the group R⁶ is selected from the group R⁶-G3a consisting of F, Cl, C₁₋₃-alkyl, cyclopropyl, HO-C₁₋₄-alkyl-, -CN, -CF₃, -OCH₃, -OCF₃, -S(=O)CH₃, and -S(=O)₂-CH₃.

10

R⁶-G4:

In another embodiment the group R⁶ is selected from the group R⁶-G4 consisting of F, -CH₃, CN, and -OCH₃.

15 **R⁶-G4a:**

In another embodiment the group R⁶ is selected from the group R⁶-G4a consisting of F, -CH₃, -CH₂-CH₃, -CH(CH₃)₂, cyclopropyl, HO-C(CH₃)₂-, HO-CH₂-C(CH₃)₂-, HO-C(CH₃)₂-CH₂-, -CF₃, CN, and -OCH₃.

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

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

R^N-G2:

25 In another embodiment the group R^N is selected from the group R^N-G2 consisting of H, C₁₋₃-alkyl, H₃C-C(=O)-, and C₁₋₃-alkyl-S(=O)₂-.

R^N-G3:

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

m:

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

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

According to another embodiment the index m is 1 or 2.

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

According to another embodiment the index m is 2.

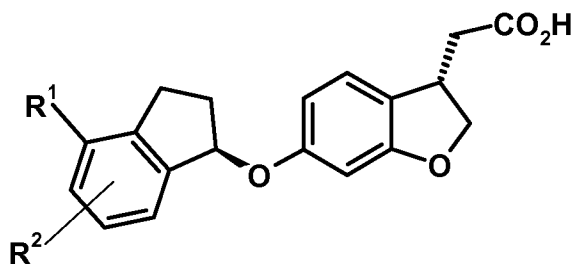
- 10 Examples of preferred subgeneric embodiments (E) according to the present invention are set forth in the following table, wherein each substituent group of each embodiment is defined according to the definitions set forth hereinbefore and wherein all other substituents of the formula I are defined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

E	R ¹ -	R ² -	R ³ -	R ⁴ -	R ⁵ -	R ⁶ -	R ^N -	m
E-1	R ¹ -G1	R ² -G1	R ³ -G1	R ⁴ -G1	R ⁵ -G1	R ⁶ -G1	R ^N -G1	0, 1, 2
E-2	R ¹ -G2	R ² -G2	R ³ -G2	R ⁴ -G2	R ⁵ -G2	R ⁶ -G2	R ^N -G2	0, 1, 2
E-2a	R ¹ -G2a	R ² -G2	R ³ -G2	R ⁴ -G2	R ⁵ -G2	R ⁶ -G2	R ^N -G2	1, 2
E-2b	R ¹ -G2b	R ² -G2	R ³ -G2	R ⁴ -G2	R ⁵ -G2	R ⁶ -G2	R ^N -G2	1, 2
E-3	R ¹ -G3a	R ² -G3	R ³ -G2	R ⁴ -G3	R ⁵ -G3	R ⁶ -G3	R ^N -G3	1, 2
E-4	R ¹ -G3a	R ² -G3	R ³ -G3	R ⁴ -G3	R ⁵ -G3	R ⁶ -G3	R ^N -G3	1, 2
E-5	R ¹ -G4a	R ² -G3	R ³ -G2	R ⁴ -G3	R ⁵ -G3	R ⁶ -G3	R ^N -G3	1, 2
E-6	R ¹ -G4a	R ² -G3	R ³ -G3	R ⁴ -G3	R ⁵ -G3	R ⁶ -G3	R ^N -G3	1, 2
E-7	R ¹ -G4a	R ² -G3	R ³ -G4	R ⁴ -G3	R ⁵ -G3	R ⁶ -G3	R ^N -G3	1, 2
E-8	R ¹ -G4a	R ² -G3	R ³ -G4	R ⁴ -G3	R ⁵ -G3	R ⁶ -G4	R ^N -G3	1, 2
E-9	R ¹ -G4a	R ² -G3	R ³ -G4	R ⁴ -G3	R ⁵ -G4	R ⁶ -G4	R ^N -G3	1, 2
E-10	R ¹ -G4a	R ² -G4	R ³ -G4	R ⁴ -G3	R ⁵ -G5	R ⁶ -G4	R ^N -G3	1, 2
E-11	R ¹ -G5	R ² -G3	R ³ -G4	-	R ⁵ -G4	R ⁶ -G4	R ^N -G3	1, 2
E-12	R ¹ -G5	R ² -G3	R ³ -G4	-	R ⁵ -G3	R ⁶ -G3	R ^N -G3	1, 2
E-13	R ¹ -G5	R ² -G4	R ³ -G4	-	R ⁵ -G3	R ⁶ -G3	R ^N -G2	1, 2
E-14	R ¹ -G5	R ² -G4	R ³ -G4	-	R ⁵ -G3	R ⁶ -G3	R ^N -G3	1, 2
E-15	R ¹ -G5	R ² -G4	R ³ -G4	-	R ⁵ -G3	R ⁶ -G4	R ^N -G3	1, 2
E-16	R ¹ -G5	R ² -G4	R ³ -G4	-	R ⁵ -G4	R ⁶ -G4	R ^N -G3	1, 2
E-17	R ¹ -G5	R ² -G4	R ³ -G3	-	R ⁵ -G5	R ⁶ -G4	R ^N -G3	1, 2
E-18	R ¹ -G5	R ² -G4	R ³ -G4	-	R ⁵ -G5	R ⁶ -G4	R ^N -G3	1, 2

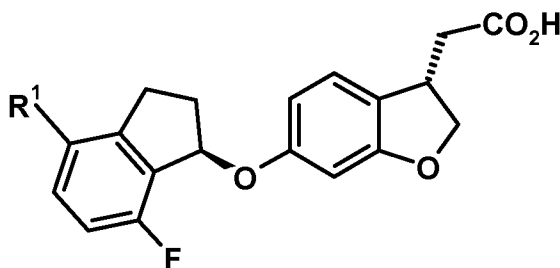
E	R ¹ -	R ² -	R ³ -	R ⁴ -	R ⁵ -	R ⁶ -	R ^N -	m
E-19	R ¹ -G5	R ² -G4	R ³ -G5	-	-	-	-	1, 2
E-20	R ¹ -G5	R ² -G4	R ³ -G6	-	-	-	-	1, 2
E-21	R ¹ -G4a	R ² -G4a	R ³ -G2a	R ⁴ -G3	R ⁵ -G2a	R ⁶ -G2a	R ^N -G3	1
E-22	R ¹ -G4a	R ² -G4a	R ³ -G3a	R ⁴ -G3	R ⁵ -G3a	R ⁶ -G3a	R ^N -G3	1
E-23	R ¹ -G5a	R ² -G4a	R ³ -G3a	-	R ⁵ -G3a	R ⁶ -G3a	R ^N -G3	1
E-24	R ¹ -G5a	R ² -G4a	R ³ -G4a	-	R ⁵ -G4a	R ⁶ -G3a	R ^N -G3	1
E-25	R ¹ -G5a	R ² -G4a	R ³ -G5a	-	-	-	-	1
E-26	R ¹ -G5a	R ² -G4a	R ³ -G6a	-	-	-	-	1
E-27	R ¹ -G5	R ² -G4a	R ³ -G1	-	R ⁵ -G1	R ⁶ -G1	R ^N -G3	1
E-28	R ¹ -G5	R ² -G4a	R ³ -G2a	-	R ⁵ -G2a	R ⁶ -G2a	R ^N -G3	1
E-29	R ¹ -G5	R ² -G4a	R ³ -G2a	-	R ⁵ -G3a	R ⁶ -G3a	R ^N -G3	1
E-30	R ¹ -G5	R ² -G4a	R ³ -G3a	-	R ⁵ -G3a	R ⁶ -G3a	R ^N -G3	1
E-31	R ¹ -G5	R ² -G4a	R ³ -G3a	-	R ⁵ -G4a	R ⁶ -G3a	R ^N -G3	1
E-32	R ¹ -G5	R ² -G4a	R ³ -G4a	-	R ⁵ -G4a	R ⁶ -G3a	R ^N -G3	1
E-33	R ¹ -G5	R ² -G4a	R ³ -G4a	-	R ⁵ -G5a	R ⁶ -G4a	R ^N -G3	1
E-34	R ¹ -G5	R ² -G4a	R ³ -G5a	-	-	-	-	1
E-35	R ¹ -G5	R ² -G4a	R ³ -G6a	-	-	-	-	1

The following preferred embodiments of compounds of the formula I are described using generic formulas (I.1) to (I.3), wherein any tautomers, solvates, hydrates and salts thereof, in particular the pharmaceutically acceptable salts thereof, are encompassed.

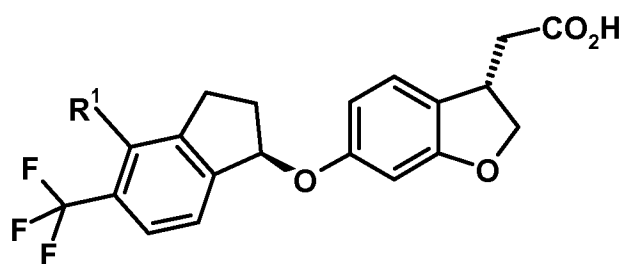
(I.1)



(I.2)

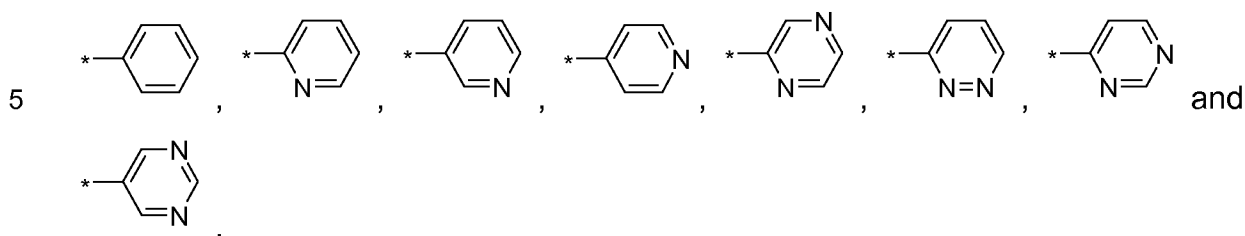


(I.3)



Preferred are those compounds of formula I, wherein

R^1 is selected from the group consisting of



wherein each group is substituted with one group R^3 and optionally additionally substituted with 1 or 2 groups independently selected from R^4 ;

10 R^2 is selected from the group consisting of F, Cl, Br, H_2FC- , F_3C- , $NC-$, and F_3C-O- ;

R^3 is selected from the group consisting of C_{1-4} -alkyl, C_{3-6} -cycloalkyl-, C_{1-4} -alkyl-O-, and C_{3-6} -cycloalkyl-O-,

15 wherein each alkyl and cycloalkyl group and each alkyl and cycloalkyl sub-group within the groups mentioned is substituted with 1 to 3 groups independently selected from R^5 and optionally substituted with 1 or more F atoms;

or from $H_3C-C(=O)-$, heterocyclyl- $C(=O)-$, $H_2N-C(=O)-$, C_{1-3} -alkyl- $NR^N-C(=O)-$, C_{1-4} -alkyl- $C(=O)NR^N-$, C_{3-6} -cycloalkyl- $C(=O)NR^N-$, heterocyclyl- $C(=O)NR^N-$, C_{1-4} -alkyl- $S(=O)_2NR^N-$, heterocyclyl-O-, phenyl-O-, heteroaryl-O-, heterocyclyl- $S(=O)_2-$, H_2N-
 20 $S(=O)_2-$, heterocyclyl, phenyl, and heteroaryl,

wherein each alkyl, cycloalkyl, and heterocyclyl group or sub-group within the groups mentioned is optionally substituted with 1 or 2 groups independently selected from R^5 and optionally substituted with 1 or more F atoms; and

25 wherein each phenyl and heteroaryl group is optionally substituted with 1 to 3 substituents independently selected from R^6 ;

wherein heterocyclyl is selected from

a cyclobutyl group wherein 1 CH₂ group is replaced by -NH- or -O-;

a saturated or mono-unsaturated C₅₋₆-cycloalkyl group wherein 1 CH₂ group is replaced by -C(=O)-, -NH-, -O- or -S(=O)₂- and/or 1 CH group by N;

5 a saturated or mono-unsaturated C₅₋₆-cycloalkyl group wherein 1 CH₂ group is replaced by -NH- or -O-, a second CH₂ group is replaced by -C(=O)- or -S(=O)₂- and/or 1 CH group is replaced by N; and

wherein heteroaryl is selected from a pyridin-2-onyl ring, a 5-membered heteroaromatic ring which contains 1, 2, or 3 heteroatoms independently of each other selected from =N-, -NH-, O, and S, and a 6-membered heteroaromatic ring
10 which contains 1 or 2 =N- atoms,

and wherein in heteroaryl and heterocyclyl rings with one or more NH groups each of them is replaced by NR^N or NR⁵;

with the proviso that R³ in total cannot be C₁₋₄-alkyl-, C₁₋₄-alkyl-O-C₁₋₄-alkyl, HO-C₁₋₄-alkyl, and C₁₋₄-alkyl-O-;
15

R⁴ is selected from the group consisting of F, Cl, CN, -CH₃, -CF₃, isopropyl, cyclopropyl, H₃C-O-CH₂-, H₃C-O-, and F₃C-O-;

20 R⁵ is selected from the group consisting of C₁₋₄-alkyl-, -CN, C₃₋₆-cycloalkyl-, heterocyclyl-C(=O)-, H₂N-C(=O)-, C₁₋₄-alkyl-NR^N-C(=O)-, C₁₋₄-alkyl-NR^N-, C₁₋₄-alkyl-C(=O)NR^N-, C₁₋₄-alkyl-S(=O)₂NR^N-, -OH, C₁₋₄-alkyl-O-, C₁₋₄-alkyl-O-C₁₋₄-alkyl-O-, C₃₋₆-cycloalkyl-O-, heterocyclyl-O-, C₁₋₄-alkyl-S(=O)-, C₁₋₄-alkyl-S(=O)₂-, heterocyclyl, and heteroaryl,

25 wherein any alkyl, cycloalkyl, and heterocyclyl group or sub-group within the groups mentioned is optionally substituted with 1 or more F atoms and optionally substituted with 1 or 2 groups independently selected from H₃C-, H₃C-O-, and -CN,

wherein heterocyclyl is selected from

30 a cyclobutyl group wherein 1 CH₂ group is replaced by -NR^N- or -O-;

a saturated or partially unsaturated C₅₋₆-cycloalkyl group wherein 1 CH₂ group is replaced by -C(=O)-, -NR^N-, -O-, -S(=O)- or -S(=O)₂- and/or 1 CH group by N;

a saturated or partially unsaturated C₅₋₆-cycloalkyl group wherein 1 CH₂ group is replaced by -NR^N-, or -O-, a second CH₂ group is replaced by -NR^N-, -C(=O)-, -S(=O)- or -S(=O)₂- and/or 1 CH group is replaced by N; and

a saturated or partially unsaturated C₅₋₆-cycloalkyl group wherein 2 CH₂ group are replaced by -NR^N- or 1 CH₂ group by -NR^N- and the other by -O-, and a third CH₂ group is replaced by -C(=O)-, -S(=O)- or -S(=O)₂- and/or 1 CH group by N;

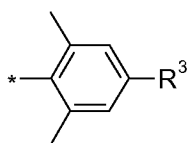
and wherein heteroaryl is selected from a pyridin-2-onyl ring, a 5-membered heteroaromatic ring which contains 1 or 2 heteroatoms independently of each other selected from =N-, -NH-, -O-, and -S-, and a 6-membered heteroaromatic ring which contains 1 or 2 =N- atoms, and wherein in heteroaromatic rings with one or more NH groups each of them is replaced by NR^N, and each heteroaryl group is optionally substituted with 1 or 2 substituents independently selected from F, Cl, -CH₃, -CN, and -O-CH₃;

R⁶ is selected from the group consisting of F, Cl, -CN, -CH₃, -CF₃, -OCH₃, -OCF₃, -S(=O)CH₃, and -S(=O)₂-CH₃;

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

m is 1 or 2; and the pharmaceutically acceptable salts thereof.

More preferred are those compounds of formula I, wherein



R¹ is ;

R² is selected from the group consisting of F, Cl, and NC-;

R³ is selected from the group consisting of C₁₋₄-alkyl, C₃₋₆-cycloalkyl-, C₁₋₄-alkyl-O-, and C₃₋₆-cycloalkyl-O-,

wherein each alkyl and cycloalkyl group and each alkyl and cycloalkyl sub-group within the groups mentioned is substituted with 1 group selected from R^5 and optionally substituted with 1 or 2 H_3C - group;

or from $H_3C-C(=O)-$, heterocyclyl- $C(=O)-$, $H_2N-C(=O)-$, $H_3C-NR^N-C(=O)-$,
 5 heterocyclyl-O-, heteroaryl-O-, $H_2N-S(=O)_2-$, heterocyclyl, phenyl, and heteroaryl,

wherein each heterocyclyl group or sub-group within the groups mentioned is optionally substituted with 1 or 2 groups independently selected from R^5 and optionally substituted with 1 or more F atoms; and

wherein each phenyl and heteroaryl group is optionally substituted with 1 or 2
 10 substituents independently selected from R^6 ;

wherein heterocyclyl is selected from

a cyclobutyl group wherein 1 CH_2 group is replaced by -NH- or -O-;

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

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

wherein heteroaryl is selected from a 5-membered heteroaromatic ring which contains 1 or 2 heteroatoms independently of each other selected from =N-, -NH-,
 20 , -O-, and -S-, and a 6-membered heteroaromatic ring which contains 1 or 2 =N-atoms, and wherein in heteroaryl and heterocyclyl rings with one ore more NH group each of them is replaced with NR^N or NR^5 ;

with the proviso that R^3 in total cannot be C_{1-4} -alkyl-, C_{1-4} -alkyl-O- C_{1-4} -alkyl, HO- C_{1-4} -alkyl, and C_{1-4} -alkyl-O-;
 25

R^5 is selected from the group consisting of C_{1-4} -alkyl-, -CN, C_{3-6} -cycloalkyl-, heterocyclyl- $C(=O)-$, $H_2N-C(=O)-$, C_{1-4} -alkyl- $NR^N-C(=O)-$, C_{1-4} -alkyl- NR^N- , C_{1-4} -alkyl- $C(=O)NR^N-$, C_{1-4} -alkyl- $S(=O)_2NR^N-$, -OH, C_{1-4} -alkyl-O-, C_{1-4} -alkyl-O- C_{1-4} -alkyl-O-, C_{3-6} -
 30 cycloalkyl-O-, heterocyclyl-O-, C_{1-4} -alkyl- $S(=O)-$, C_{1-4} -alkyl- $S(=O)_2-$, heterocyclyl, and heteroaryl,

wherein any alkyl, cycloalkyl, and heterocyclyl group or sub-group within the groups mentioned is optionally substituted with 1 or more F atoms and optionally substituted with 1 or 2 groups independently selected from H_3C -, H_3C-O -, and

-CN,

wherein heterocyclyl is selected from

a cyclobutyl group wherein 1 CH₂ group is replaced by -NR^N- or -O-;

a saturated or partially unsaturated C₅₋₆-cycloalkyl group wherein 1 CH₂ group is replaced by -C(=O)-, -NR^N-, -O-, -S(=O)- or -S(=O)₂- and/or 1 CH group by N;

a saturated or partially unsaturated C₅₋₆-cycloalkyl group wherein 1 CH₂ group is replaced by -NR^N-, or -O-, a second CH₂ group is replaced by -NR^N-, -C(=O)-, -S(=O)- or -S(=O)₂- and/or 1 CH group is replaced by N; and

a saturated or partially unsaturated C₅₋₆-cycloalkyl group wherein 2 CH₂ group are replaced by -NR^N- or 1 CH₂ group by -NR^N- and the other by -O-, and a third CH₂ group is replaced by -C(=O)-, -S(=O)- or -S(=O)₂- and/or 1 CH group by N;

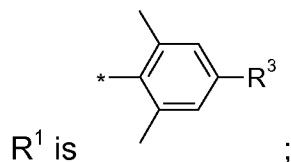
and wherein heteroaryl is selected from a pyridin-2-onyl ring, a 5-membered heteroaromatic ring which contains 1 or 2 heteroatoms independently of each other selected from =N-, -NH-, -O-, and -S-, and a 6-membered heteroaromatic ring which contains 1 or 2 =N- atoms, and wherein in heteroaromatic rings with one or more NH group each of them is replaced by NR^N, and each heteroaryl group is optionally substituted with 1 or 2 substituents independently selected from F, Cl, -CH₃, -CN, and -O-CH₃;

R⁶ is selected from the group consisting of F, -CH₃, CN, and -OCH₃;

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

m is 1 or 2; and the pharmaceutically acceptable salts thereof.

Preferred are those compounds of formula (I.2), wherein



R³ is selected from the group consisting of C₁₋₄-alkyl, C₃₋₆-cycloalkyl-, C₁₋₄-alkyl-O-, and C₃₋₆-cycloalkyl-O-,

wherein each alkyl and cycloalkyl group and each alkyl and cycloalkyl sub-group within the groups mentioned is substituted with 1 to 3 groups independently selected from R^5 and optionally substituted with 1 to 3 F atoms;

or selected from

- 5 C_3 -alkyl- $S(=O)_2$ - substituted with 1 HO- or H_3C-O - group;

$H_3C-C(=O)-$, heterocyclyl- $C(=O)-$, $H_2N-C(=O)-$, tetrahydropyran-4-yl- $NH-C(=O)-$, C_{1-3} -alkyl- $NR^N-C(=O)-$, C_{1-4} -alkyl- $C(=O)NR^N-$, C_{3-6} -cycloalkyl- $C(=O)NR^N-$, heterocyclyl- $C(=O)NR^N-$, C_{1-4} -alkyl- $S(=O)_2NR^N-$, heterocyclyl-O-, phenyl-O-, heteroaryl-O-, heterocyclyl- $S(=O)_2-$, $H_2N-S(=O)_2-$, heterocyclyl, phenyl and heteroaryl,

- 10 wherein each alkyl, cycloalkyl, and heterocyclyl group or sub-group within the groups mentioned is optionally substituted with 1 or 2 groups independently selected from R^5 and optionally substituted with 1 to 3 F atoms; and

wherein each phenyl and heteroaryl group is optionally substituted with 1 to 3 substituents independently selected from R^6 ;

- 15 wherein heterocyclyl is selected from

a cyclobutyl group wherein 1 CH_2 group is replaced by -NH- or -O-,

a saturated or mono-unsaturated C_{5-7} -cycloalkyl group wherein 1 CH_2 group is replaced by - $C(=O)-$, -NH-, -O- or - $S(=O)_2-$ and/or 1 CH group by N;

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

wherein heteroaryl is selected from

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

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

wherein in heteroaryl and heterocyclyl rings with one or more NH groups each of them is replaced by NR^N or NR^5 ;

- 30 with the proviso that R^3 in total cannot be C_{1-4} -alkyl-, C_{1-4} -alkyl-O- C_{1-4} -alkyl, HO- C_{1-4} -alkyl, and C_{1-4} -alkyl-O-;

R^5 is selected from the group consisting of C_{1-4} -alkyl-, -CN, C_{3-6} -cycloalkyl-, heterocyclyl- $C(=O)-$, $H_2N-C(=O)-$, C_{1-4} -alkyl- $NR^N-C(=O)-$, -NHC(=O)-O- $C(CH_3)_3$, C_{1-4} -

alkyl-NR^N-, C₁₋₄-alkyl-C(=O)NR^N-, C₁₋₄-alkyl-S(=O)₂NR^N-, -OH, C₁₋₄-alkyl-O-, C₁₋₄-alkyl-O-C₁₋₄-alkyl-O-, C₃₋₆-cycloalkyl-O-, heterocyclyl-O-, C₁₋₄-alkyl-S(=O)-, C₁₋₄-alkyl-S(=O)₂-, heterocyclyl, phenyl and heteroaryl,

wherein any alkyl, cycloalkyl, and heterocyclyl group or sub-group within the groups

5 mentioned is optionally substituted with 1 or more F atoms and optionally substituted with 1 or 2 groups independently selected from H₃C-, HO-, H₃C-O- and -CN,

wherein heterocyclyl is selected from

a cyclobutyl group wherein 1 CH₂ group is replaced by -NR^N- or -O-,

10 a saturated or partially unsaturated C₅₋₆-cycloalkyl group wherein 1 CH₂ group is replaced by -C(=O)-, -NR^N-, -O-, -S(=O)- or -S(=O)₂- and/or 1 CH group by N;

a saturated or partially unsaturated C₅₋₆-cycloalkyl group wherein 1 CH₂ group is replaced by -NR^N- or -O-, a second CH₂ group is replaced by -NR^N-, -C(=O)-, -S(=O)- or -S(=O)₂- and/or 1 CH group is replaced by N; and

15 a saturated or partially unsaturated C₅₋₆-cycloalkyl group wherein 2 CH₂ groups are replaced by -NR^N- or 1 CH₂ group by -NR^N- and the other by -O-, and a third CH₂ group is replaced by -C(=O)-, -S(=O)- or -S(=O)₂- and/or 1 CH group by N;

and wherein heteroaryl is selected from

20 a pyridin-2-onyl ring, a 5-membered heteroaromatic ring which contains 1 or 2 heteroatoms independently of each other selected from =N-, -NH-, -O-, and -S-, and a 6-membered heteroaromatic ring which contains 1 or 2 =N- atoms, and wherein in heteroaromatic rings with one ore more NH groups each of them is replaced by NR^N, and each heteroaryl group is optionally substituted with 1 or 2 substituents independently selected from F, Cl, -CH₃, -CN, and -O-CH₃;

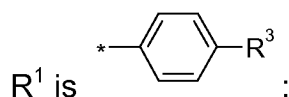
25

R⁶ is selected from the group consisting of F, Cl, C₁₋₃-alkyl, cyclopropyl, HO-C₁₋₄-alkyl-, -CN, -CF₃, -OCH₃, -OCF₃, -S(=O)CH₃, and -S(=O)₂-CH₃;

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

and the pharmaceutically acceptable salts thereof.

Preferred are those compounds of formula (I.3), wherein



R³ is selected from the group consisting of C₁₋₄-alkyl, C₃₋₆-cycloalkyl-, C₁₋₄-alkyl-O-, and C₃₋₆-cycloalkyl-O-,

- 5 wherein each alkyl and cycloalkyl group and each alkyl and cycloalkyl sub-group within the groups mentioned is substituted with 1 to 3 groups independently selected from R⁵ and optionally substituted with 1 to 3 F atoms;

or selected from

C₃-alkyl-S(=O)₂- substituted with 1 HO- or H₃C-O- group;

- 10 H₃C-C(=O)-, heterocyclyl-C(=O)-, H₂N-C(=O)-, tetrahydropyran-4-yl-NH-C(=O)-, C₁₋₃-alkyl-NR^N-C(=O)-, C₁₋₄-alkyl-C(=O)NR^N-, C₃₋₆-cycloalkyl-C(=O)NR^N-, heterocyclyl-C(=O)NR^N-, C₁₋₄-alkyl-S(=O)₂NR^N-, heterocyclyl-O-, phenyl-O-, heteroaryl-O-, heterocyclyl-S(=O)₂-, H₂N-S(=O)₂-, heterocyclyl, phenyl and heteroaryl,

wherein each alkyl, cycloalkyl, and heterocyclyl group or sub-group within the groups

- 15 mentioned is optionally substituted with 1 or 2 groups independently selected from R⁵ and optionally substituted with 1 to 3 F atoms; and

wherein each phenyl and heteroaryl group is optionally substituted with 1 to 3 substituents independently selected from R⁶;

wherein heterocyclyl is selected from

- 20 a cyclobutyl group wherein 1 CH₂ group is replaced by -NH- or -O-,
a saturated or mono-unsaturated C₅₋₇-cycloalkyl group wherein 1 CH₂ group is replaced by -C(=O)-, -NH-, -O- or -S(=O)₂- and/or 1 CH group by N;
a saturated or mono-unsaturated C₅₋₆-cycloalkyl group wherein 1 CH₂ group is replaced by -NH- or -O-, a second CH₂ group is replaced by -C(=O)- or -S(=O)₂-
25 and/or 1 CH group is replaced by N; and

wherein heteroaryl is selected from

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

wherein in heteroaryl and heterocyclyl rings with one or more NH groups each of them is replaced by NR^N or NR⁵;

with the proviso that R³ in total cannot be C₁₋₄-alkyl-, C₁₋₄-alkyl-O-C₁₋₄-alkyl, HO-C₁₋₄-alkyl, and C₁₋₄-alkyl-O-;

- 5 R⁵ is selected from the group consisting of C₁₋₄-alkyl-, -CN, C₃₋₆-cycloalkyl-, heterocyclyl-C(=O)-, H₂N-C(=O)-, C₁₋₄-alkyl-NR^N-C(=O)-, -NHC(=O)-O-C(CH₃)₃, C₁₋₄-alkyl-NR^N-, C₁₋₄-alkyl-C(=O)NR^N-, C₁₋₄-alkyl-S(=O)₂NR^N-, -OH, C₁₋₄-alkyl-O-, C₁₋₄-alkyl-O-C₁₋₄-alkyl-O-, C₃₋₆-cycloalkyl-O-, heterocyclyl-O-, C₁₋₄-alkyl-S(=O)-, C₁₋₄-alkyl-S(=O)₂-, heterocyclyl, phenyl and heteroaryl,
- 10 wherein any alkyl, cycloalkyl, and heterocyclyl group or sub-group within the groups mentioned is optionally substituted with 1 or more F atoms and optionally substituted with 1 or 2 groups independently selected from H₃C-, HO-, H₃C-O- and -CN,

wherein heterocyclyl is selected from

- 15 a cyclobutyl group wherein 1 CH₂ group is replaced by -NR^N- or -O-,
 a saturated or partially unsaturated C₅₋₆-cycloalkyl group wherein 1 CH₂ group is replaced by -C(=O)-, -NR^N-, -O-, -S(=O)- or -S(=O)₂- and/or 1 CH group by N;
 a saturated or partially unsaturated C₅₋₆-cycloalkyl group wherein 1 CH₂ group is replaced by -NR^N- or -O-, a second CH₂ group is replaced by -NR^N-, -C(=O)-,
 20 -S(=O)- or -S(=O)₂- and/or 1 CH group is replaced by N; and
 a saturated or partially unsaturated C₅₋₆-cycloalkyl group wherein 2 CH₂ groups are replaced by -NR^N- or 1 CH₂ group by -NR^N- and the other by -O-, and a third CH₂ group is replaced by -C(=O)-, -S(=O)- or -S(=O)₂- and/or 1 CH group by N;

and wherein heteroaryl is selected from

- 25 a pyridin-2-onyl ring, a 5-membered heteroaromatic ring which contains 1 or 2 heteroatoms independently of each other selected from =N-, -NH-, -O-, and -S-, and a 6-membered heteroaromatic ring which contains 1 or 2 =N- atoms, and wherein in heteroaromatic rings with one or more NH groups each of them is replaced by NR^N, and each heteroaryl group is optionally substituted with 1 or 2
 30 substituents independently selected from F, Cl, -CH₃, -CN, and -O-CH₃;

R⁶ is selected from the group consisting of F, Cl, C₁₋₃-alkyl, cyclopropyl, HO-C₁₋₄-alkyl-, -CN, -CF₃, -OCH₃, -OCF₃, -S(=O)CH₃, and -S(=O)₂-CH₃;

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

and the pharmaceutically acceptable salts thereof.

5

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

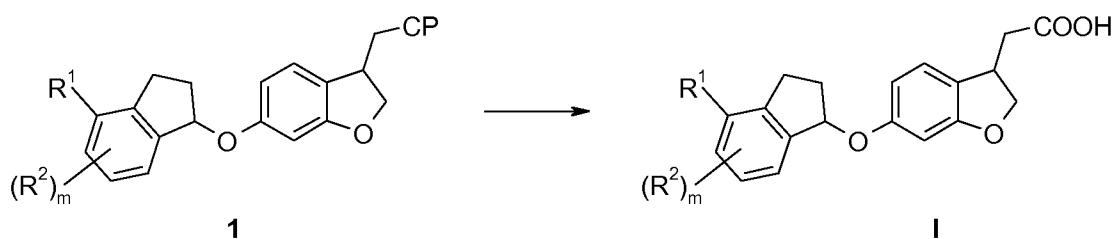
10 The compounds according to the invention and their intermediates may be obtained using methods of synthesis which are known to the one skilled in the art and described in the literature of organic synthesis. Preferably the compounds are obtained analogously to the methods of preparation explained more fully hereinafter, in particular as described in the experimental section. In some cases the sequence
15 adopted in carrying out the reaction schemes may be varied. Variants of these reactions that are known to the skilled man but are not described in detail here may also be used. The general processes for preparing the compounds according to the invention will become apparent to the skilled man on studying the schemes that follow. Starting compounds are commercially available or may be prepared by
20 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.

25

The compounds of the invention I are preferably accessed from a precursor **1** that bears the carboxylic acid function in a protected or masked form as sketched in Scheme 1; R^1 , R^2 , and m have the meanings as defined hereinbefore and hereinafter. Suited precursor groups for the carboxylic acid may be, e.g., a carboxylic
30 ester, a carboxylic amide, cyano, an olefin, oxazole, or a thiazole. All these groups have been transformed into the carboxylic acid function by different means which are described in the organic chemistry literature and are known to the one skilled in the art. The preferred precursor group is a C_{1-4} -alkyl or benzyl carboxylate, each of which may be additionally mono- or polysubstituted with fluorine, methyl, and/or methoxy.

These ester groups may be hydrolysed with an acid, such as hydrochloric acid or sulfuric acid, or an alkali metal hydroxide, such as lithium hydroxide, sodium hydroxide, or potassium hydroxide, to yield the carboxylic acid function; the hydrolysis is preferably conducted in aqueous solvents, such as water and tetrahydrofuran, 1,4-dioxane, alcohol, e.g. methanol, ethanol, and isopropanol, or dimethyl sulfoxide, at 0 to 120 °C. A tert-butyl ester is preferably cleaved under acidic conditions, e.g. trifluoroacetic acid or hydrochloric acid, in a solvent such as dichloromethane, 1,4-dioxane, isopropanol, or ethyl acetate. A benzyl ester is advantageously cleaved using hydrogen in the presence of a transition metal, preferably palladium on carbon. Benzyl esters bearing electron donating groups, such as methoxy groups, on the aromatic ring may also be removed under oxidative conditions; ceric ammonium nitrate (CAN) or 2,3-dichloro-5,6-dicyanoquinone (DDQ) are two commonly used reagents for this approach.

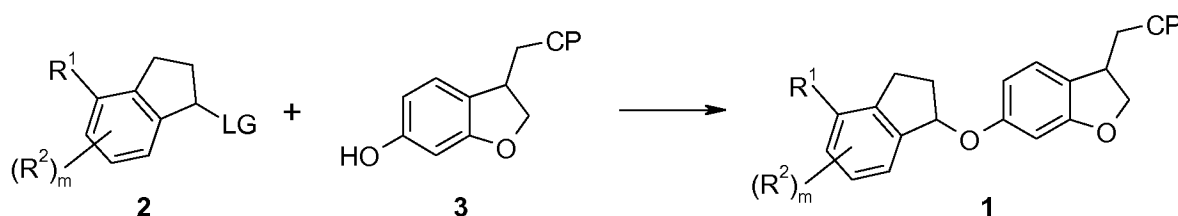
Scheme 1: Liberation of carboxylic acid function to access compounds of the invention



CP = masked or protected form of COOH, e.g., CO₂C₁₋₄-alkyl, CO₂CH₂aryl, CON(C₁₋₄-alkyl)₂, CN, CH=CH₂, thiazol-2-yl, oxazol-2-yl

Compound **1**, in turn, may be obtained from indane **2**, which bears a leaving group, and phenol **3**, which is decorated with the carboxylic acid precursor group (Scheme 2); R¹, R², and m in Scheme 2 have the meanings as defined hereinbefore and hereinafter. The leaving group LG in **2** is replaced with the O in **3** via a nucleophilic substitution; suited LG may be Cl, Br, I, methylsulfonyloxy, phenylsulfonyloxy, p-tolylsulfonyloxy, and trifluoromethylsulfonyloxy. The reaction is usually carried out in the presence of a base, such as triethylamine, ethyldiisopropylamine, 1,8-diazabicyclo[5.4.0]undecene, carbonates, e.g. Li₂CO₃, Na₂CO₃, K₂CO₃, and Cs₂CO₃, hydroxides, e.g. LiOH, NaOH, and KOH, alcoholates, e.g. NaOMe, NaOEt, and KOtBu, hydrides, e.g. NaH and KH, amides, e.g. NaNH₂, KN(SiMe₃)₂, and LiN(iPr)₂,

and oxides, e.g. CaO and Ag₂O. Additives, such as silver salts, e.g. AgNO₃, AgOSO₂CF₃, and Ag₂CO₃, crown ethers, e.g. 12-crown-4, 15-crown-5, and 18-crown-6, hexamethylphosphorus triamide (HMPT), and 1,3-dimethyl-3,4,5,6-dihydro-2-pyrimidinone (DMPU), may be beneficial or even essential for the reaction to proceed. Preferred solvents are dimethylsulfoxide, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidinone, acetonitrile, acetone, 1,4-dioxane, tetrahydrofuran, alcohol, e.g. ethanol or isopropanol, water, or mixtures thereof, while not all of the solvents can be combined with each additive and base mentioned above. Suited reaction temperatures range from -20 to 140 °C.

Scheme 2: Preparation of precursor **1**

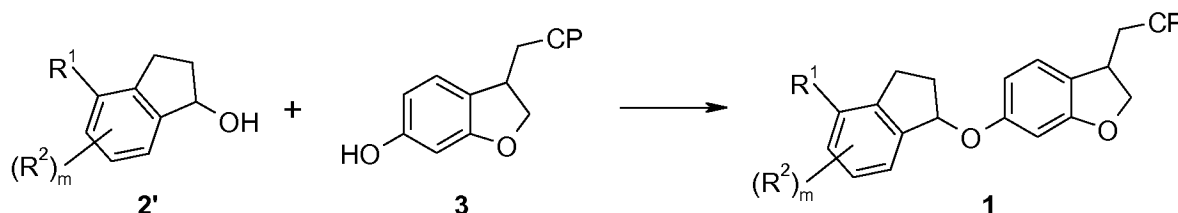
LG = leaving group, e.g., Cl, Br, I, OSO₂Me, OSO₂Ph, OSO₂Tol, OSO₂CF₃

CP = masked or protected form of COOH, e.g., CO₂C₁₋₄-alkyl, CO₂CH₂aryl,

CON(C₁₋₄-alkyl)₂, CN, CH=CH₂, thiazol-2-yl, oxazol-2-yl

An alternative reaction to combine building blocks **2** and **3** is the Mitsunobu reaction or variations thereof (Scheme 3); R^1 , R^2 , and m in Scheme 3 have the meanings 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: Mitsunobu reaction to access precursor **1**

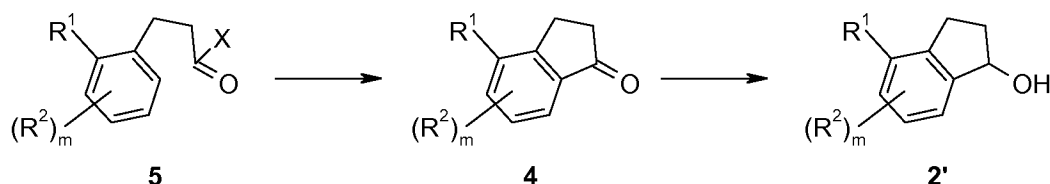


CP = masked or protected form of COOH, e.g., CO₂C₁₋₄-alkyl, CO₂CH₂aryl, CON(C₁₋₄-alkyl)₂, CN, CH=CH₂, thiazol-2-yl, oxazol-2-yl

Intermediate **2'** is conveniently obtained from indanone **4** which, in turn, may be prepared from phenylpropionic acid derivative **5** (Scheme 4); R¹, R², and m in Scheme 4 have the meanings as defined hereinbefore and hereinafter. For the intramolecular acylation (Friedel-Crafts acylation), **5**→**4**, 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.

The subsequent reduction of the keto group in Scheme 4 is a standard transformation in organic synthesis, which may be accomplished with lithium borohydride, sodium borohydride, lithium aluminum hydride, or diisobutylaluminum hydride. While sodium borohydride is employed in aqueous or alcoholic solution at 0 to 60 °C, the other reducing agents mentioned are preferably used in inert solvents, such as tetrahydrofuran, diethyl ether, dichloromethane, and toluene, at -80 to 60 °C. The reduction of the keto group may also be conducted in a stereoselective fashion providing the alcohol in enantiomerically enriched or pure form. Suited chiral reducing agents are boranes combined with an enantiomerically pure [1,3,2]oxazaborol

(Corey-Bakshi-Shibata reaction or Corey-Itsuno reaction) or formic acid, formates, hydrogen, or silanes in the presence of an enantiomerically pure transition metal catalyst. Typical reaction conditions for the former approach are borane (complexed with, e.g., dimethyl sulfide) and (*R*)- or (*S*)-3,3-diphenyl-1-methyltetrahydro-1*H*,3*H*-pyrrolo[1,2-*c*][1,3,2]oxazaborol in, e.g., dichloromethane, toluene, methanol, tetrahydrofuran, or mixtures thereof, at 0 to 60 °C. Using a chiral transition metal catalyst, such as a ruthenium complex, e.g. chloro{[(1*S*,2*S*)-(-)-2-amino-1,2-diphenylethyl](4-toluenesulfonyl)-amido}-(mesitylene)ruthenium(II), may deliver the hydroxy compound 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.

Scheme 4: Preparation of intermediate **2'**

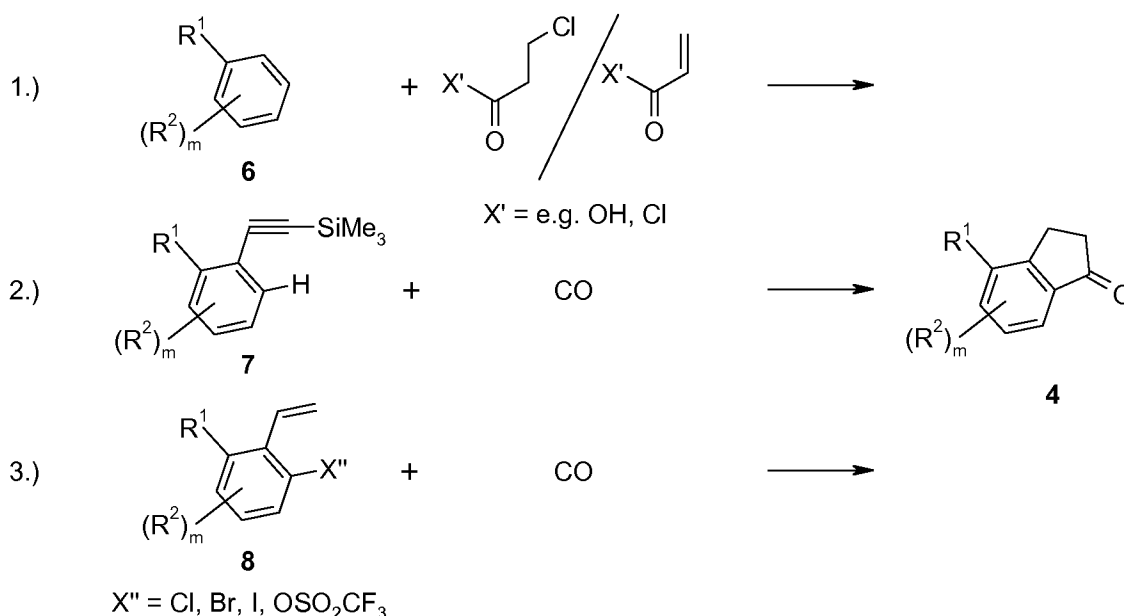
X = e.g. OH, Cl

Alternatively, indanone **4** can be synthesized as described in Scheme 5; R^1 , R^2 , and m have the meanings as defined hereinbefore and hereinafter. Starting with benzene **6** and 3-halo-propionic acid or a derivative thereof or acrylic acid or a derivative thereof the required indanone **4** may be obtained via the combination of a Friedel-Crafts alkylation and acylation reaction in one pot or two separate reactions (eq. 1.)). These reactions are catalyzed by a Lewis acid, such as triflic acid, sulfuric acid, phosphoric acid, AlCl_3 , ZnCl_2 , and phosphorus pentoxide, and preferably conducted without additional solvent in an excess of the Lewis acid or in dichloromethane, 1,2-dichloroethane, cyclohexane, or carbon disulfide, at 0 to 140 °C. A preferred combination comprises compound **6**, 3-chloro-propionyl chloride, and AlCl_3 in dichloromethane or 1,2-dichloroethane at 20 to 80 °C.

Starting with ethynylbenzene **7** indanone **4** is accessible by a transition metal catalyzed reaction with carbon monoxide (eq. 2.)). Rhodium is a preferred catalyst basis which is combined with a phosphine, e.g. triphenylphosphine, and a base, e.g. triethylamine, and used in a solvent, preferably tetrahydrofuran, at high carbon monoxide pressure, preferably 50 to 150 bar, at 150 to 200 °C (see e.g. *J. Org. Chem.* **1993**, 58, 5386-92).

Combination of 2-halo or pseudo-halo substituted styrene **8** and carbon monoxide in the presence of a transition metal also allows the preparation of indanone **4** (eq. 3.)). Palladium catalysts are preferred and used with carbon monoxide or molybdenum hexacarbonyl as carbon monoxide source. Preferred solvents are N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidone, and 1,4-dioxane which are preferably employed at 20 to 150 °C by conventional heating or microwave irradiation. Pyridine and tetrabutylammonium chloride are preferred additives for this transformation (see e.g. *J. Am. Chem. Soc.* **2003**, 125, 4804-7 and *J. Org. Chem.* **2005**, 70, 346-9).

Scheme 5: Preparation of intermediate **4**



Common synthetic routes to building block **3** are summarized in Scheme 6. 2-Iodo or bromo ether **9** can be transformed into indane **3** via addition of an *in situ* generated carbon anion or radical to the double bond and subsequent trapping of the cyclic anion by a proton and the cyclic radical by a hydride source (eq. 1.)). nBuLi, iPrMgCl, iPrMgCl*LiCl, Mg, Mg*LiCl, Zn, and Zn*LiCl are preferred reagents to convert the C-I or C-Br bond into a C-M bond (M = Li, MgI, ZnI etc.) with sufficient nucleophilicity to add to the double bond. The reactions with lithium and magnesium reagents are preferably conducted in hexanes, tetrahydrofuran, diethyl ether, 1,2-dimethoxyethane, toluene, or mixtures thereof, at -100 to 60 °C. Zn is preferably used in tetrahydrofuran, dimethyl sulfoxide, N-methylpyrrolidinone, or mixtures

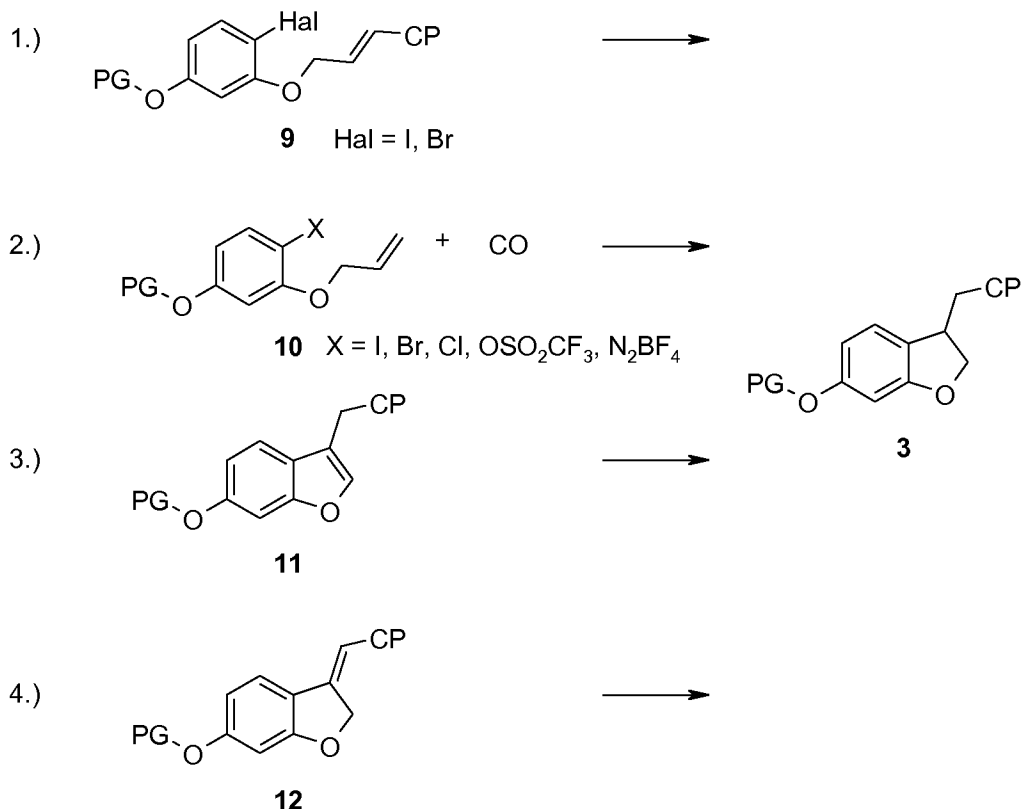
thereof, at 0 to 100 °C. Frequently employed reaction conditions for the radical pathway are, e.g., tributyltin hydride, azobisisobutyronitrile, in benzene, at 60 to 100 °C (see e.g. *J. Org. Chem.* **1987**, 52, 4072-8); and NaH₃B(CN) in N,N-dimethylformamide under UV irradiation at 20 to 120 °C (see e.g. *Synlett* **2005**, 2248-50).

Combination of allyl ether **10** with carbon monoxide is another possibility to obtain indane **3** (equation 2.)). The reaction is preferably conducted with a palladium catalyst in the presence of carbon monoxide or molybdenum hexacarbonyl as carbon monoxide source (see e.g. *Tetrahedron Lett.* **2010**, 51, 2102-5).

Starting from benzofuran **11** or dihydrobenzofuran **12** indane **3** is yielded after reduction of the double bond. Hydrogen is the preferred reducing agent which is mainly employed in combination with a transition metal catalyst, such as palladium on carbon, Raney nickel, and PtO₂. N,N-dimethylformamide, tetrahydrofuran, ethyl acetate, alcohol, e.g. methanol and ethanol, acetic acid, water, or mixtures thereof are preferably used as solvent, at hydrogen pressures of 1 to 100 bar, and temperatures of 20 to 120 °C. This reaction may also be carried out stereoselectively providing compound **3** in enantiomerically enriched or pure form.

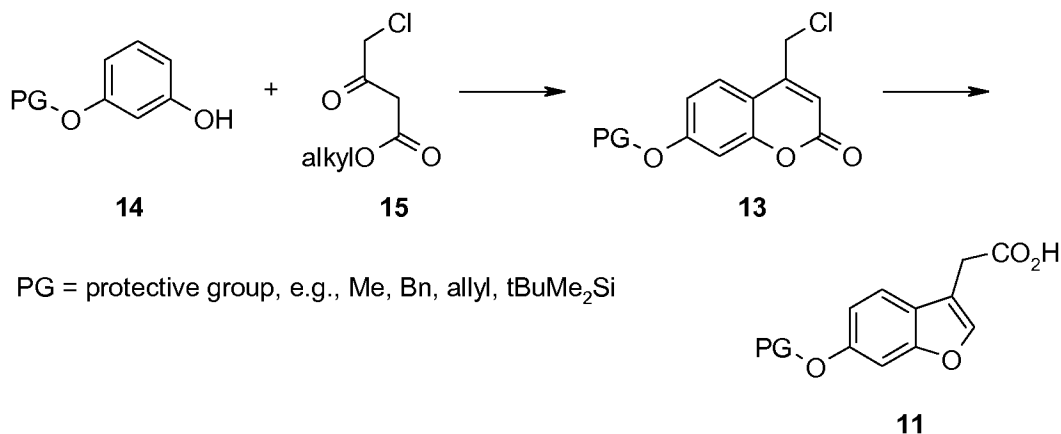
Scheme 6: Preparation of building block **3**

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PG = protective group, e.g., Me, Bn, allyl, tBuMe₂SiCP = masked or protected form of COOH, e.g., CO₂C₁₋₄-alkyl, CO₂CH₂aryl,
CON(C₁₋₄-alkyl)₂, CN, CH=CH₂, thiazol-2-yl, oxazol-2-yl

The syntheses of the starting compounds in Scheme 6 comprise standard procedures used in organic synthesis. Intermediate **11** can, for example, be prepared as described in Scheme 7. Compound **11** may thus be obtained from compound **13** which, in turn, may be assembled from phenol **14** and ester **15**. The latter transformation may be achieved in the presence of a Lewis acid, e.g. sulfuric acid, ZrCl₄, InCl₃, methanesulfonic acid, p-toluenesulfonic acid, HI, or amberlyst, in toluene, dichloromethane, acetic acid, ethanol, water, or without a solvent in an excess of the Lewis acid, at 0 to 120 °C. Transformation of compound **13** into intermediate **11** is preferably accomplished under basic conditions with sodium hydroxide in an aqueous solution at 0 to 100 °C.

Scheme 7: Preparation of starting compound **11**



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 into their enantiomers.

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

The racemates are preferably resolved by column chromatography on chiral phases or by crystallization from an optically active solvent or by reacting with an optically active substance which forms salts or derivatives such as esters or amides with the

racemic compound. Salts may be formed with enantiomerically pure acids for basic compounds and with enantiomerically pure bases for acidic compounds. Diastereomeric derivatives are formed with enantiomerically pure auxiliary compounds, e.g. acids, their activated derivatives, or alcohols. Separation of the
5 diastereomeric mixture of salts or derivatives thus obtained may be achieved by taking advantage of their different physico-chemical properties, e.g. differences in solubility; the free antipodes may be released from the pure diastereomeric salts or derivatives by the action of suitable agents. Optically active acids commonly used for such a purpose as well as optically active alcohols applicable as auxiliary residues
10 are known to those skilled in the art.

As mentioned above, the compounds of formula I may be converted into salts, particularly for pharmaceutical use into the pharmaceutically acceptable salts. As used herein, "pharmaceutically acceptable salts" refer to derivatives of the disclosed
15 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
20 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
25 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)
30 according to the present invention including their tautomers, stereoisomers and mixtures thereof and the salts thereof, in particular the pharmaceutically acceptable salts thereof, and the solvates and hydrates of such compounds, including the solvates and hydrates of such tautomers, stereoisomers and salts thereof.

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

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

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

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

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

The term "substituted" as used herein, means that any one or more hydrogens on the designated atom, radical or moiety is replaced with a selection from the indicated

group, provided that the atom's normal valence is not exceeded, and that the substitution results in an acceptably stable compound.

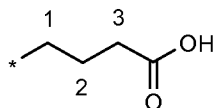
In the groups, radicals, or moieties defined below, the number of carbon atoms is often specified preceding the group, for example, C₁₋₆-alkyl means an alkyl group or radical having 1 to 6 carbon atoms. In general, for groups comprising two or more subgroups, the last named subgroup is the radical attachment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

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

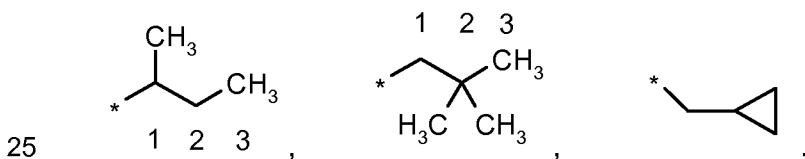
An asterisk may be used in sub-formulas to indicate the bond which is connected to the core molecule as defined.

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

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



wherein the carboxy group is attached to the third carbon atom of the propyl group. The terms "1-methylpropyl-", "2,2-dimethylpropyl-" or "cyclopropylmethyl-" group represent the following groups:



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

In a definition of a group the term "wherein each X, Y and Z group is optionally

substituted with" and the like denotes that each group X, each group Y and each group Z either each as a separate group or each as part of a composed group may be substituted as defined. For example a definition "R^{ex} denotes H, 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 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 enantiomers, mixtures of diastereomers, or mixtures of any of the foregoing forms where such isomers and enantiomers exist, as well as salts, including pharmaceutically acceptable salts thereof and solvates thereof such as for instance hydrates including solvates of the free compounds or solvates of a salt of the compound.

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

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

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

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

The term "C_{1-n}-alkyl", wherein n is an integer from 1 to n, either alone or in combination with another radical denotes an acyclic, saturated, branched or linear hydrocarbon radical with 1 to n C atoms. For example the term 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-, H₃C-CH₂-CH₂-CH(CH₃)-, H₃C-CH₂-CH(CH₃)-CH₂-, H₃C-CH(CH₃)-CH₂-CH₂-, H₃C-CH₂-C(CH₃)₂-, H₃C-C(CH₃)₂-CH₂-, H₃C-CH(CH₃)-CH(CH₃)- and H₃C-CH₂-CH(CH₂CH₃)-.

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 C₁₋₄-alkylene includes -(CH₂)-, -(CH₂-CH₂)-, -(CH(CH₃))-, -(CH₂-CH₂-CH₂)-, -(C(CH₃)₂)-, -(CH(CH₂CH₃))-, -(CH(CH₃)-CH₂)-, -(CH₂-CH(CH₃))-, -(CH₂-CH₂-CH₂-CH₂)-, -(CH₂-CH₂-CH(CH₃))-, -(CH(CH₃)-CH₂-CH₂)-, -(CH₂-CH(CH₃)-CH₂)-, -(CH₂-C(CH₃)₂)-, -(C(CH₃)₂-CH₂)-, -(CH(CH₃)-CH(CH₃))-, -(CH₂-CH(CH₂CH₃))-, -(CH(CH₂CH₃)-CH₂)-, -(CH(CH₂CH₂CH₃))-, -(CHCH(CH₃)₂)- and -C(CH₃)(CH₂CH₃)-.

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 C₂₋₃-alkenyl includes -CH=CH₂, -CH=CH-CH₃, -CH₂-CH=CH₂.

The term "C_{2-n}-alkenylene" is used for a group as defined in the definition for "C_{1-n}-alkylene" with at least two carbon atoms, if at least two of those carbon atoms of said group are bonded to each other by a double bond. For example the term C₂₋₃-alkenylene includes -CH=CH-, -CH=CH-CH₂-, -CH₂-CH=CH-.

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 C₂₋₃-alkynyl includes -C≡CH, -C≡C-CH₃, -CH₂-C≡CH.

The term " C_{2-n} -alkynylene" is used for a group as defined in the definition for " C_{1-n} -alkylene" with at least two carbon atoms, if at least two of those carbon atoms of said group are bonded to each other by a triple bond. For example the term C_{2-3} -alkynylene includes $-C\equiv C-$, $-C\equiv C-CH_2-$, $-CH_2-C\equiv C-$.

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 the term C_{3-10} -carbocyclyl includes C_{3-10} -cylcoalkyl, C_{3-10} -cycloalkenyl, octahydropentalenyl, octahydroindenyl, decahydronaphthyl, indanyl, tetrahydronaphthyl. Most preferably the term C_{3-n} -carbocyclyl denotes C_{3-n} -cylcoalkyl, in particular C_{3-7} -cycloalkyl.

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

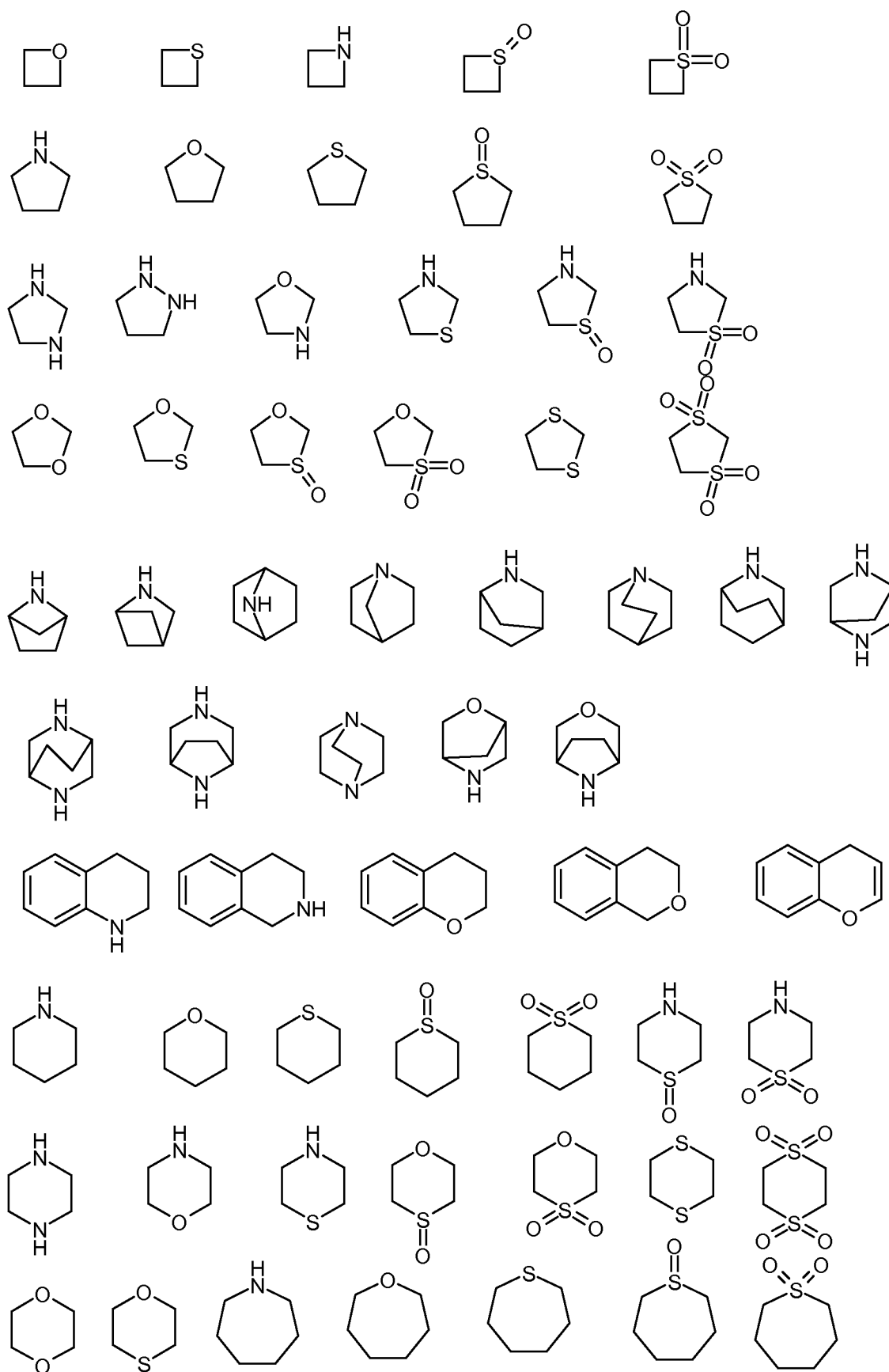
The term " C_{3-n} -cycloalkenyl", wherein n is an integer 3 to n, either alone or in combination with another radical, denotes a cyclic, unsaturated but nonaromatic, unbranched hydrocarbon radical with 3 to n C atoms, at least two of which are bonded to each other by a double bond. For example the term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

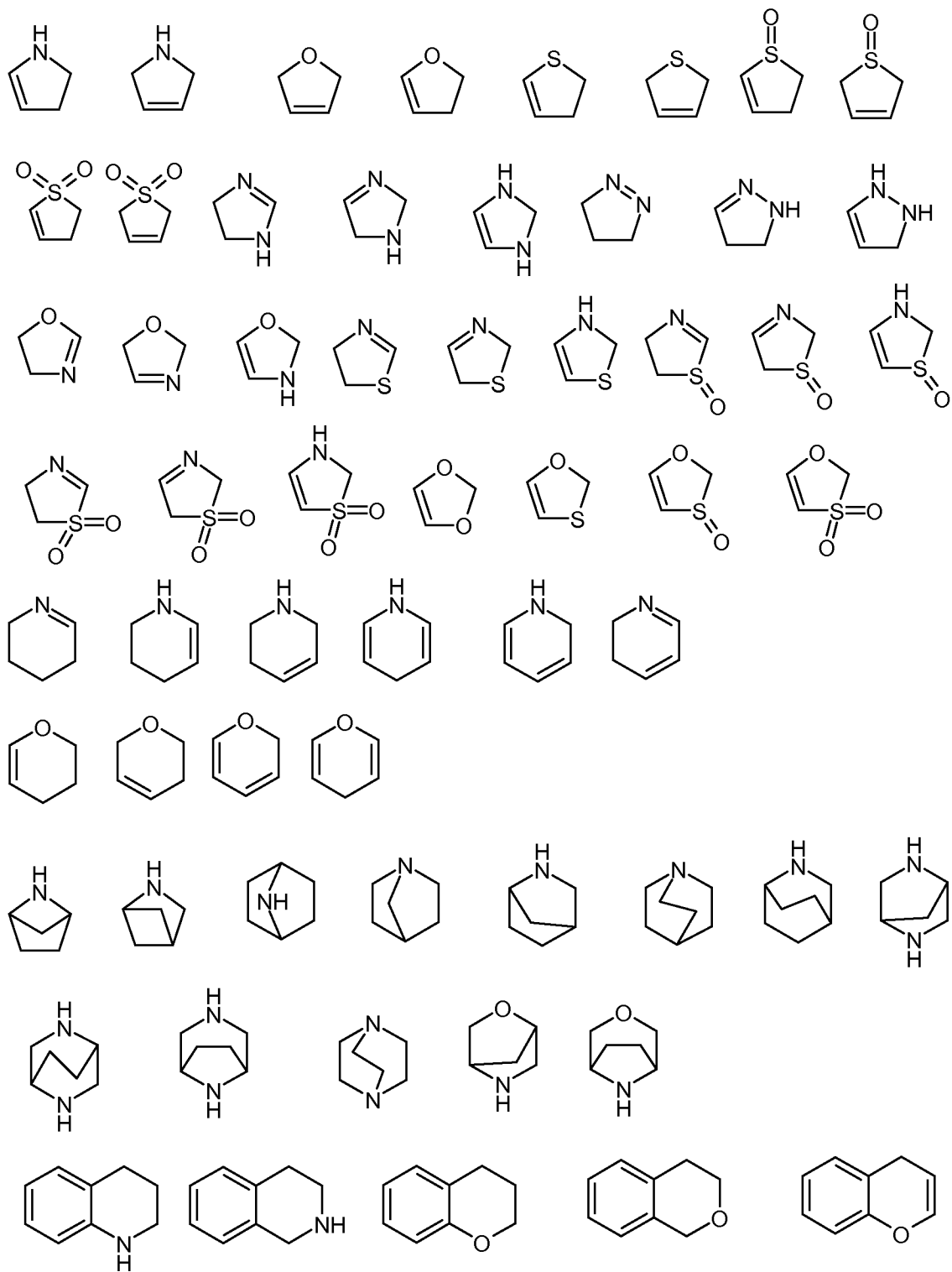
The term "aryl" as used herein, either alone or in combination with another radical, unless specified otherwise, denotes a carbocyclic aromatic monocyclic group

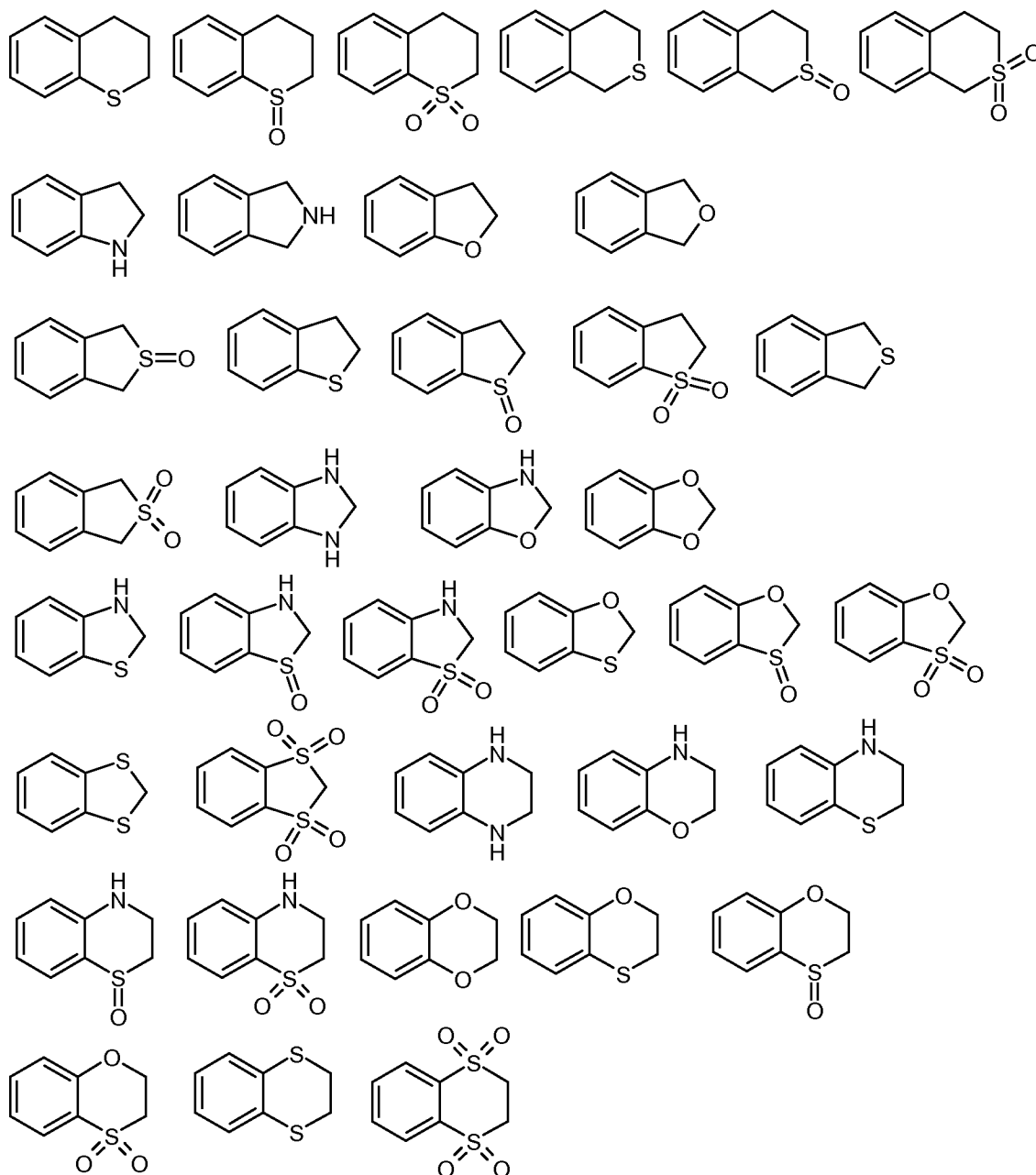
containing 6 carbon atoms which may be further fused to a second 5- or 6-membered carbocyclic group which may be aromatic, saturated or unsaturated. Aryl includes, but is not limited to, phenyl, indanyl, indenyl, naphthyl, anthracenyl, phenanthrenyl, tetrahydronaphthyl and dihydronaphthyl. More preferably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

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

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



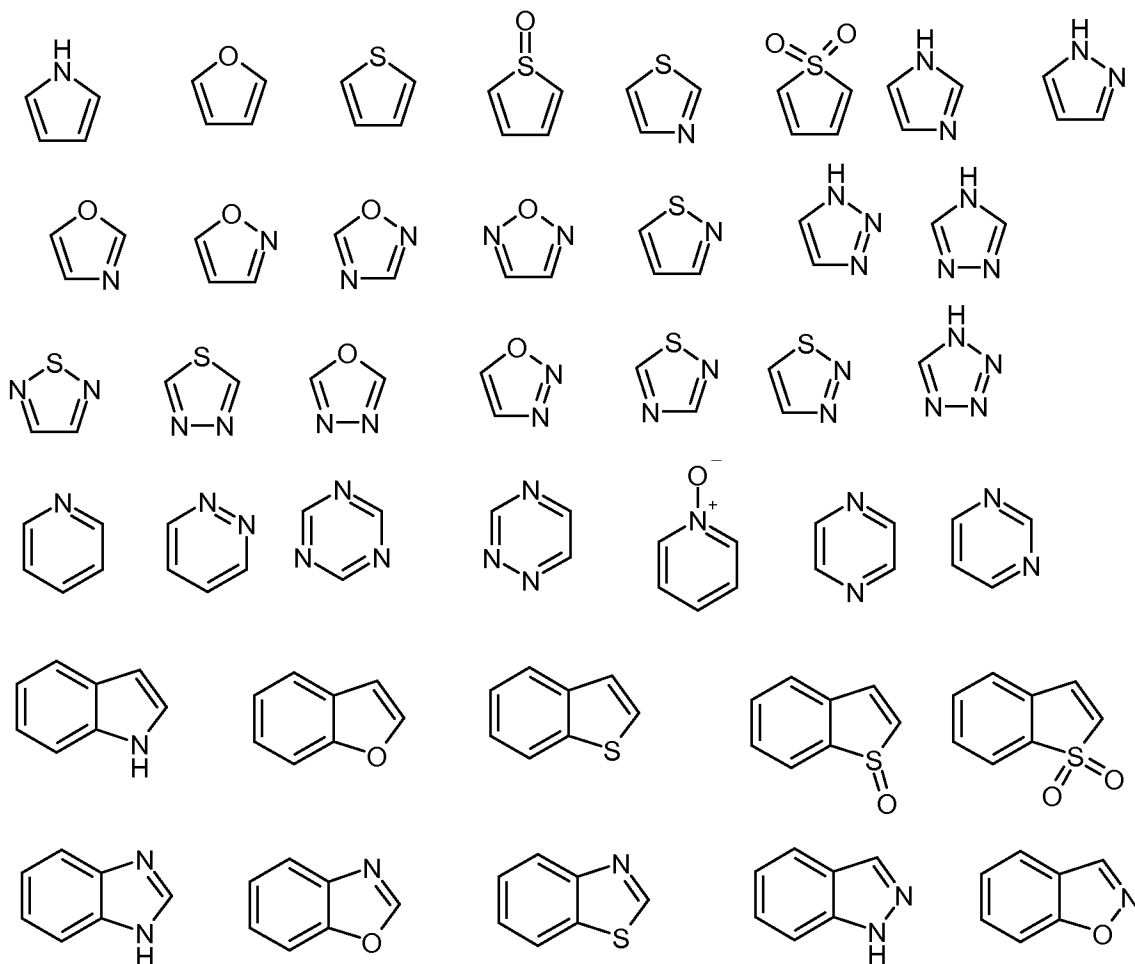


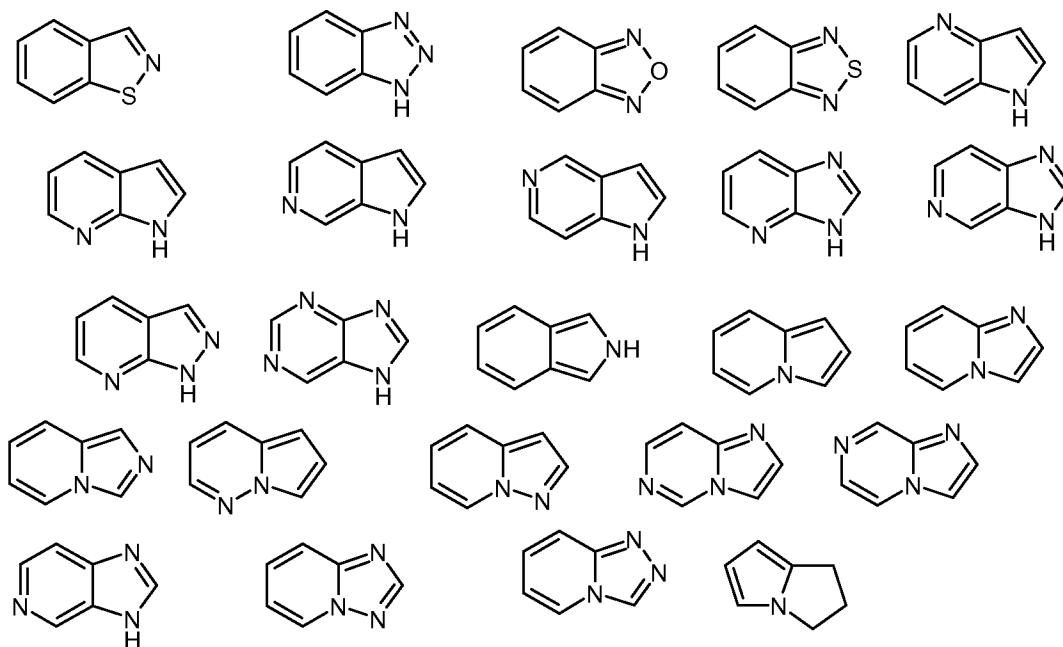


The term "heteroaryl", unless specified otherwise, means a mono- or polycyclic, preferably mono- or bicyclic-ring system containing one or more heteroatoms selected from N, O or S(O)_r, with r=0, 1 or 2 wherein at least one of the heteroatoms is part of an aromatic ring, and wherein said ring system may have a carbonyl group.

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

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





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

5

Pharmacological Activity

The activity of the compounds of the invention may be demonstrated using the following assays.

10 Assay I:

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 black clear-bottom collagen-coated 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 the culture medium by stimulation buffer (Hepes 10 mM, CaCl₂ 1 mM, MgCl₂ 0.5 mM, KCl 4.2 mM, NaCl 146 mM and glucose 5.5 mM, pH 7.4) without LiCl. Cells are stimulated for 1 hour at 37 °C, 10% CO₂ by addition of the compounds that are diluted in stimulation buffer containing LiCl yielding a final LiCl concentration of 50 mM. Assays are stopped by adding HTRF-conjugates (IP1-d2 and Anti-IP1 cryptate Tb) and lysis buffer, provided by the manufacturer. After an incubation time of 1 hour at room temperature plates are measured using an

20

EnVision™, Perkin Elmer. The obtained fluorescence ratios at 665/615 nm are then used to calculate the pEC₅₀ values using GraphPad Prism 5 (Graphpad Software Inc, USA) by interpolation using an IP₁ reference curve and subsequent sigmoidal curve fitting allowing for a variable hill slope.

5

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.

- 10 EC₅₀ values for compounds according to the invention determined in Assay I 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	211	2	64	3	568	4	52
5	52	6	38	7	17	8	30
9	7	10	85	11	51	12	4
13	5	14	68	15	6	16	5
17	17	18	11	19	912	20	279
21	92	22	684	23	19	24	22
25	6	26	15	27	50	28	68
29	9	30	4	31	9	32	2
33	18	34	17	35	9	36	5
37	16	38	63	39	12	40	5
41	5	42	12	43	4	44	4
45	3	46	9	47	8	48	17
49	10	50	3	51	35	52	17
53	9	54	6	55	11	56	7
57	17	58	19	59	12	60	11
61	57	62	52	63	26	64	9
65	58	66	36	67	35	68	1514
69	2917	70	36	71	20	72	23
73	81	74	43	75	9	76	211

77	15	78	6	79	5	80	17
81	17	82	51	83	25	84	118
85	15	86	26	87	27	88	355
89	23	90	117	91	26	92	51
93	11	94	38	62s	1223	62c	76
62d	8	98	34	190	8	193	2
197	3						

Assay II:

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 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. 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.

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.

EC₅₀ values for compounds according to the invention determined in Assay II 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]
48a	93	48b	19	48c	117	62a	8
62b	6	62e	13	62f	18	62g	11
62h	22	62i	10	62j	17	62k	9
62l	7	62m	8	62n	14	62o	10
62p	20	62q	7	62t	13	62u	25
62w	43	62aa	21	62ab	21	62ac	6
62ad	12	62ae	13	62af	6	62ag	43
62ah	13	62ai	14	62aj	27	62ak	14
62al	129	62am	5	62an	3	62ao	7
62ap	2	62aq	3	62ar	7	62as	23
62at	5	62au	17	62aw	6	62ax	6
62ay	19	62az	29	62ba	6	62bb	29
62bc	4	62be	7	62bf	5	62bg	4
62bh	6	62bi	13	62bj	8	62bk	9
62bl	21	62bm	22	62bn	23	62bo	79
62bp	22	62bq	37	62br	30	62bs	50
62bt	14	62bu	9	62bw	15	62bx	19
62by	5	62bz	8	62ca	10	62cb	8
62cc	17	62cd	31	62ce	29	62cf	4
62cg	12	62ch	7	62ci	8	62cj	5
62ck	6	62cl	4	62cm	8	62cn	17
62co	17	62cp	9	62cq	6	62cr	2
62cs	3	62ct	4	62cu	9	62cw	5
62cx	6	62cy	19	62cz	7	62da	18
62db	15	62dc	7	62dd	4	62de	5
62df	7	62dg	5	62dh	6	62di	12
62dj	11	62dk	13	62dl	5	62dm	4
62dn	5	62do	5	62dp	25	62dq	9
62dr	5	62ds	5	62dt	20	62du	34
62dw	5	62dx	5	62dy	8	62dz	6
62ea	9	62eb	18	62ec	13	62ed	14
62ee	11	62ef	5	62eg	10	62eh	7
62ei	8	62ej	4	62ek	8	95	8

96	10	97	37	99	36	100	5
101	7	102	10	103	8	104	60
105	28	106	23	107	13	108	40
109	17	110	27	111	10	112	4
113	5	114	137	115	18	116	7
117	11	118	8	119	82	120	12
121	7	122	14	123	6	124	9
125	7	126	8	127	24	128	3
129	9	130	45	131	3	132	9
133	5	134	3	135	5	136	4
137	82	138	3	139	20	140	5
141	3	142	4	143	21	144	279
145	58	146	3	147	2239	148	1429
149	7	150	582	151	59	152	4
154	8	155	351	156	4	157	5
158	1	159	2	160	2	161	3
162	2	163	2	164	1	165	2
166	2	167	2	168	7	169	339
170	4	171	6	172	48	173	288
174	4	175	5	176	2	177	2
178	2	179	3	180	7	181	3
182	2	183	9	184	2	185	2
186	3	187	16	188	3	189	17
191	16	192	7	194	13	195	12
196	6	198	19				

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 medicament.

Furthermore, the present invention relates to the use of a compound of general formula I or a pharmaceutical composition according to this invention for the treatment and/or prevention of diseases or conditions which are mediated by the activation of the G-protein-coupled receptor GPR40 in a patient, preferably in a human.

In yet another aspect the present invention relates to a method for treating a disease or condition mediated by the activation of the G-protein-coupled receptor GPR40 in a mammal that includes the step of administering to a patient, preferably a human, in need of such treatment a therapeutically effective amount of a compound or a pharmaceutical composition of the present invention.

Diseases and conditions mediated by agonists of the G-protein-coupled receptor GPR40 embrace metabolic diseases or conditions. According to one aspect the compounds and pharmaceutical compositions of the present invention are particularly suitable for treating diabetes mellitus, in particular Type 2 diabetes, Type 1 diabetes, complications of diabetes (such as e.g. retinopathy, nephropathy or neuropathies, diabetic foot, ulcers or macroangiopathies), metabolic acidosis or ketosis, reactive hypoglycaemia, hyperinsulinaemia, glucose metabolic disorder, insulin resistance, metabolic syndrome, dyslipidaemias of different origins, atherosclerosis and related diseases, obesity, high blood pressure, chronic heart failure, oedema and hyperuricaemia.

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

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

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

5

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.

30

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.

5 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.

10 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.

15

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.

20

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, 25 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.

30

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
5 methods known *per se* that are familiar to the skilled man, such as for example by mixing or combining at least one compound of formula I according to the invention, or a pharmaceutically acceptable salt of such a compound, and one or more excipients, carriers and/or diluents.

10 **Combination Therapy**

The compounds of the invention may further be combined with one or more, preferably one additional therapeutic agent. According to one embodiment the additional therapeutic agent is selected from the group of therapeutic agents useful in the treatment of diseases or conditions described hereinbefore, in particular
15 associated with metabolic diseases or conditions such as for example diabetes mellitus, obesity, diabetic complications, hypertension, hyperlipidemia. Additional therapeutic agents which are suitable for such combinations include in particular those which for example potentiate the therapeutic effect of one or more active substances with respect to one of the indications mentioned and/or which allow the
20 dosage of one or more active substances to be reduced.

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

Antidiabetic agents are for example metformin, sulphonylureas, nateglinide, repaglinide, thiazolidinediones, PPAR-(alpha, gamma or alpha/gamma) agonists or modulators, alpha-glucosidase inhibitors, DPPIV inhibitors, SGLT2-inhibitors, insulin
30 and insulin analogues, GLP-1 and GLP-1 analogues or amylin and amylin analogues, 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, alpha2-antagonists, CCR-2 antagonists or glucokinase activators. One or more lipid lowering agents are also suitable as combination partners, such as for example HMG-CoA-reductase inhibitors, fibrates, nicotinic acid and the derivatives thereof, PPAR-(alpha, gamma or alpha/gamma) agonists or modulators, PPAR-delta agonists, ACAT inhibitors or cholesterol absorption inhibitors such as, bile acid-binding substances such as, inhibitors of ileac bile acid transport, MTP inhibitors, or HDL-raising compounds such as CETP inhibitors or ABC1 regulators.

Therapeutic agents for the treatment of overweight and/or obesity are for example antagonists of the cannabinoid1 receptor, MCH-1 receptor antagonists, MC4 receptor agonists, NPY5 or NPY2 antagonists, β 3-agonists, leptin or leptin mimetics, agonists of the 5HT2c receptor.

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

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

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

Therefore, in another aspect, this invention relates to the use of a compound according to the invention in combination with one or more additional therapeutic

agents described hereinbefore and hereinafter for the treatment of diseases or conditions which may be affected or which are mediated by the activation of the G-protein-coupled receptor GPR40, in particular diseases or conditions as described hereinbefore and hereinafter.

5

In yet another aspect the present invention relates a method for treating a disease or condition mediated by the activation of the G-protein-coupled receptor GPR40 in a patient that includes the step of administering to the patient, preferably a human, in need of such treatment a therapeutically effective amount of a compound of the present invention in combination with a therapeutically effective amount of one or more additional therapeutic agents described in hereinbefore and hereinafter,

10

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 together with one or more inert carriers and/or diluents.

25

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**

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

Preliminary remarks:

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

- 5 Analytical HPLC parameters employed for characterization of products (TFA denotes trifluoroacetic 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% TFA]	% Solvent [Methanol]	Flow [mL/min]	Temperature [°C]
0.0	50	50	2.2	60
0.05	50	50	2.2	60
1.40	0	100	2.2	60
1.80	0	100	2.2	60

Method:		3		
Device:		Agilent 1100 with DA and MS detector		
Column:		XBridge C18, 4,6 x 30 mm, 3.5 μm		
Column Supplier:		Waters		

Gradient/Solvent Time [min]	% Solvent [H ₂ O,0.1%HCOOH]	% Solvent [Methanol]	Flow [mL/min]	Temperature [°C]
0.0	50	50	4	60
0.15	50	50	4	60
1.7	0	100	4	60
2.25	0	100	4	60

Method:		4		
Device:		Agilent 1100 with DA and MS detector		
Column:		XBridge C18, 4,6 x 30 mm, 3.5 µm		
Column Supplier:		Waters		
Gradient/Solvent Time [min]	% Solvent [H ₂ O,0.1%HCOOH]	% Solvent [Methanol]	Flow [mL/min]	Temperature [°C]
0.0	95	5	4	60
0.15	95	5	4	60
1.7	0	100	4	60
2.25	0	100	4	60

Method:		5		
Device:		Agilent 1100 with DA and MS detector		
Column:		XBridge C18, 4,6 x 30 mm, 3.5 µm		
Column Supplier:		Waters		
Gradient/Solvent Time [min]	% Solvent [H ₂ O,0.1%NH ₃]	% Solvent [Methanol]	Flow [mL/min]	Temperature [°C]
0.0	50	50	4	60
0.15	50	50	4	60
1.7	0	100	4	60
2.25	0	100	4	60

Method:		6		
Device:		Agilent 1100 with DA and MS detector		
Column:		XBridge C18, 4,6 x 30 mm, 3.5 µm		

Column Supplier:		Waters		
Gradient/Solvent Time [min]	% Solvent [H ₂ O,0.1%NH ₃]	% Solvent [Methanol]	Flow [mL/min]	Temperature [°C]
0.0	95	5	4	60
0.15	95	5	4	60
1.7	0	100	4	60
2.25	0	100	4	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%TFA]	% Solvent [CH ₃ CN]	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:		8		
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 [CH ₃ CN]	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:		9		
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 [CH ₃ CN]	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:		Stable Bond, 3 x 30 mm, 1.8 µm		
Column Supplier:		Agilent		
Gradient/Solvent Time [min]	% Solvent [H ₂ O,0.1%TFA]	% Solvent [CH ₃ CN]	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:		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 [CH ₃ CN]	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:		12		
Device:		Agilent 1200 with DA and MS detector		
Column:		Stable Bond, 3 x 30 mm, 1.8 µm		
Column Supplier:		Agilent		
Gradient/Solvent Time [min]	% Solvent [H ₂ O,0.1%TFA]	% Solvent [CH ₃ CN]	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:		13		
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 [CH ₃ CN]	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:		14		
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 [CH ₃ CN]	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:		15		
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%TFA]	% Solvent [CH ₃ CN]	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:		16		
Device:		LC/MS Waters Alliance 2695 HPLC System DAD, Quattro Micro Triple quadrupole		
Column:		Gemini, C18 3 µm, 4.6 x 50 mm		
Gradient/Solvent Time [min]	% Solvent [H ₂ O/CH ₃ CN 90:10,0.1%TFA]	% Solvent [CH ₃ CN]	Flow [mL/min]	Temperature [°C]
0.00	50	50	1.3	35
3.5	10	90	1.3	35
4.5	10	90	1.3	35
4.6	50	50	1.3	35

Method:		17		
Device:		LC/MS Waters Acquity UPLC System DAD, SQD single quadrupole		
Column:		BEH C18, 1.7 μ m, 2.1 x 50 mm		
Gradient/Solvent Time [min]	% Solvent [H ₂ O/CH ₃ CN 90:10, 5 mM NH ₄ COOH]	% Solvent [CH ₃ CN/H ₂ O 90:10]	Flow [mL/min]	Temperature [°C]
0.00	100	0	0.70	35
1.20	0	100	0.70	35
1.45	0	100	0.70	35
1.55	100	0	0.70	35
1.75	100	0	0.70	35

Method:		18		
Device:		LC/MS Waters Acquity UPLC System DAD, SQD single quadrupole		
Column:		HSS C18, 1.8 μ m, 2.1 x 50 mm		
Gradient/Solvent Time [min]	% Solvent [H ₂ O/CH ₃ CN 90:10, 0.1% TFA]	% Solvent [CH ₃ CN/H ₂ O 90:10]	Flow [mL/min]	Temperature [°C]
0.00	100	0	0.70	35
0.70	0	100	0.70	35
2.30	0	100	0.70	35
2.40	100	0	0.70	35
2.60	100	0	0.70	35

Method:		19		
Device:		LC/MS Waters Acquity UPLC System DAD, SQD single quadrupole		
Column:		BEH C18, 1.7 μ m, 2.1 x 50 mm		
Gradient/Solvent	% Solvent	% Solvent	Flow [mL/min]	Temperature

Time [min]	[H ₂ O/CH ₃ CN 90:10, 5 mM NH ₄ COOH]	[CH ₃ CN/H ₂ O 90:10]		[°C]
0.00	100	0	0.70	35
1.20	0	100	0.70	35
1.45	0	100	0.70	35
1.55	100	0	0.70	35
1.75	100	0	0.70	35

Method:		20	
Device:		LC/MS ThermoFinnigan HPLC Surveyor DAD, MSQ single quadrupole	
Column:		Synergi Hydro RP100A, 2.5 µm, 3 x 50 mm	
Gradient/Solvent Time [min]	% Solvent [H ₂ O/CH ₃ CN 90:10, 10 mM NH ₄ COOH]	% Solvent [CH ₃ CN/H ₂ O 90:10, 10 mM NH ₄ COOH]	Flow [mL/min]
0.00	100	0	0.7
1.50	100	0	0.7
8.00	0	100	0.7
10.00	0	100	0.7
11.00	100	0	0.7
12.00	100	0	0.7

Method:		20A	
Device:		LC/MS ThermoFinnigan HPLC Surveyor DAD, LCQFleet Ion Trap	
Column:		Simmetry Shield RP8, 5µm, 4,6 x 150 mm	
Gradient/Solvent Time [min]	% Solvent [H ₂ O/CH ₃ CN 90:10, 10 mM HCOOH]	% Solvent [CH ₃ CN/H ₂ O 90:10, 10 mM HCOOH]	Flow [mL/min]
0.00	70	30	8.50

1.50	50	50	8.50
8.50	0	100	8.50
13.05	0	100	8.50
14.00	70	30	8.50
15	70	30	8.50

Method:		20B	
Device:		LC/MS ThermoFinnigan HPLC Surveyor DAD, MSQ single quadrupole	
Column:		Synergi Hydro RP100A, 2,5 µm, 3 x 50 mm	
Gradient/Solvent Time [min]	% Solvent [H ₂ O/CH ₃ CN 90:10, 5 mM NH ₄ COOH]	% Solvent [CH ₃ CN/H ₂ O 90:10]	Flow [mL/min]
0.00	100	0	1.2
4.00	0	100	1.2
5.30	0	100	1.2
5.50	100	0	1.2
6.00	100	0	1.2

Method:		20C	
Device:		LC/MS ThermoFinnigan HPLC Surveyor DAD, MSQ single quadrupole	
Column:		Synergi Hydro RP100A, 2,5 µm, 3 x 50 mm	
Gradient/Solvent Time [min]	% Solvent [H ₂ O/CH ₃ CN 90:10, 5 mM NH ₄ COOH]	% Solvent [CH ₃ CN/H ₂ O 90:10]	Flow [mL/min]
0.00	100	0	1.2
1.50	100	0	1.2
9.00	0	100	1.2
10.50	0	100	1.2
11.00	100	0	1.2

12.00	100	0	1.2

Method:		20D	
Device:		LC/MS ThermoFinnigan HPLC Surveyor DAD, LCQFleet Ion Trap	
Column:		Xselect CSH, 2.5 µm, 4,6 x 50 mm	
Gradient/Solvent Time [min]	% Solvent [H ₂ O/CH ₃ CN 90:10, 10 mM HCOOH]	% Solvent [CH ₃ CN/H ₂ O 90:10, 10 mM HCOOH]]	Flow [mL/min]
0.00	100	0	1.4
4.00	0	100	1.4
5.30	0	100	1.4
5.50	100	0	1.4
6.00	100	0	1.4
12.00	100	0	1.2

Method:		20E	
Device:		LC/MS ThermoFinnigan HPLC Surveyor DAD, LCQFleet Ion Trap	
Column:		Xselect CSH, 2.5 µm, 4,6 x 50 mm	
Gradient/Solvent Time [min]	% Solvent [H ₂ O/CH ₃ CN 90:10, 10 mM HCOOH]	% Solvent [CH ₃ CN/H ₂ O 90:10, 10 mM HCOOH]]	Flow [mL/min]
0.00	100	0	1.4
1.00	100	0	1.4
8.05	0	100	1.4
10.00	0	100	1.4
10.02	100	0	1.4
11.00	100	0	1.4

Method:		20F	

Device:		LC/MS Waters Alliance 2695 HPLC System DAD, Quattro Micro Triple	
Column:		Zorbax Eclipse XDB-C18 3.5µm 4,6 x 50 mm, Temp 35°	
Gradient/Solvent Time [min]	% Solvent [H ₂ O/CH ₃ CN 90:10, 5 mM NH ₄ COOH]	% Solvent [CH ₃ CN/H ₂ O 90:10, 10 mM HCOOH]	Flow [mL/min]
0.00	100	0	1.3
4.50	0	100	1.3
5.80	0	100	1.3
6.00	100	0	1.3

Method:		21	
Device:		LC/MS ThermoFinnigan HPLC Surveyor DAD, LCQFleet Ion Trap	
Column:		Symmetry Shield RP8, 5 µm, 4.6 x 150 mm	
Gradient/Solvent Time [min]	% Solvent [H ₂ O/CH ₃ CN 90:10, 0.1% HCOOH]	% Solvent [CH ₃ CN/H ₂ O 90:10, 0.1% HCOOH]	Flow [mL/min]
0.00	95	5	1
1.50	95	5	1
11.05	5	95	1
13	5	95	1
13.03	95	5	1
15	95	5	1

Method:		22		
Device:		Agilent 1200 with DA and MS detector		
Column:		Sunfire C18, 3 x 30 mm, 2.5 µm		
Column Supplier:		Waters		
Gradient/Solvent	% Solvent	% Solvent	Flow [ml/min]	Temperature

Time [min]	[H ₂ O,0.1%TFA]	[MeOH]		[°C]
0.00	95	5	1.8	60
0.25	95	5	1.8	60
1.70	0	100	1.8	60
1.75	0	100	2.5	60
1.90	0	100	2.5	60

Method:		23		
Device:		Waters 1525 with DA and MS Detector		
Column:		Sunfire C18, 4.6 x 30 mm, 2.5 µm		
Column Supplier:		Waters		
Gradient/Solvent Time [min]	% Solvent [H ₂ O,0.1%TFA]	% Solvent [CH ₃ CN]	Flow [ml/min]	Temperature [°C]
0.0	97	3	4	60
0.15	97	3	3	60
2.15	0	100	3.0	60
2.20	0	100	4.5	60
2.40	0	100	4,5	60

Method:		24		
Device:		Agilent 1100 with DAD, CTC Autosampler and Waters MS Detector		
Column:		XBridge C18, 4.6 x 30 mm, 3.5 µm		
Column Supplier:		Waters		
Gradient/Solvent Time [min]	% Solvent [H ₂ O,0.1%NH ₄ OH]	% Solvent [CH ₃ CN]	Flow [ml/min]	Temperature [°C]
0.0	98.0	2.0	2.5	60.0
1.5	0.0	100.0	2.5	60.0
1.8	0.0	100.0	2.5	60.0

Method:		25		
Device:		LC/MS Waters Acquity UPLC System DAD, SQD		

		single quadrupole		
Column:		HSS C18, 1.8 µm, 2.1 x 50 mm		
Gradient/Solvent Time [min]	% Solvent [H ₂ O/CH ₃ CN 90:10,0.1%TFA]	% Solvent [CH ₃ CN/H ₂ O 90:10]	Flow [ml/min]	Temperature [°C]
0.00	100	0	0.70	35
1.20	0	100	0.70	35
1.45	0	100	0.70	35
1.55	100	0	0.70	35
1.75	100	0	0.70	35

Method:		26		
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 [CH ₃ CN]	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:		27		
Device:		Agilent 1100 with DAD, Waters Autosampler and MS Detector		
Column:		Sunfire C18, 4.6 x 30 mm, 3.5 µm		
Column Supplier:		Waters		
Gradient/Solvent Time [min]	% Solvent [H ₂ O,0.1%TFA]	% Solvent [CH ₃ CN]	Flow [mL/min]	Temperature [°C]
0.00	95	5	4	50
1.20	0	100	4	50

1.8	0	100	4	50

Analytical GC parameters employed for characterization of products:

Method:	1
Device:	GC/MS Thermo Scientific TRACE GC ULTRA, DSQ II MS single quadrupole
Column:	Agilent DB-5MS, 25 m x 0.25 mm x 0.25 µm
Carrier gas:	Helium, 1 mL/min constant flow
Oven Program:	50°C to 100°C in 10°C/min, to 200°C in 20°C/min, to 320°C in 30°C/min (hold 10 min)
Detection:	DSQ II MS single quadrupole
Ion source:	EI
Scan range:	50- 450 amu

5 Analytical chiral HPLC parameters employed for characterization of products

Method:	1a			
Device:	Agilent 1100 with DAD			
Column:	Daicel Chiralcel OJ-H			
Solvent Time [min]	% Solvent [Hexane]	% Solvent [Ethanol]	Flow [mL/min]	Temperature [°C]
isocratic	70	30	1.0	25

Method:	1b			
Device:	Agilent 1100 with DAD			
Column:	Daicel Chiralcel IA			
Solvent Time [min]	% Solvent [Hexane]	% Solvent [Isopropanol]	Flow [mL/min]	Temperature [°C]
isocratic	70	30	1.0	25

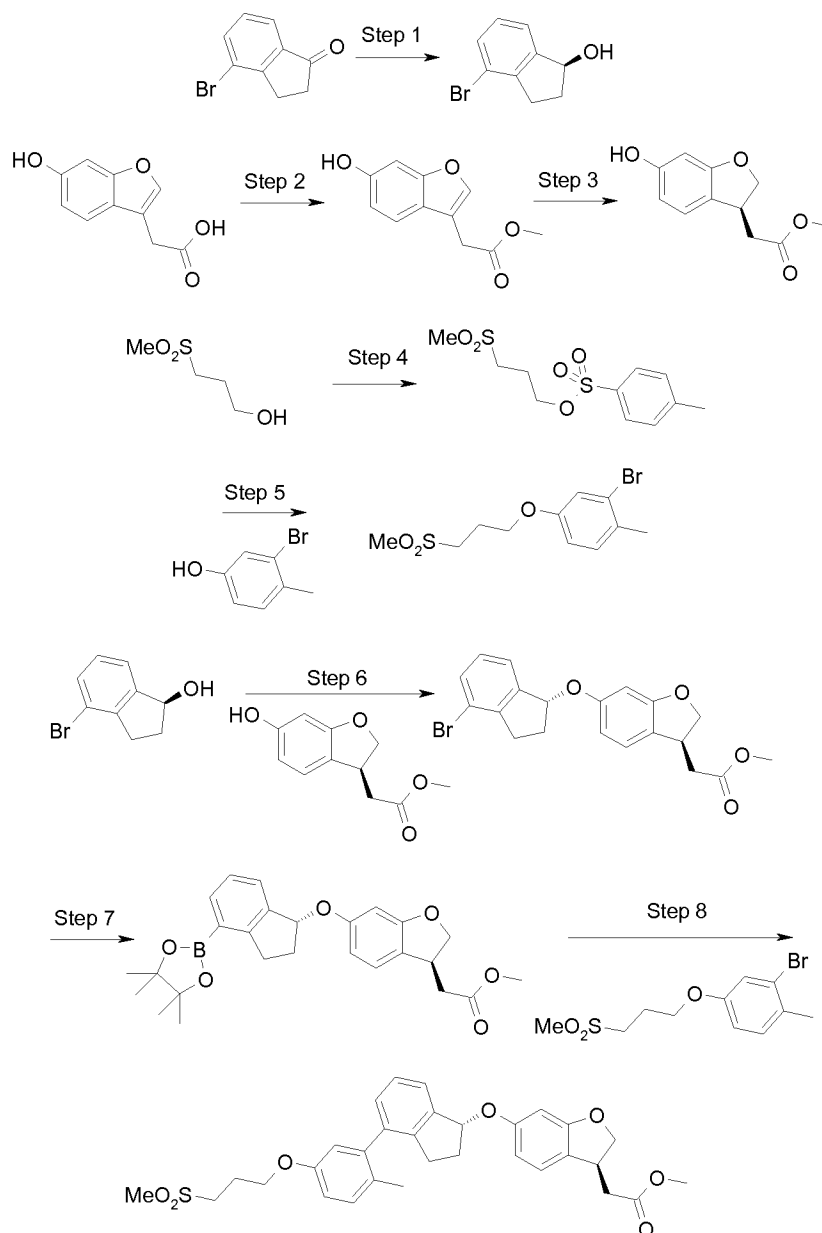
Method:	1c			
Device:	Agilent 1100 with DAD			

Column:		Daicel Chiralcel AD-H		
Solvent Time [min]	% Solvent [Hexane]	% Solvent [Isopropanol]	Flow [mL/min]	Temperature [°C]
isocratic	70	30	1.0	25

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

5 Intermediate 1

Methyl 2-((3S)-6-((1R)-4-(2-methyl-5-(3-(methylsulfonyl)propoxy)phenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate



Step 1: (S)-4-Bromo-2,3-dihydro-1H-inden-1-ol

Formic acid (3.2 mL) is added to a solution of triethylamine (10.5 mL) in dichloromethane (50 mL) chilled in an ice bath. 4-Bromo-2,3-dihydro-1H-inden-1-one (5 g) is added and the flask is purged with argon for 5 minutes. Chloro{[(1S,2S)-(-)-2-amino-1,2-diphenylethyl](4-toluenesulfonyl)amido}-(mesitylene)ruthenium(II) (700 mg; alternatively, the catalyst is formed in situ from N-[(1S,2S)-2-amino-1,2-diphenylethyl]-4-methylbenzenesulfonamide and dichloro(p-cymene)-ruthenium(II) dimer) is added and the mixture is stirred at room temperature for 16 hours. Water is added and the resulting mixture is extracted with dichloromethane. The combined
10 extract is washed with saturated aqueous NaHCO₃ solution and dried (MgSO₄). The solvent is evaporated and the residue is chromatographed on silica gel (cyclohexane/ethyl acetate 99:1→50:50) to give the title compound. Yield: 4.5 g; LC (method 1): t_R = 1.04 min; Mass spectrum (ESI⁺): m/z = 195 [M+H-H₂O]⁺.

Step 2: Methyl 2-(6-hydroxybenzofuran-3-yl)acetate

15 A mixture of 2-(6-hydroxybenzofuran-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
20 (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. Yield: 9.0 g; Mass spectrum (ESI⁺): m/z = 207 [M+H]⁺.

Step 3: (S)-Methyl 2-(6-hydroxy-2,3-dihydrobenzofuran-3-yl)acetate

A mixture of methyl 2-(6-hydroxybenzofuran-3-yl)acetate (5.00 g), 10% palladium on carbon (0.50 g), and methanol (50 mL) is shaken under hydrogen atmosphere (3 bar)
25 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 methyl 2-(6-hydroxy-2,3-dihydrobenzofuran-3-yl)acetate as an oil that solidified upon standing. Yield: 2.60 g; Mass spectrum (ESI⁺): m/z = 209
30 [M+H]⁺.

The enantiomers are 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)-Methyl 2-(6-hydroxy-2,3-dihydrobenzofuran-3-yl)acetate: t_R = 2.33 min.

(R)-Methyl 2-(6-hydroxy-2,3-dihydrobenzofuran-3-yl)acetate: $t_R = 2.75$ min.

Alternatively, the title compound may be obtained as described in WO 2008001931.

Step 4: 3-(Methylsulfonyl)propyl 4-methylbenzenesulfonate

To a solution of 3-(methylsulfonyl)propan-1-ol (1.0 g) in dichloromethane (10 mL) and pyridine (1.5 mL) is added at 0°C p-toluene-sulfonylchloride (1.38 g) in portions. The mixture is stirred for 12 hours at room temperature, diluted with dichloromethane and washed with 1 M aqueous HCl solution and brine. After drying ($MgSO_4$) the solvent is evaporated to give the title compound. Yield: 1.6 g; LC (method 1): $t_R = 0.82$ min; Mass spectrum (ESI^+): $m/z = 293$ $[M+H]^+$.

Step 5: 2-Bromo-1-methyl-4-(3-(methylsulfonyl)propoxy)benzene

To a solution of 3-bromo-4-methylphenol (200 mg) and K_2CO_3 (193 mg) in N,N-dimethylformamide (5 mL) is added 3-(methylsulfonyl)propyl 4-methylbenzenesulfonate (375 mg). The mixture is stirred for 12 hours at 90°C and then partitioned between water and ethyl acetate. The organic phase is washed with brine and dried ($MgSO_4$). The solvent is evaporated and the residue is chromatographed on silica gel (cyclohexane/ethyl acetate 80:20→20:80) to give the title compound. Yield: 268 mg; LC (method 1): $t_R = 1.12$ min; Mass spectrum (ESI^+): $m/z = 307$ $[M+H]^+$.

Step 6: Methyl 2-((S)-6-((R)-4-bromo-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

A solution of di-tert.-butyl azodicarboxylate (7.5 g) in tetrahydrofuran (15 mL) is added dropwise to a solution of (S)-methyl 2-(6-hydroxy-2,3-dihydrobenzofuran-3-yl)acetate (4.4 g), (S)-4-Bromo-2,3-dihydro-1H-inden-1-ol (4.5 g) and triphenylphosphine (8.3 g) in tetrahydrofuran (30 mL) at 5-10°C. The resulting solution is stirred for 12 hours diluted with ethyl acetate and then washed successively with water, saturated aqueous $NaHCO_3$ solution and brine. The organic phase is dried ($MgSO_4$) and concentrated. The residue is chromatographed on silica gel (cyclohexane/ethyl acetate 99:1→50:50) to give the title compound. Yield: 5.5 g; LC (method 1): $t_R = 1.44$ min; Mass spectrum (ESI^+): $m/z = 403$ $[M+H]^+$.

Step 7: Methyl 2-((S)-6-((R)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

In a microwave vial methyl 2-((S)-6-((R)-4-bromo-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate (4.4 g), bis-(pinacolato)-diboron (3.7 g) and potassium acetate (2.8 g) are suspended in 1,4-dioxane and purged for 10 minutes

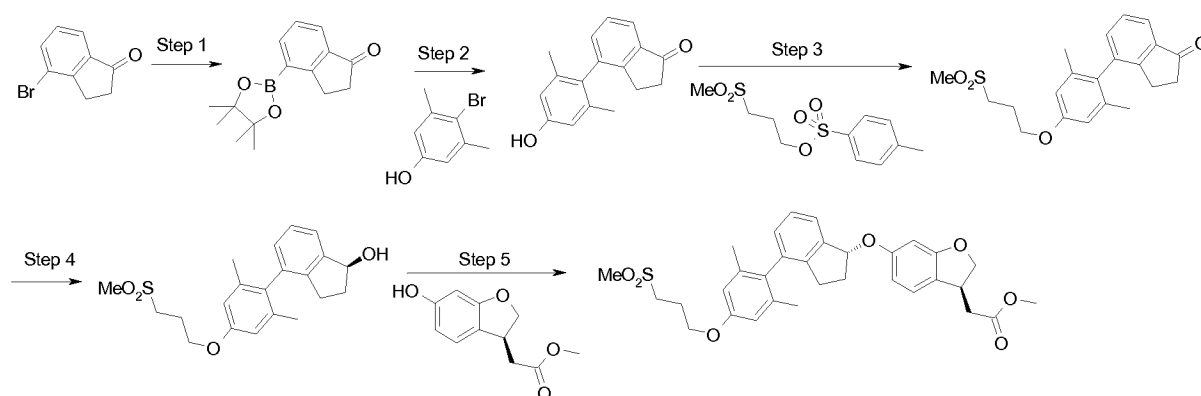
with argon. [1,1'-Bis(diphenylphosphino)-ferrocene]-dichloropalladium-(II) (400 mg) is added, the vial is sealed and the mixture is stirred at 100°C for 2 hours. After cooling to room temperature the mixture is diluted with ethyl acetate and washed with saturated aqueous NH₄Cl solution and brine. The organic phase is dried (MgSO₄) and concentrated. The residue is chromatographed on silica gel (cyclohexane/ethyl acetate 99:1→60:40) to give the title compound. Yield: 2.3 g; LC (method 1): t_R = 1.48 min; Mass spectrum (ESI⁺): m/z = 451 [M+H]⁺.

Step 8: Methyl 2-((3S)-6-((1R)-4-(2-methyl-5-(3-(methylsulfonyl)propoxy)phenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

In a microwave vial methyl 2-((S)-6-((R)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate (50 mg), 2-bromo-1-methyl-4-(3-(methylsulfonyl)propoxy)benzene (38 mg), K₂CO₃ (46 mg) and tetrabutyl-ammonium bromide (9 mg) are suspended in toluene (1 mL) and water (1 mL) and purged for 5 minutes with argon. Tetrakis-triphenylphosphine-palladium-(0) (26 mg) is added, the vial is sealed and the mixture is stirred at 120°C for 2 hours. After cooling to room temperature the mixture is diluted with ethyl acetate and washed with brine. The organic phase is dried (MgSO₄) and concentrated. The residue is chromatographed on silica gel (cyclohexane/ethyl acetate 99:1→50:50) to give the title compound. Yield: 34 mg; LC (method 1): t_R = 1.37 min; Mass spectrum (ESI⁺): m/z = 551 [M+H]⁺.

Intermediate 2

Methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-(3-(methylsulfonyl)propoxy)phenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate



Step 1: 4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-one

The title compound is prepared from 4-bromo-2,3-dihydro-1H-inden-1-one following a procedure analogous to that described in Step 7 of Intermediate 1. LC (method 1): t_R = 1.26 min; Mass spectrum (ESI⁺): m/z = 259 [M+H]⁺.

Step 2: 4-(4-Hydroxy-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-one

- 5 In a microwave vial a mixture of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-one (610 mg), 4-bromo-3,5-dimethylphenol (475 mg), Na₂CO₃ (8 mL of a 1 M aqueous solution), toluene (8 mL) and ethanol (2.5 mL) is purged for 5 minutes with argon. Tetrakis-triphenylphosphine-palladium-(0) (140 mg) is added, the vial is sealed and the mixture is stirred at 110°C for 12 hours. After cooling to room
- 10 temperature the mixture is diluted with diethylether and washed with saturated aqueous NH₄Cl and brine. The organic phase is dried (MgSO₄) and concentrated. The residue is chromatographed on silica gel (cyclohexane/ethyl acetate 90:10→60:40) to give the title compound. Yield: 210 mg; LC (method 1): t_R = 1.07 min; Mass spectrum (ESI⁺): m/z = 253 [M+H]⁺.

- 15 Step 3: 4-(2,6-Dimethyl-4-(3-(methylsulfonyl)propoxy)phenyl)-2,3-dihydro-1H-inden-1-one

The title compound is prepared from 4-(4-hydroxy-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-one following a procedure analogous to that described in Step 5 of Intermediate 1. The mixture is heated for 6 days at 90°C. LC (method 1): t_R = 1.12

20 min; Mass spectrum (ESI⁺): m/z = 373 [M+H]⁺.

Step 4: (S)-4-(2,6-Dimethyl-4-(3-(methylsulfonyl)propoxy)phenyl)-2,3-dihydro-1H-inden-1-ol

The title compound is prepared from 4-(2,6-dimethyl-4-(3-(methylsulfonyl)propoxy)phenyl)-2,3-dihydro-1H-inden-1-one following a procedure

25 analogous to that described in Step 1 of Intermediate 1. LC (method 1): t_R = 1.08 min; Mass spectrum (ESI⁺): m/z = 357 [M+H-H₂O]⁺.

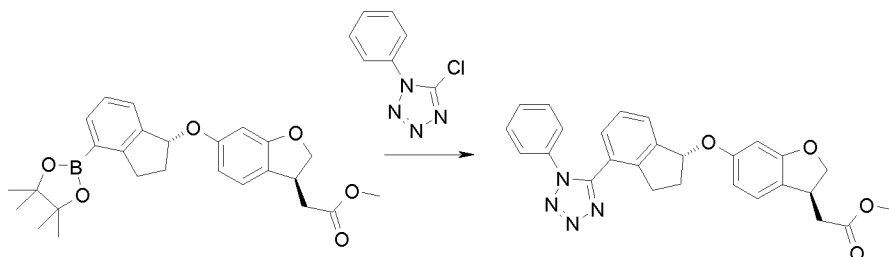
Step 5: Methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-(3-(methylsulfonyl)propoxy)phenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

The title compound is prepared from (S)-4-(2,6-dimethyl-4-(3-(methylsulfonyl)propoxy)phenyl)-2,3-dihydro-1H-inden-1-ol and (S)-methyl 2-(6-hydroxy-2,3-dihydrobenzofuran-3-yl)acetate following a procedure analogous to that

30 described in Step 6 of Intermediate 1. The mixture is stirred for 1 hour. LC (method 1): t_R = 1.38 min; Mass spectrum (ESI⁺): m/z = 582 [M+NH₄]⁺.

Intermediate 3

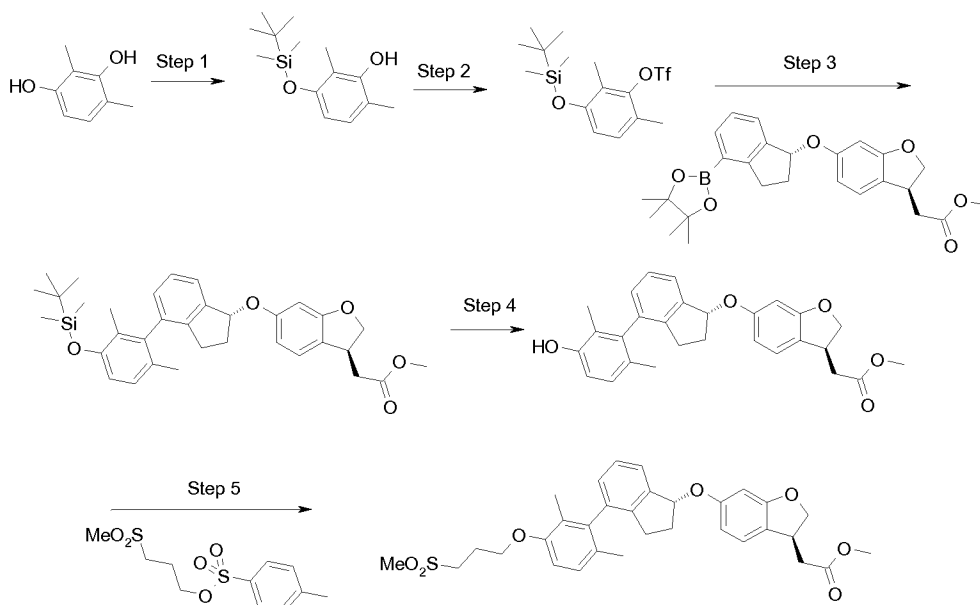
Methyl 2-((3S)-6-((1R)-4-(1-phenyl-1H-tetrazol-5-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate



- 5 In a microwave vial methyl 2-((S)-6-((R)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate (150 mg), 5-chloro-1-phenyl-1H-tetrazole (66 mg) and Ba(OH)₂ (171 mg) are suspended in 1,4-dioxane (1.3 mL) and purged for 5 minutes with argon. Bis-(dibenzylideneacetone)-palladium(0) (19 mg) and 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (27 mg),
- 10 are added, the vial is sealed and the mixture is stirred at 100°C for 1 hour and at 120°C for 30 minutes. After cooling to room temperature the mixture is diluted with tetrahydrofuran, filtered and used directly in the next step (example 3).

Intermediate 4

- 15 Methyl 2-((3S)-6-((1R)-4-(2,6-dimethyl-3-(3-(methylsulfonyl)propoxy)phenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate



Step 1: 3-(tert-Butyldimethylsilyloxy)-2,6-dimethylphenol

2,4-Dimethylbenzene-1,3-diol (1.5 g) and triethylamine (2.3 mL) are dissolved in dichloromethane (15 mL), cooled to 0 °C and treated with tert-butylchlorodimethylsilane (1.7 g) and 4-dimethylaminopyridine (133 mg). The mixture is stirred for 12 hours at room temperature, diluted with dichloromethane and washed with 1 M hydrochloric acid, saturated aqueous NaHCO₃ solution and brine. After drying (MgSO₄) the solvents are evaporated in vacuo and the residue is chromatographed on silica gel (cyclohexane/ethyl acetate 99:1→60:40) to give the title compound. Yield: 2.1 g; LC (method 1): t_R = 1.44 min; Mass spectrum (ESI⁺): m/z = 253 [M+H]⁺.

Step 2: 3-(tert-Butyldimethylsilyloxy)-2,6-dimethylphenyl trifluoromethane-sulfonate 3-(tert-Butyldimethylsilyloxy)-2,6-dimethylphenol (2.1 g) and 2,6-dimethylpyridine (lutidine) (2 mL) are dissolved in dichloromethane (20 mL) cooled to 0 °C and treated with trifluoromethanesulfonic anhydride (1.6 mL). The mixture is stirred for 3 hours at room temperature, diluted with dichloromethane and washed with saturated aqueous NH₄Cl solution and brine. After drying (MgSO₄) the solvents are evaporated in vacuo and the residue is chromatographed on silica gel (cyclohexane/ethyl acetate 99:1→70:30) to give the title compound. Yield: 2.6 g; LC (method 1): t_R = 1.60 min.

Step 3: Methyl 2-((3S)-6-((1R)-4-(3-(tert-butyldimethylsilyloxy)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

The title compound is prepared from 3-(tert-Butyldimethylsilyloxy)-2,6-dimethylphenyl trifluoromethanesulfonate and methyl 2-((S)-6-((R)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate following a procedure analogous to that described in Step 8 of Intermediate 1. LC (method 1): t_R = 1.66 min; Mass spectrum (ESI⁺): m/z = 559 [M+H-H₂O]⁺.

Step 4: Methyl 2-((3S)-6-((1R)-4-(3-hydroxy-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

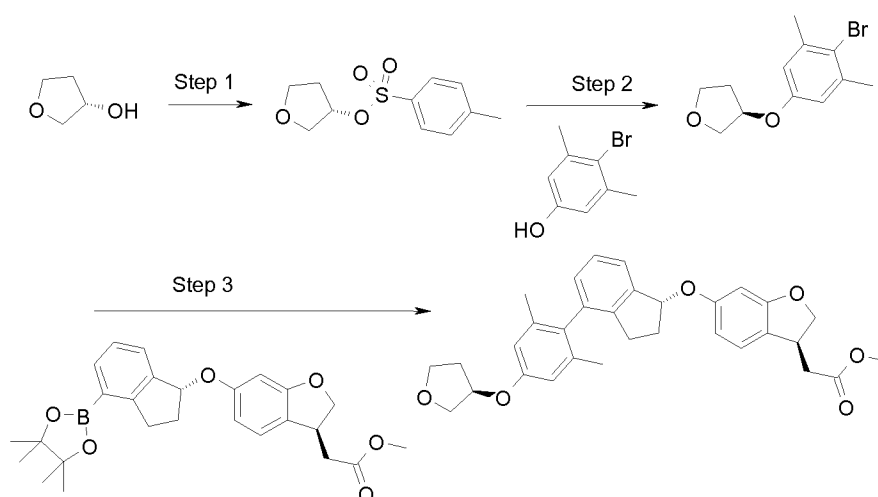
To a solution of methyl 2-((3S)-6-((1R)-4-(3-(tert-butyldimethylsilyloxy)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate (95 mg) in tetrahydrofuran (3 mL) is added at 0 °C tetrabutylammonium fluoride (700 µL of a 1 M solution in tetrahydrofuran). The mixture is stirred for 3 hours at room temperature, diluted with ethyl acetate and washed with water and brine. After drying (MgSO₄) the solvents are evaporated and the residue is chromatographed on silica gel (cyclohexane/ethyl acetate 99:1→50:50) to give the title compound. Yield: 33 mg; LC (method 1): t_R = 1.37 min; Mass spectrum (ESI⁺): m/z = 445 [M+H]⁺.

Step 5: Methyl 2-((3S)-6-((1R)-4-(2,6-dimethyl-3-(3-(methylsulfonyl)propoxy)phenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

The title compound is prepared from methyl 2-((3S)-6-((1R)-4-(3-hydroxy-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate and 3-(methylsulfonyl)propyl 4-methylbenzenesulfonate following a procedure analogous to that described in Step 5 of Intermediate 1. LC (method 1): $t_R = 1.36$ min; Mass spectrum (ESI⁺): $m/z = 565$ [M+H-H₂O]⁺.

Intermediate 5

10 Methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-((R)-tetrahydrofuran-3-yloxy)phenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate



Step 1: (S)-Tetrahydrofuran-3-yl 4-methylbenzenesulfonate

15 The title compound is prepared from (S)-tetrahydrofuran-3-ol following a procedure analogous to that described in Step 4 of Intermediate 1. Mass spectrum (ESI⁺): $m/z = 243$ [M+H]⁺.

Step 2: (R)-3-(4-Bromo-3,5-dimethylphenoxy)tetrahydrofuran

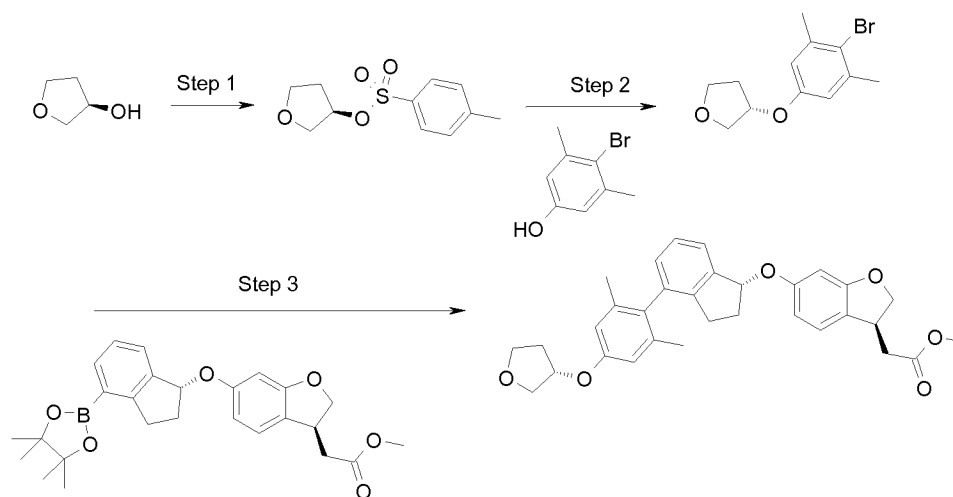
20 The title compound is prepared from (S)-tetrahydrofuran-3-yl 4-methylbenzenesulfonate following a procedure analogous to that described in Step 5 of Intermediate 1. LC (method 1): $t_R = 1.40$ min; Mass spectrum (ESI⁺): $m/z = 271$ [M+H]⁺.

Step 3: Methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-((R)-tetrahydrofuran-3-yloxy)phenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

In a microwave vial methyl 2-((S)-6-((R)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate (100 mg) and (R)-3-(4-bromo-3,5-dimethylphenoxy)tetrahydrofuran (66 mg) are suspended in N,N-dimethylformamide (2 mL) and Na₂CO₃ (390 µL of a 2M aqueous solution). The mixture is purged for 5 minutes with argon. [1,1'-Bis(diphenylphosphino)-ferrocene]-dichloropalladium dichloromethane complex (10 mg) is added, the vial is sealed and the mixture is stirred at 90°C for 2 hours. After cooling to room temperature the mixture is diluted with methanol and purified by HPLC on reversed phase. Yield: 35 mg; LC (method 2): t_R = 1.12 min; Mass spectrum (ESI⁺): m/z = 515 [M+H]⁺.

Intermediate 6

Methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-((S)-tetrahydrofuran-3-yloxy)phenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate



Step 1: (R)-Tetrahydrofuran-3-yl 4-methylbenzenesulfonate

The title compound is prepared from (R)-tetrahydrofuran-3-ol following a procedure analogous to that described in Step 4 of Intermediate 1. The reaction is performed in the presence of a catalytic amount of 4-dimethylaminopyridine. Mass spectrum (ESI⁺): m/z = 243 [M+H]⁺.

Step 2: (S)-3-(4-Bromo-3,5-dimethylphenoxy)tetrahydrofuran

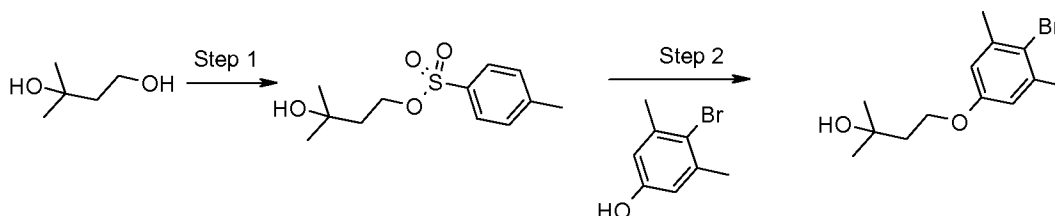
The title compound is prepared from (R)-tetrahydrofuran-3-yl 4-methylbenzenesulfonate following a procedure analogous to that described in Step 5 of Intermediate 1. LC (method 1): t_R = 1.30 min; Mass spectrum (ESI⁺): m/z = 271 [M+H]⁺.

Step 3: Methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-((S)-tetrahydrofuran-3-yloxy)phenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

The title compound is prepared from 2-((S)-6-((R)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate and (S)-3-(4-Bromo-3,5-dimethylphenoxy)tetrahydrofuran following a procedure analogous to that described in Step 8 of Intermediate 1. LC (method 1): $t_R = 1.46$ min; Mass spectrum (ESI^+): $m/z = 515 [M+H]^+$.

Intermediate 7

4-(4-Bromo-3,5-dimethylphenoxy)-2-methylbutan-2-ol



Step 1: 3-Hydroxy-3-methylbutyl 4-methylbenzenesulfonate

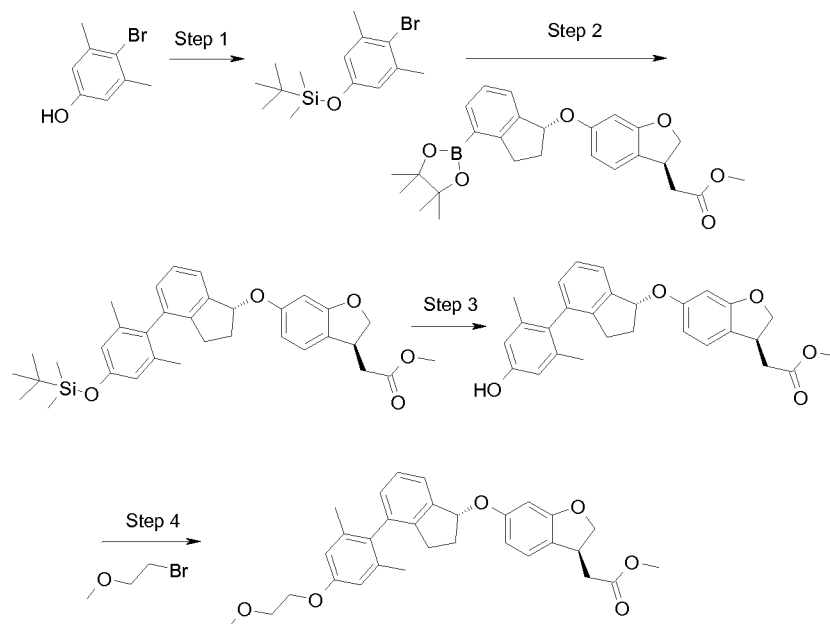
The title compound is prepared from 3-methylbutane-1,3-diol and 4-methylbenzene-1-sulfonyl chloride following a procedure analogous to that described in Step 4 of Intermediate 1. The crude product is purified by chromatography on silica gel (cyclohexane/ethyl acetate 90:10→70:30). Mass spectrum (ESI^+): $m/z = 276 [M+NH_4]^+$.

Step 2: 4-(4-Bromo-3,5-dimethylphenoxy)-2-methylbutan-2-ol

The title compound is prepared from 4-bromo-3,5-dimethylphenol and 3-hydroxy-3-methylbutyl 4-methylbenzenesulfonate following a procedure analogous to that described in Step 5 of Intermediate 1. LC (method 1): $t_R = 1.35$ min; Mass spectrum (ESI^+): $m/z = 269 [M+H-H_2O]^+$.

Intermediate 8

Methyl 2-((S)-6-((R)-4-(4-(2-methoxyethoxy)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate



Step 1: (4-Bromo-3,5-dimethylphenoxy)(tert-butyl)dimethylsilane

The title compound is prepared from 4-bromo-3,5-dimethylphenol and tert-butylchlorodimethylsilane following a procedure analogous to that described in Step 1 of Intermediate 4. LC (method 1): $t_R = 1.62$ min; Mass spectrum (ESI^+): $m/z = 315$ $[M+H]^+$.

Step 2: Methyl 2-((S)-6-((R)-4-(4-(tert-butyldimethylsilyloxy)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

The title compound is prepared from (4-bromo-3,5-dimethylphenoxy)(tert-butyl)dimethylsilane and methyl 2-((S)-6-((R)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate following a procedure analogous to that described in Step 8 of Intermediate 1. LC (method 1): $t_R = 1.65$ min; Mass spectrum (ESI^+): $m/z = 559$ $[M+H-H_2O]^+$.

Step 3: Methyl 2-((S)-6-((R)-4-(4-hydroxy-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

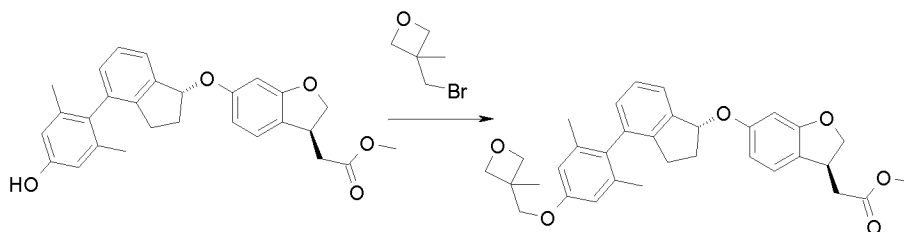
The title compound is prepared from methyl 2-((S)-6-((R)-4-(4-(tert-butyldimethylsilyloxy)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate following a procedure analogous to that described in Step 4 of Intermediate 4. LC (method 1): $t_R = 1.36$ min; Mass spectrum (ESI^+): $m/z = 445$ $[M+H]^+$.

Step 4: Methyl 2-((S)-6-((R)-4-(4-(2-methoxyethoxy)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

To a solution of methyl 2-((S)-6-((R)-4-(4-hydroxy-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate (37 mg) and K₂CO₃ (24 mg) in N,N-dimethylformamide (2 mL) is added 1-bromo-2-methoxyethane (10 µL). The mixture is stirred for 12 hours at room temperature. 1-Bromo-2-methoxyethane (10 µL) is added and the mixture is stirred for 4 hours at 50°C. After addition of 1-bromo-2-methoxyethane (10 µL) the mixture is stirred for 12 hours at 50°C, followed by addition of 1-bromo-2-methoxyethane (20 µL) and K₂CO₃ (12 mg). The mixture is stirred for further 5 hours at 50°C, then diluted with ethyl acetate and washed with water and brine. After drying (MgSO₄) the solvents are evaporated and the residue is chromatographed on silica gel (cyclohexane/ethyl acetate 99:1→50:50) to give the title compound. Yield: 28 mg; LC (method 1): t_R = 1.47 min; Mass spectrum (ESI⁺): m/z = 503 [M+H]⁺.

Intermediate 9

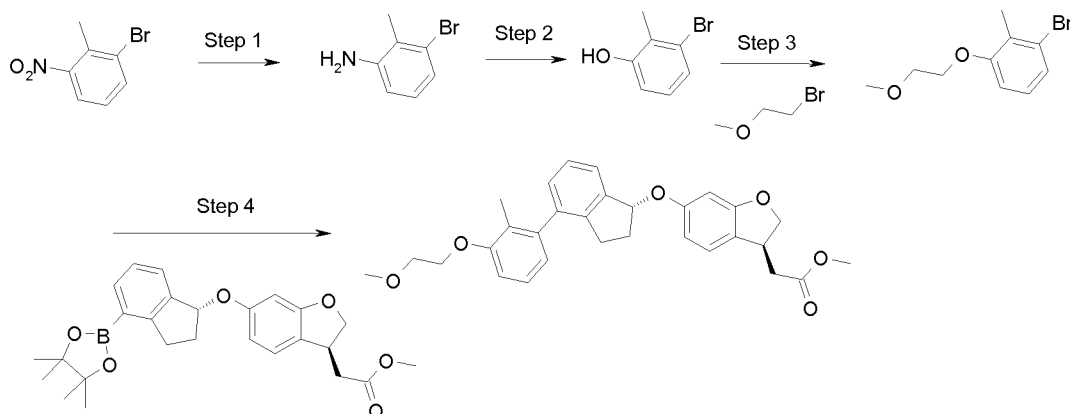
Methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-((3-methyloxetan-3-yl)methoxy)phenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate



To a solution of methyl 2-((S)-6-((R)-4-(4-hydroxy-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate (37 mg) and K₂CO₃ (24 mg) in N,N-dimethylformamide (2 mL) is added 3-(bromomethyl)-3-methyloxetane (17 mg). The mixture is stirred for 12 hours at room temperature. 1-Bromo-2-methoxyethane (10 mg) is added and the mixture is stirred for 4 hours at 50°C. The mixture is diluted with ethyl acetate and washed with water and brine. After drying (MgSO₄) the solvents are evaporated and the residue is chromatographed on silica gel (cyclohexane/ethyl acetate 80:20→20:80) to give the title compound. Yield: 33 mg; LC (method 1): t_R = 1.50 min; Mass spectrum (ESI⁺): m/z = 529 [M+H]⁺.

Intermediate 10

Methyl 2-((3S)-6-((1R)-4-(3-(2-methoxyethoxy)-2-methylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate



Step 1: 3-Bromo-2-methylaniline

1-Bromo-2-methyl-3-nitrobenzene (4 g) is dissolved in ethanol (30 mL) and acetic acid (6 mL) and heated to gentle reflux. Iron powder (4.1 g) is added in small portions and the mixture is heated for 2 hours. After addition of 3 N hydrochloric acid (0.5 mL) iron powder (1 g) is cautiously added and the mixture is heated for 8 hours to reflux. After cooling to room temperature 2 N aqueous sodium hydroxide (50 mL) is added, the mixture is filtered over celite and the filter cake is rinsed with ethyl acetate. The organic phase is separated, washed with brine and dried (MgSO₄). Evaporation of the solvents gives the title compound. Yield: 3.1 g; TLC: r_f = 0.34 (silicagel, petrole ether/ethyl acetate 5:1).

Step 2: 3-Bromo-2-methylphenol

At -5°C 3-bromo-2-methylaniline is dissolved in 1 M sulfuric acid (20 mL). A solution of sodium nitrite (1.4 g) in water (3 mL) is added dropwise and the mixture is stirred for 15 minutes. Then concentrated sulfuric acid (6.8 mL) is added dropwise and the mixture is heated for 1 hour to 100°C. The mixture is cooled to 0°C, diluted with water and extracted twice with diethylether. The combined organic phases are dried (MgSO₄) and concentrated. The residue is chromatographed on silica gel (cyclohexane/ethyl acetate 83:17→50:50) to give the title compound. Yield: 1.6 g; Mass spectrum (ESI⁻): m/z = 185 [M-H]⁻.

Step 3: 1-Bromo-3-(2-methoxyethoxy)-2-methylbenzene

Under argon NaH (ca. 60% in mineral oil; 26 mg) is added to a cold (0°C) solution of 3-bromo-2-methylphenol (100 mg) in tetrahydrofuran (3 mL). The mixture is stirred for 10 minutes and then 1-bromo-2-methoxyethane (60 µL) is added. The mixture is then stirred for 12 hours at room temperature and 6 hours at 50°C. NaH (ca. 60% in mineral oil; 20 mg) and 1-bromo-2-methoxyethane (50 µL) are added successively and the mixture is heated to reflux for 8 hours. After cooling to room temperature the

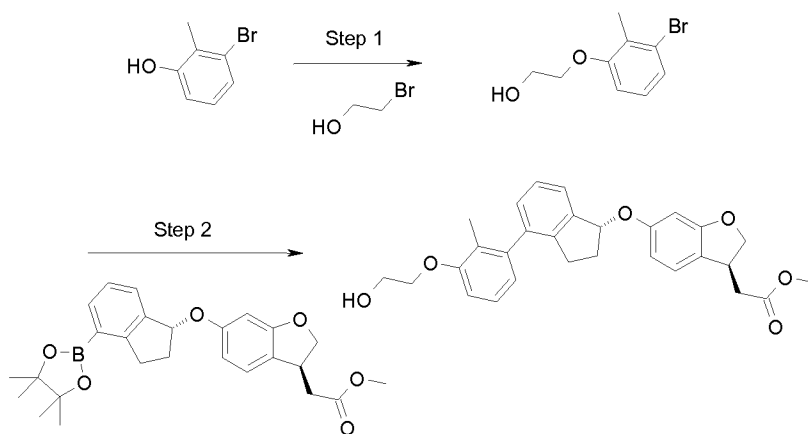
mixture is partitioned between water and ethyl acetate. The organic phase is dried (MgSO_4) and concentrated. The residue is chromatographed on silica gel (cyclohexane/ethyl acetate 95:5) to give the title compound. Yield: 74 mg; LC (method 3): $t_R = 1.07$ min; TLC: $r_f = 0.40$ (silicagel, petrole ether/ethyl acetate 9:1).

5 **Step 4:** Methyl 2-((3S)-6-((1R)-4-(3-(2-methoxyethoxy)-2-methylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

In a microwave vial methyl 2-((S)-6-((R)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate (50 mg) and 1-bromo-3-(2-methoxyethoxy)-2-methylbenzene (33 mg) and K_3PO_4 (100 mg) are
 10 suspended in tetrahydrofuran (5 mL). The mixture is purged for 5 minutes with argon. [1,1'-Bis(diphenylphosphino)-ferrocene]-dichloropalladium dichloromethane complex (8 mg) is added, the vial is sealed and the mixture is stirred at 100°C for 1.5 hours. After cooling to room temperature the mixture is diluted with ethyl acetate and washed with brine. The organic phase is dried (MgSO_4) and concentrated. The
 15 residue is chromatographed on silica gel (cyclohexane/ethyl acetate 90:10→70:30) to give the title compound. Yield: 34 mg; LC (method 3): $t_R = 1.59$ min; Mass spectrum (ESI^+): $m/z = 489$ $[\text{M}+\text{H}]^+$.

Intermediate 11

20 **Methyl 2-((3S)-6-((1R)-4-(3-(2-hydroxyethoxy)-2-methylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate**



Step 1: 2-(3-Bromo-2-methylphenoxy)ethanol

To a solution of 3-bromo-2-methylphenol (145 mg) and K_2CO_3 (200 mg) in N,N-dimethylformamide (3 mL) is added 2-bromoethanol (60 μL). The mixture is stirred for
 25 2 hours at 80°C . 2-bromoethanol (350 μL) is added, the mixture is heated for 2 hours

at 80°C and for 18 hours to 120°C. After cooling to room temperature the mixture is diluted with ethyl acetate and washed with water and brine. The organic phase is dried (MgSO₄) and concentrated. The residue is chromatographed on silica gel (cyclohexane/ethyl acetate 90:10→70:30) to give the title compound. Yield: 87 mg;

5 TLC: r_f = 0.30 (silicagel, petrole ether/ethyl acetate 2:1).

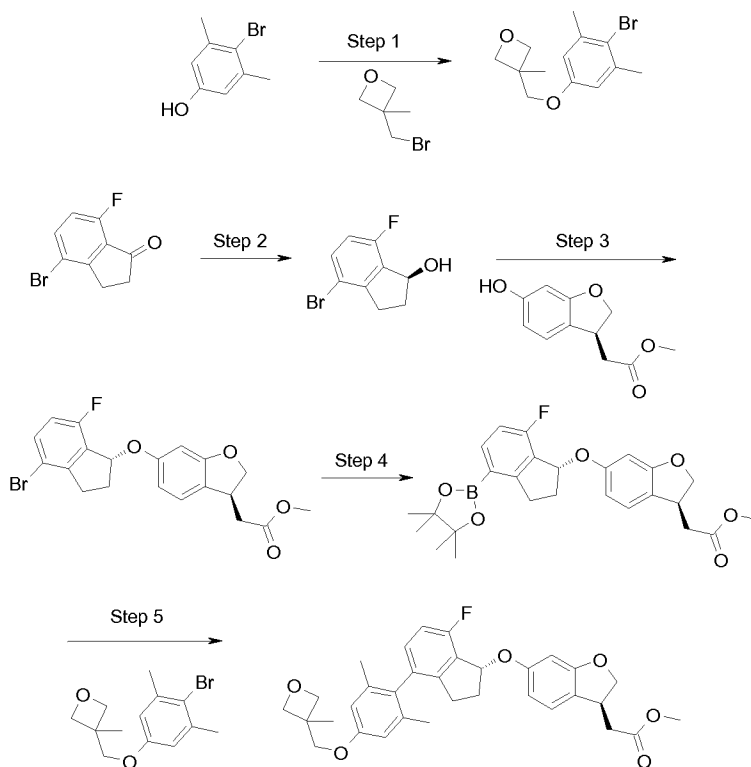
Step 2: Methyl 2-((3S)-6-((1R)-4-(3-(2-hydroxyethoxy)-2-methylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

The title compound is prepared from methyl 2-((S)-6-((R)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-

10 yl)acetate and 2-(3-bromo-2-methylphenoxy)ethanol following a procedure analogous to that described in Step 4 of Intermediate 10. LC (method 3): t_R = 1.41 min; Mass spectrum (ESI⁺): m/z = 475 [M+H]⁺.

Intermediate 12

15 Methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-((3-methyloxetan-3-yl)methoxy)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate



Step 1: 3-((4-Bromo-3,5-dimethylphenoxy)methyl)-3-methyloxetane

To a solution of 4-bromo-3,5-dimethylphenol (3.0 g) and K₂CO₃ (5.5 g) in N,N-dimethylformamide (10 mL) is added 3-(bromomethyl)-3-methyloxetane (2.95 g). The

20

mixture is stirred for 12 hours at room temperature and then partitioned between saturated aqueous NaHCO₃ solution and ethyl acetate. The aqueous phase is extracted with ethyl acetate and the combined organic phases are dried (MgSO₄). The solvent is evaporated and the residue is chromatographed on silica gel (cyclohexane/ethyl acetate 100:0→70:30) to give the title compound. Yield: 3.5 g; LC (method 4): t_R = 1.81 min; Mass spectrum (ESI⁺): m/z = 285 [M+H]⁺.

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

The title compound is prepared from 4-bromo-7-fluoro-2,3-dihydro-1H-inden-1-one following a procedure analogous to that described in Step 1 of Intermediate 1. LC (method 1): t_R = 1.04 min; Mass spectrum (ESI⁺): m/z = 213 [M+H-H₂O]⁺.

Step 3: Methyl 2-((S)-6-((R)-4-bromo-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

A solution of di-tert.-butyl azodicarboxylate (18 g) in tetrahydrofuran (80 mL) is added dropwise over 45 minutes to a solution of (S)-methyl 2-(6-hydroxy-2,3-dihydrobenzofuran-3-yl)acetate (11 g), (S)-4-bromo-7-fluoro-2,3-dihydro-1H-inden-1-ol (11.95 g) and tributylphosphine (19.3 mL) in tetrahydrofuran (320 mL) at -10°C. The resulting solution is stirred for 30 minutes and then partitioned between saturated aqueous NaHCO₃ solution and dichloromethane. The aqueous phase is extracted with dichloromethane. 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. Yield: 10.35 g; LC (method 1): t_R = 1.41 min; Mass spectrum (ESI⁺): m/z = 421 [M+H]⁺.

Step 4: Methyl 2-((S)-6-((R)-7-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

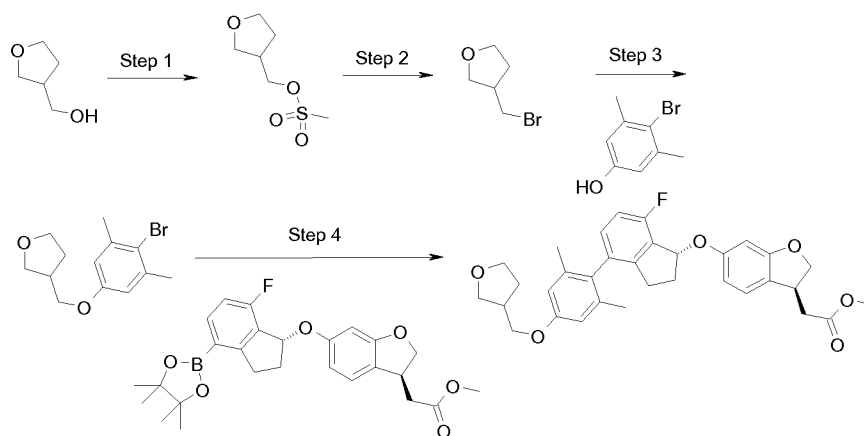
In a microwave vial methyl 2-((S)-6-((R)-4-bromo-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate (7.0 g), bis-(pinacolato)-diboron (5.6 g) and potassium acetate (4.2 g) are suspended in 1,4-dioxane and purged for 10 minutes with argon. [1,1'-Bis(diphenylphosphino)-ferrocene]-dichloropalladium-(II) (600 mg) is added, the vial is sealed and the mixture is stirred at 100°C for 4 hours. After cooling to room temperature the mixture is partitioned between diethylether and saturated aqueous NH₄Cl solution. The organic phase is dried (MgSO₄) and concentrated. The residue is chromatographed on silica gel (cyclohexane/ethyl acetate 99:1→70:30) to give the title compound. Yield: 5.85 g; LC (method 1): t_R = 1.48 min; Mass spectrum (ESI⁺): m/z = 469 [M+H]⁺.

Step 5: Methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-((3-methyloxetan-3-yl)methoxy)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

In a microwave vial methyl 2-((S)-6-((R)-7-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate (500 mg), 3-((4-bromo-3,5-dimethylphenoxy)methyl)-3-methyloxetane (450 mg), K_3PO_4 (450 mg) are suspended in toluene (2.5 mL) and water (250 μ L) and purged for 10 minutes with argon. Palladium-(II)-acetate (12 mg) and dicyclohexyl(2',6'-dimethoxybiphenyl-2-yl)phosphine (S-Phos) (44 mg) are added, the vial is sealed and the mixture is stirred at 100°C for 4 hours. After cooling to room temperature the mixture is partitioned between diethylether and saturated aqueous NH_4Cl solution. The organic phase is dried ($MgSO_4$) and concentrated. The residue is chromatographed on silica gel (cyclohexane/ethyl acetate 90:10→60:40) to give the title compound. Yield: 420 mg; LC (method 4): t_R = 1.93 min; Mass spectrum (ESI^+): m/z = 569 $[M+Na]^+$.

Intermediate 13

Methyl 2-((3S)-6-((1R)-4-(2,6-dimethyl-4-((tetrahydrofuran-3-yl)methoxy)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate



Step 1: (Tetrahydrofuran-3-yl)methyl methanesulfonate

To a cooled (0°C) solution of (tetrahydrofuran-3-yl)methanol (3.0 mL) and triethylamine (5.7 mL) in dichloromethane (30 mL) is added methanesulfonyl chloride (3.1 mL). The mixture is stirred for 12 hours at room temperature. After cooling to 0°C triethylamine (1.3 mL) and methanesulfonyl chloride (0.7 mL) are added and the mixture is stirred for 12 hours at room temperature. The mixture is partitioned

between dichloromethane and saturated aqueous NaHCO_3 solution and stirred vigorously for 30 minutes. The organic phase is separated, washed with brine and dried (MgSO_4). The solvent is evaporated to give the title compound. Yield: 5.6 g; TLC: $r_f = 0.35$ (silicagel, cyclohexane/ethyl acetate 1:1); Mass spectrum (ESI^+): $m/z = 181$ $[\text{M}+\text{H}]^+$.

Step 2: 3-(Bromomethyl)tetrahydrofuran

To solution of (tetrahydrofuran-3-yl)methyl methanesulfonate (5.6 g) in acetone (80 mL) is added lithium bromide (13.6 g). The mixture is heated to reflux for 4 hours. Then the solvent is evaporated in vacuo and the residue is partitioned between dichloromethane and water. The organic phase is separated and dried (MgSO_4). The solvents are evaporated. The residue is dissolved in dichloromethane and filtered over a small plug of silica gel. Concentration gives the title compound. Yield: 3.9 g; TLC: $r_f = 0.80$ (silicagel, cyclohexane/ethyl acetate 1:1).

Step 3: 3-((4-Bromo-3,5-dimethylphenoxy)methyl)tetrahydrofuran

The title compound is prepared from 4-bromo-3,5-dimethylphenol and 3-(bromomethyl)tetrahydrofuran following a procedure analogous to that described in Step 5 of Intermediate 1. LC (method 1): $t_R = 1.37$ min; Mass spectrum (ESI^+): $m/z = 285$ $[\text{M}+\text{H}]^+$.

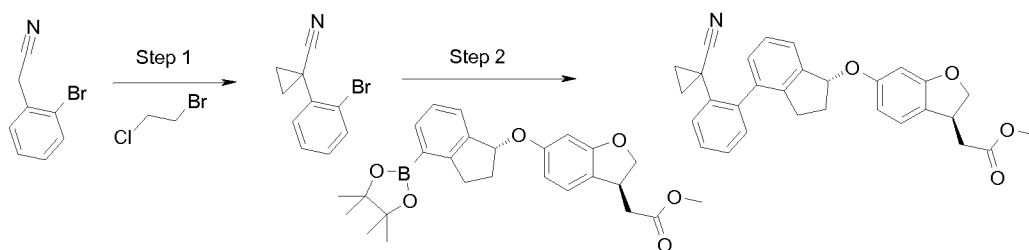
Step 4: Methyl 2-((3S)-6-((1R)-4-(2,6-dimethyl-4-((tetrahydrofuran-3-

yl)methoxy)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

In a microwave vial methyl 2-((S)-6-((R)-7-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate (170 mg) and 3-((4-bromo-3,5-dimethylphenoxy)methyl)tetrahydrofuran (170 mg) and K_3PO_4 (290 mg) are suspended in tetrahydrofuran (10 mL). The mixture is purged for 5 minutes with argon. [1,1'-Bis(diphenylphosphino)-ferrocene]-dichloropalladium (27 mg) is added, the vial is sealed and the mixture is stirred at 100°C for 12 hours. After cooling to room temperature the mixture is diluted with diethylether and washed with saturated aqueous NH_4Cl solution. The organic phase is dried (MgSO_4) and concentrated. The residue is chromatographed on silica gel (cyclohexane/ethyl acetate 90:10→50:50) to give the title compound. Yield: 47 mg; LC (method 1): $t_R = 1.48$ min; Mass spectrum (ESI^+): $m/z = 569$ $[\text{M}+\text{Na}]^+$.

Intermediate 14

Methyl 2-((3S)-6-((1R)-4-(2-(1-cyanocyclopropyl)phenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate



Step 1: 1-(2-Bromophenyl)cyclopropanecarbonitrile

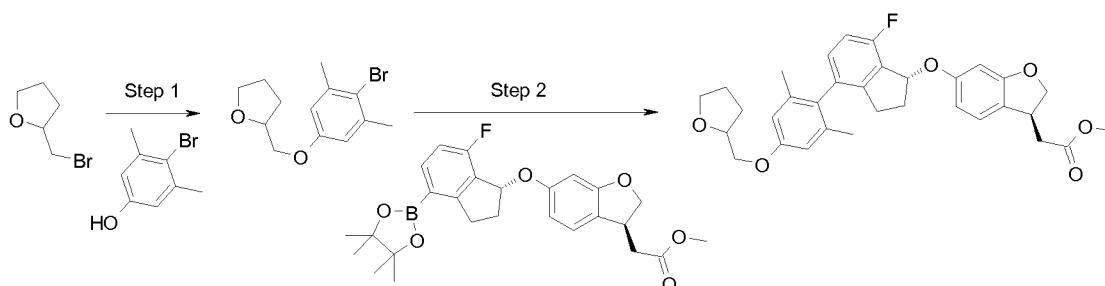
- 5 To a mixture of 2-(2-bromophenyl)acetonitrile (1.7 mL), 1-bromo-2-chloroethane (3.2 mL) and benzyltriethylammonium chloride (60 mg) is added dropwise at 0°C a solution of NaOH (10.6 g) in water (11 mL). The mixture is stirred for 15 minutes at 0°C and for 3 hours at 55°C. After cooling to room temperature the mixture is diluted with ethyl acetate and washed with water, 1 N hydrochloric acid, water and brine.
- 10 The organic phase is dried (MgSO₄) and concentrated to give the title compound. Yield: 2.9 g; LC (method 6): t_R = 1.44 min; Mass spectrum (ESI⁺): m/z = 222 [M+H]⁺.

Step 2: Methyl 2-((3S)-6-((1R)-4-(2-(1-cyanocyclopropyl)phenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

- The title compound is prepared from methyl 2-((S)-6-((R)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate and 1-(2-bromophenyl)cyclopropanecarbonitrile following a procedure analogous to that described in Step 4 of Intermediate 13. The reaction temperature is 120°C. LC (method 4): t_R = 1.78 min; Mass spectrum (ESI⁺): m/z = 466 [M+H]⁺.

20 **Intermediate 15**

Methyl 2-((3S)-6-((1R)-4-(2,6-dimethyl-4-((tetrahydrofuran-2-yl)methoxy)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate



Step 1: 2-((4-Bromo-3,5-dimethylphenoxy)methyl)tetrahydrofuran

The title compound is prepared from 4-bromo-3,5-dimethylphenol and 2-(bromomethyl)tetrahydrofuran following a procedure analogous to that described in Step 5 of Intermediate 1. LC (method 1): $t_R = 1.37$ min; Mass spectrum (ESI^+): $m/z = 285 [M+H]^+$.

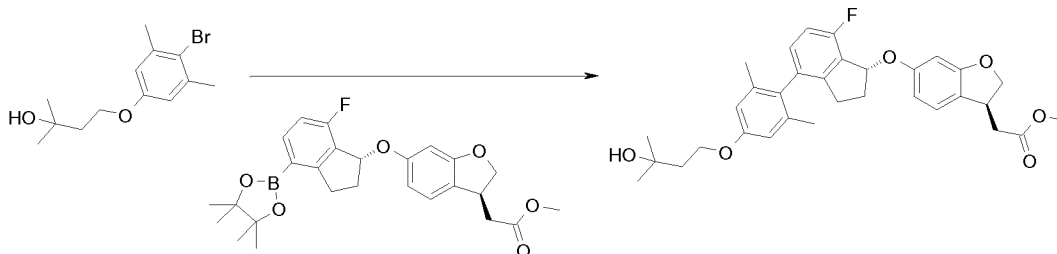
- 5 **Step 2:** Methyl 2-((3S)-6-((1R)-4-(2,6-dimethyl-4-((tetrahydrofuran-2-yl)methoxy)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

The title compound is prepared from methyl 2-((S)-6-((R)-7-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-

- 10 dihydrobenzofuran-3-yl)acetate and 2-((4-bromo-3,5-dimethylphenoxy)methyl)-tetrahydrofuran following a procedure analogous to that described in Step 5 of Intermediate 12. LC (method 1): $t_R = 1.48$ min; Mass spectrum (ESI^+): $m/z = 569 [M+Na]^+$.

15 Intermediate 16

Methyl 2-((S)-6-((R)-7-fluoro-4-(4-(3-hydroxy-3-methylbutoxy)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

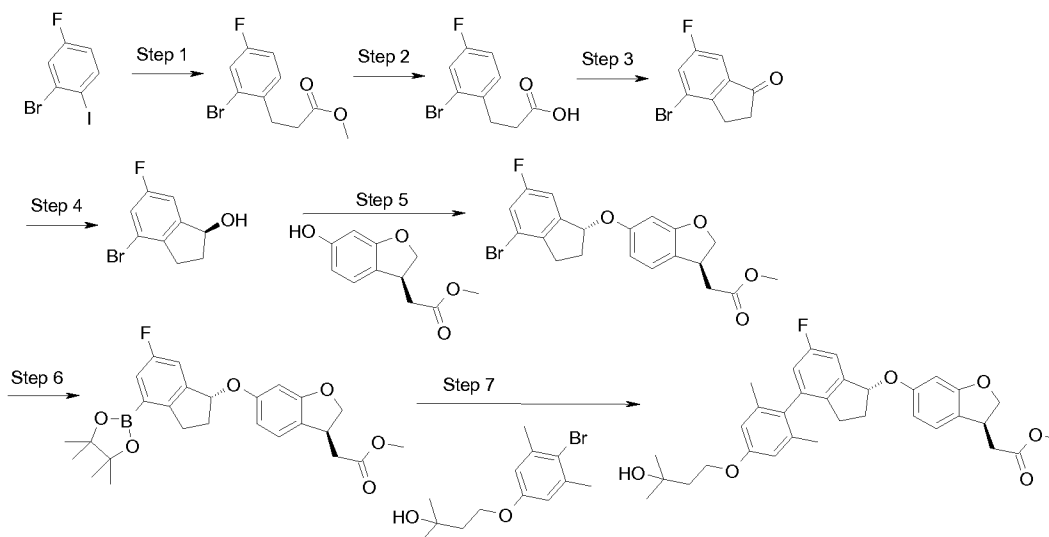


- 20 The title compound is prepared from methyl 2-((S)-6-((R)-7-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate and 4-(4-bromo-3,5-dimethylphenoxy)-2-methylbutan-2-ol following a procedure analogous to that described in Step 5 of Intermediate 12. LC (method 4): $t_R = 1.90$ min; Mass spectrum (ESI^+): $m/z = 571 [M+Na]^+$.

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Intermediate 17

Methyl 2-((S)-6-((R)-6-fluoro-4-(4-(3-hydroxy-3-methylbutoxy)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate



Step 1: Methyl 3-(2-bromo-4-fluorophenyl)propanoate

To a solution of 2-bromo-4-fluoro-1-iodobenzene (3.1 g) and 3,3-dimethoxyprop-1-ene (1.8 mL) in N,N-dimethylformamide (40 mL) are added tetrabutylammonium chloride (2.9 g) and N-ethyl-diisopropylamine (3.5 mL) and the mixture is purged for 10 minutes with argon. Palladium-(II)-acetate (118 mg) is added and the mixture is heated for 2 hours to 90°C. After cooling to room temperature the mixture is diluted with diethylether and washed with 1 N hydrochloric acid. The organic phase is dried (MgSO₄) and concentrated. The residue is chromatographed on silica gel (cyclohexane/ethyl acetate 95:5→90:10) to give the title compound (1.4 g), which is used directly in the next step.

Step 2: 3-(2-Bromo-4-fluorophenyl)propanoic acid

To a solution of methyl 3-(2-bromo-4-fluorophenyl)propanoate (1.4 g) in tetrahydrofuran (10 mL) and methanol (10 mL) is added 4 M aqueous NaOH solution (10 mL) and the mixture is heated to 50°C for 3 hours. The organic solvents are evaporated in vacuo the residue is diluted with water and washed with tert.-butyl-methyl-ether. The aqueous phase is neutralized by addition of 4 M hydrochloric acid (10 mL) and the mixture is stirred for 1 hour. The precipitate formed is filtered off, washed with water and dried to give the title compound. Yield: 1.2 g; LC (method 3): $t_R = 0.71$ min; Mass spectrum (ESI⁺): $m/z = 245$ [M-H]⁺.

Step 3: 4-Bromo-6-fluoro-2,3-dihydro-1H-inden-1-one

Under argon 3-(2-bromo-4-fluorophenyl)propanoic acid (1.2 g) is added in small portions to trifluoromethanesulfonic acid (15 mL) at room temperature. The mixture is stirred for 2 hours at 60°C and for 16 hours at 80°C. After cooling to room

temperature the mixture is poured slowly in ice-water. The aqueous phase is extracted twice with ethyl acetate. The combined organic phases are washed with saturated aqueous Na₂CO₃ solution and brine. After drying (MgSO₄) the solvent is evaporated. The residue is stirred with dichloromethane (40 mL), filtered and washed
5 with dichloromethane. The combined dichloromethane phases are concentrated to give the title compound. Yield: 970 mg; LC (method 3): t_R = 0.60 min; Mass spectrum (ESI⁺): m/z = 229 [M+H]⁺.

Step 4: (S)-4-Bromo-6-fluoro-2,3-dihydro-1H-inden-1-ol

The title compound is prepared from 4-bromo-6-fluoro-2,3-dihydro-1H-inden-1-one
10 following a procedure analogous to that described in Step 1 of Intermediate 1. LC (method 3): t_R = 0.72 min; Mass spectrum (ESI⁻): m/z = 229 [M-H]⁻.

Step 5: Methyl 2-((S)-6-((R)-4-bromo-6-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

The title compound is prepared from (S)-4-bromo-6-fluoro-2,3-dihydro-1H-inden-1-ol
15 and (S)-methyl 2-(6-hydroxy-2,3-dihydrobenzofuran-3-yl)acetate following a procedure analogous to that described in Step 3 of Intermediate 12. LC (method 3): t_R = 1.60 min; Mass spectrum (ESI⁺): m/z = 421 [M+H]⁺.

Step 6: Methyl 2-((S)-6-((R)-6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

The title compound is prepared from methyl 2-((S)-6-((R)-4-bromo-6-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate following a procedure
20 analogous to that described in Step 7 of Intermediate 1. LC (method 3): t_R = 1.70 min; Mass spectrum (ESI⁺): m/z = 469 [M+H]⁺.

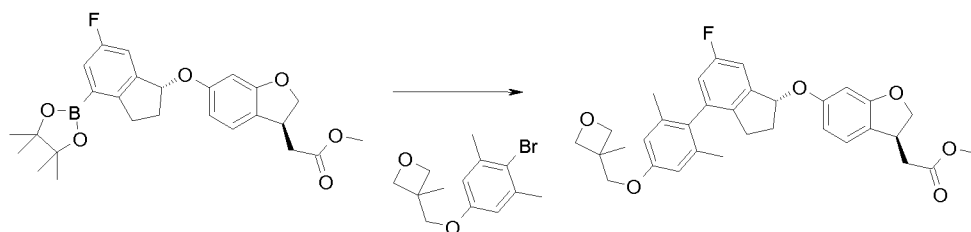
Step 7: Methyl 2-((S)-6-((R)-6-fluoro-4-(4-(3-hydroxy-3-methylbutoxy)-2,6-

25 dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

The title compound is prepared from methyl 2-((S)-6-((R)-6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate and 4-(4-bromo-3,5-dimethylphenoxy)-2-methylbutan-2-ol following a procedure analogous to that described in Step 8 of
30 Intermediate 1. LC (method 3): t_R = 1.68 min; Mass spectrum (ESI⁺): m/z = 549 [M+H]⁺.

Intermediate 18

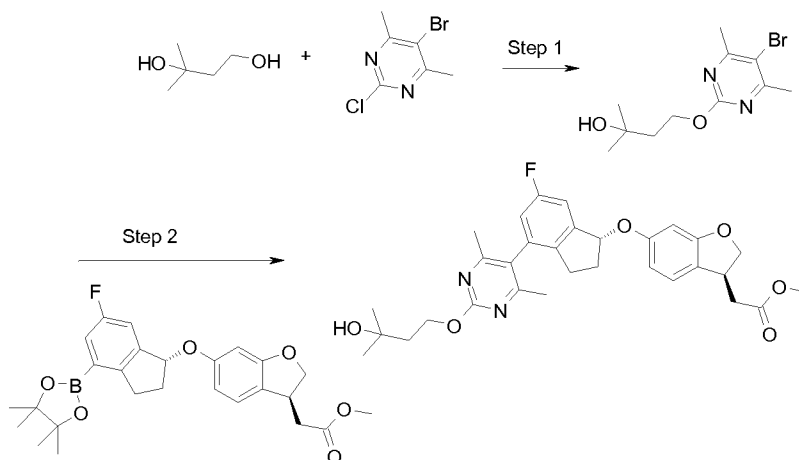
Methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-((3-methyloxetan-3-yl)methoxy)phenyl)-6-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate



The title compound is prepared from methyl 2-((S)-6-((R)-6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate and 3-((4-bromo-3,5-dimethylphenoxy)methyl)-3-methyloxetane following a procedure analogous to that described in Step 8 of Intermediate 1. LC (method 3): $t_R = 1.68$ min; Mass spectrum (ESI⁺): $m/z = 547$ [M+H]⁺.

Intermediate 19

Methyl 2-((S)-6-((R)-6-fluoro-4-(2-(3-hydroxy-3-methylbutoxy)-4,6-dimethylpyrimidin-5-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate



Step 1: 4-(5-Bromo-4,6-dimethylpyrimidin-2-yloxy)-2-methylbutan-2-ol

Under argon 3-methylbutane-1,3-diol (650 μ L) is added at 0°C to a suspension of NaH (ca. 60% in mineral oil; 400 mg). The mixture is stirred for 1 hour and then treated with 5-bromo-2-chloro-4,6-dimethylpyrimidine (1.2 g). After stirring for 2 hours at room temperature the mixture is diluted with ethyl acetate and washed with ice-water and brine. After drying (MgSO₄) the solvents are evaporated and the residue is chromatographed on silica gel (cyclohexane/ethyl acetate 70:30→50:50) to give the

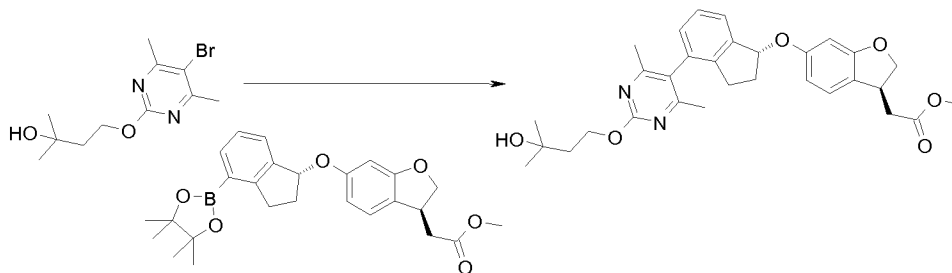
title compound. Yield: 1.1 g; LC (method 3): t_R = 0.79 min; Mass spectrum (ESI^+): m/z = 289 $[M+H]^+$.

Step 2: Methyl 2-((S)-6-((R)-6-fluoro-4-(2-(3-hydroxy-3-methylbutoxy)-4,6-
 5 dimethylpyrimidin-5-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-
yl)acetate

The title compound is prepared from methyl 2-((S)-6-((R)-6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate and 4-(5-bromo-4,6-dimethylpyrimidin-2-yloxy)-2-methylbutan-2-ol following a procedure analogous to that described in Step 8 of
 10 Intermediate 1. LC (method 3): t_R = 1.43 min; Mass spectrum (ESI^+): m/z = 551 $[M+H]^+$.

Intermediate 20

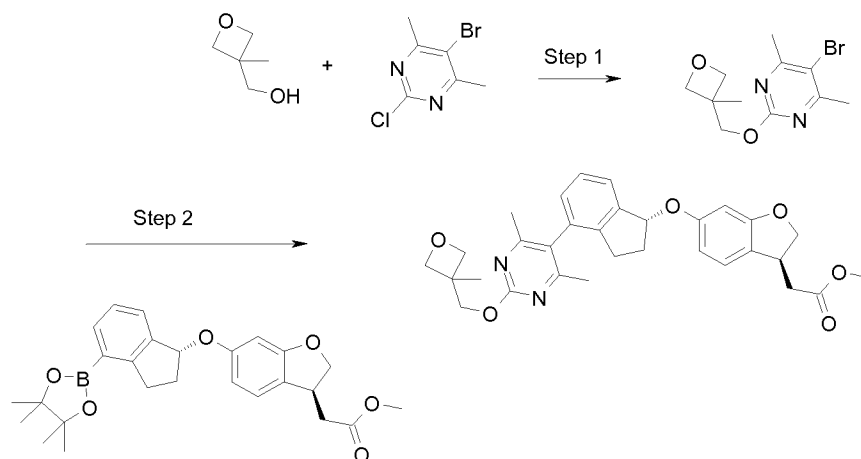
Methyl 2-((S)-6-((R)-4-(2-(3-hydroxy-3-methylbutoxy)-4,6-dimethylpyrimidin-5-yl)-2,3-
 15 dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate



The title compound is prepared from methyl 2-((S)-6-((R)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate and 4-(5-bromo-4,6-dimethylpyrimidin-2-yloxy)-2-methylbutan-2-ol
 20 following a procedure analogous to that described in Step 4 of Intermediate 10. The mixture is heated for 6 hours at 110°C. LC (method 3): t_R = 1.38 min; Mass spectrum (ESI^+): m/z = 533 $[M+H]^+$.

Intermediate 21

Methyl 2-((S)-6-((R)-4-(4,6-dimethyl-2-((3-methyloxetan-3-yl)methoxy)pyrimidin-5-yl)-
 25 2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate



Step 1: 5-Bromo-4,6-dimethyl-2-((3-methyloxetan-3-yl)methoxy)pyrimidine

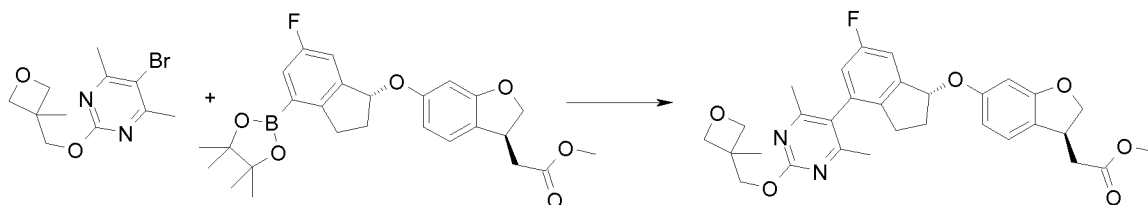
The title compound is prepared from (3-methyloxetan-3-yl)methanol and 5-bromo-2-chloro-4,6-dimethylpyrimidine following a procedure analogous to that described in Step 1 of Intermediate 19. LC (method 3): $t_R = 0.74$ min; Mass spectrum (ESI^+): $m/z = 287 [M+H]^+$.

Step 2: Methyl 2-((S)-6-((R)-4-(4,6-dimethyl-2-((3-methyloxetan-3-yl)methoxy)pyrimidin-5-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

The title compound is prepared from methyl 2-((S)-6-((R)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate and 5-bromo-4,6-dimethyl-2-((3-methyloxetan-3-yl)methoxy)pyrimidine following a procedure analogous to that described in Step 4 of Intermediate 10. The mixture is heated for 6 hours at $110^\circ C$. LC (method 3): $t_R = 1.41$ min; Mass spectrum (ESI^+): $m/z = 531 [M+H]^+$.

Intermediate 22

Methyl 2-((S)-6-((R)-4-(4,6-dimethyl-2-((3-methyloxetan-3-yl)methoxy)pyrimidin-5-yl)-6-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

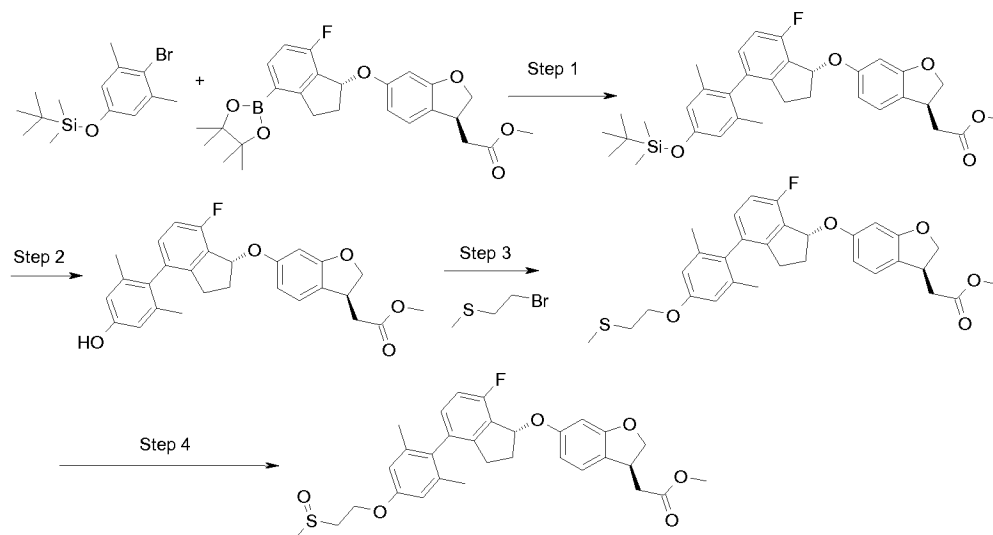


The title compound is prepared from methyl 2-((S)-6-((R)-6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate and 5-bromo-4,6-dimethyl-2-((3-methyloxetan-3-yl)methoxy)pyrimidine

dine following a procedure analogous to that described in Step 4 of Intermediate 10. The mixture is heated for 12 hours at 100°C. LC (method 3): $t_R = 1.44$ min; Mass spectrum (ESI⁺): $m/z = 549$ [M+H]⁺.

5 Intermediate 23

Methyl 2-((3S)-6-((1R)-4-(2,6-dimethyl-4-(2-(methylsulfinyl)ethoxy)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate



Step 1: Methyl 2-((S)-6-((R)-4-(4-(tert-butyldimethylsilyloxy)-2,6-dimethylphenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

The title compound is prepared from methyl 2-((S)-6-((R)-7-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate and (4-bromo-3,5-dimethylphenoxy)(tert-butyl)dimethylsilane following a procedure analogous to that described in Step 5 of Intermediate 12. LC (method 4): $t_R = 2.09$ min; Mass spectrum (ESI⁺): $m/z = 599$ [M+Na]⁺.

Step 2: Methyl 2-((S)-6-((R)-7-fluoro-4-(4-hydroxy-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

The title compound is prepared from methyl 2-((S)-6-((R)-4-(4-(tert-butyldimethylsilyloxy)-2,6-dimethylphenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate following a procedure analogous to that described in Step 4 of Intermediate 4. LC (method 4): $t_R = 1.79$ min; Mass spectrum (ESI⁺): $m/z = 485$ [M+ Na]⁺.

Step 3: Methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-(2-(methylthio)ethoxy)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

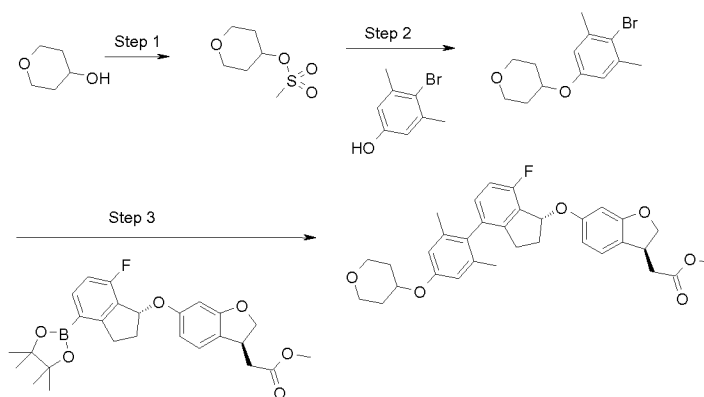
To a solution of methyl 2-((S)-6-((R)-7-fluoro-4-(4-hydroxy-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate (280 mg) and 2-(methylthio)-ethanol (54 μ L) in toluene (8 mL) are successively added 1,1'-(azodicarbonyl)-dipiperidine (240 mg) and tributylphosphine (240 μ L). The mixture is stirred for 12 hours at room temperature, partitioned between saturated aqueous NaHCO₃ solution and dichloromethane and stirred for 30 minutes. The phases are separated and the organic phase is dried (MgSO₄). The solvents are evaporated and the residue is chromatographed on silica gel (cyclohexane/ethyl acetate 90:10→70:30) to give the title compound. Yield: 235 mg; LC (method 4): t_R = 1.97 min; Mass spectrum (ESI⁺): m/z = 537 [M+H]⁺.

Step 4: Methyl 2-((3S)-6-((1R)-4-(2,6-dimethyl-4-(2-(methylsulfinyl)ethoxy)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

To a solution of methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-(2-(methylthio)ethoxy)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate (230 mg) in methanol (4 mL) and water (2 mL) is added potassium peroxomonosulfate (oxone[®]) (490 mg). The mixture is stirred for 1 hour at room temperature and then partitioned between dichloromethane and water. The organic phase is dried (MgSO₄) and concentrated to give the crude product, which is directly in the next step. Yield: 220 mg; LC (method 4): t_R = 1.79 min; Mass spectrum (ESI⁺): m/z = 553 [M+H]⁺.

Intermediate 24

Methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-(tetrahydro-2H-pyran-4-yloxy)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate



Step 1: Tetrahydro-2H-pyran-4-yl methanesulfonate

To a solution of tetrahydro-2H-pyran-4-ol (20 g) in tetrahydrofuran (150 mL) and triethylamine (28.5 mL) is slowly added methanesulfonyl chloride (15.5 mL), while

keeping the temperature below 30°C. The mixture is stirred for 12 hours at room temperature. The precipitate is filtered off and washed twice with tetrahydrofuran. The combined organic phases are concentrated and partitioned between ethyl acetate and water. The organic phase is dried (Na₂SO₄) and concentrated to give the title compound. Yield: 29.4 g; TLC: r_f = 0.36 (silicagel, petrole ether/ethyl acetate 1:1);
5 Mass spectrum (ESI⁺): m/z = 198 [M+NH₄]⁺.

Step 2: 4-(4-Bromo-3,5-dimethylphenoxy)tetrahydro-2H-pyran

To a solution of 4-bromo-3,5-dimethylphenol (3 g) in N-methyl-pyrrolidone (10 mL) is slowly added Cs₂CO₃ (9.7 g) and tetrahydro-2H-pyran-4-yl methanesulfonate (5.4 g).

10 The mixture is heated for 3 hours at 140°C. After cooling to room temperature the mixture is partitioned between saturated aqueous Na₂CO₃ solution and ethyl acetate. The aqueous phase is extracted with ethyl acetate and the combined organic phases are dried (MgSO₄). The solvents are evaporated and the residue is purified by HPLC on reversed phase to give the title compound. Yield: 1.2 g; LC (method 4):
15 t_R = 1.83 min.

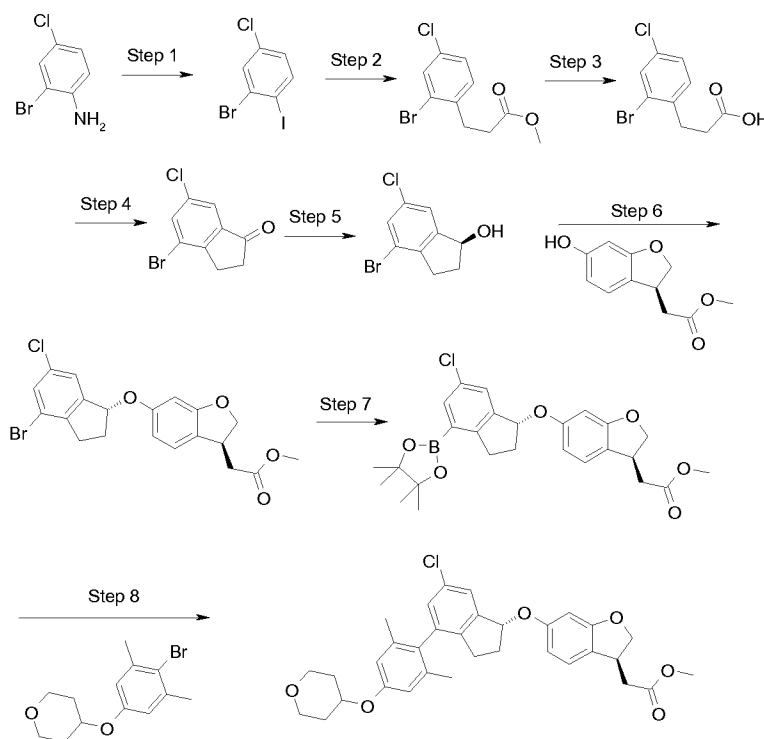
Step 3 Methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-(tetrahydro-2H-pyran-4-yloxy)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

The title compound is prepared from methyl 2-((S)-6-((R)-7-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-

20 dihydrobenzofuran-3-yl)acetate and 4-(4-bromo-3,5-dimethylphenoxy)tetrahydro-2H-pyran following a procedure analogous to that described in Step 5 of Intermediate 12. LC (method 4): t_R = 1.92 min; Mass spectrum (ESI⁺): m/z = 569 [M+Na]⁺.

Intermediate 25

25 Methyl 2-((S)-6-((R)-6-chloro-4-(2,6-dimethyl-4-(tetrahydro-2H-pyran-4-yloxy)phenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate



Step 1: 2-Bromo-4-chloro-1-iodobenzene

To a solution of 2-bromo-4-chloroaniline (15 g) in concentrated hydrochloric acid (85 mL) is added at -15°C a solution of NaNO_2 (5.5 g) in water (10 mL) and the mixture is stirred for 30 minutes. Then the mixture is added at room temperature to a solution of KI (109 g) in water (200 mL). After stirring for 18 hours the mixture is partitioned between dichloromethane and 10% aqueous $\text{Na}_2\text{S}_2\text{O}_3$ solution. The organic phase is washed with 10% aqueous $\text{Na}_2\text{S}_2\text{O}_3$ solution and brine and concentrated to give the title compound. Yield: 16.4 g; Mass spectrum (EI): $m/z = 316$ $[\text{M}]^+$.

Step 2: Methyl 3-(2-bromo-4-chlorophenyl)propanoate

The title compound is prepared from 2-bromo-4-chloro-1-iodobenzene following a procedure analogous to that described in Step 1 of Intermediate 17. LC (method 1): $t_R = 1.31$ min; Mass spectrum (ESI $^+$): $m/z = 277$ $[\text{M}+\text{H}]^+$.

Step 3: 3-(2-Bromo-4-chlorophenyl)propanoic acid

To a solution of methyl 3-(2-bromo-4-chlorophenyl)propanoate (5 g) in tetrahydrofuran (20 mL) and methanol (20 mL) is added 4 M aqueous NaOH solution (35 mL) and the mixture is heated to 50°C for 3 hours. The organic solvents are evaporated in vacuo the residue is diluted with water and washed three times with ethyl acetate. The aqueous phase is neutralized by addition of 4 M hydrochloric acid (10 mL) and extracted three times with ethyl acetate. The combined organic phases

are washed with brine and dried (Na_2SO_4). Evaporation of the solvents gives the title compound. Yield: 4.7 g; LC (method 1): $t_R = 1.21$ min.

Step 4: 4-Bromo-6-chloro-2,3-dihydro-1H-inden-1-one

Oxalylchloride (3.6 mL) is added dropwise to a solution of 3-(2-bromo-4-chlorophenyl)propanoic acid (4.4 g) in dichloromethane (40 mL). The mixture is stirred for 2 hours at 40°C and then treated with AlCl_3 (2.7 g). The mixture is heated to reflux for 1 hour, cooled to room temperature and partitioned between ethyl acetate and saturated aqueous NaHCO_3 solution. The aqueous phase is extracted twice with ethyl acetate and the combined organic phases are washed with brine. After drying (Na_2SO_4) the solvents are evaporated. The residue is chromatographed on silica gel (cyclohexane/ethyl acetate 95:5→90:10) to give the title compound. Yield: 3.7 g; LC (method 1): $t_R = 1.20$ min; Mass spectrum (ESI^+): $m/z = 245$ $[\text{M}+\text{H}]^+$.

Step 5: (S)-4-Bromo-6-chloro-2,3-dihydro-1H-inden-1-ol

The title compound is prepared from 4-bromo-6-fluoro-2,3-dihydro-1H-inden-1-one following a procedure analogous to that described in Step 1 of Intermediate 1. LC (method 1): $t_R = 1.20$ min; Mass spectrum (ESI^-): $m/z = 245$ $[\text{M}-\text{H}]^-$.

Step 6: Methyl 2-((S)-6-((R)-4-bromo-6-chloro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

The title compound is prepared from (S)-4-bromo-6-chloro-2,3-dihydro-1H-inden-1-ol and (S)-methyl 2-(6-hydroxy-2,3-dihydrobenzofuran-3-yl)acetate following a procedure analogous to that described in Step 3 of Intermediate 12. LC (method 1): $t_R = 1.52$ min; Mass spectrum (ESI^+): $m/z = 437$ $[\text{M}+\text{H}]^+$.

Step 7: Methyl 2-((S)-6-((R)-6-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

The title compound is prepared from methyl 2-((S)-6-((R)-4-bromo-6-chloro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate following a procedure analogous to that described in Step 7 of Intermediate 1. LC (method 7): $t_R = 1.31$ min; Mass spectrum (ESI^+): $m/z = 485$ $[\text{M}+\text{H}]^+$.

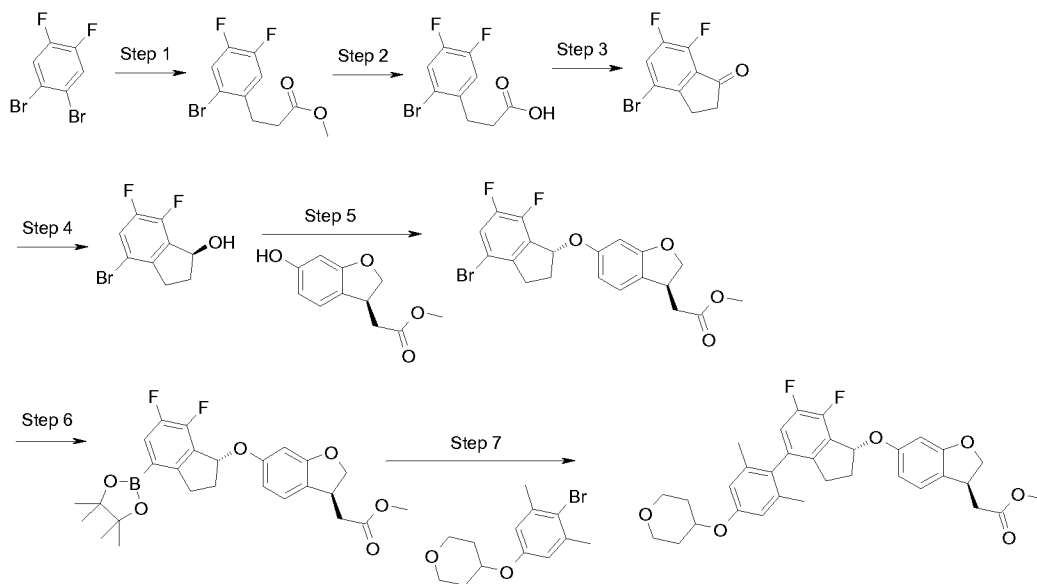
Step 8: Methyl 2-((S)-6-((R)-6-chloro-4-(2,6-dimethyl-4-(tetrahydro-2H-pyran-4-

yloxy)phenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate
In a microwave vial methyl 2-((S)-6-((R)-6-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate (300 mg), 4-(4-bromo-3,5-dimethylphenoxy)tetrahydro-2H-pyran (194 mg), K_3PO_4 (394 mg) are suspended in toluene (3 mL) and water (0.5 mL) and purged for 10

minutes with argon. Dicyclohexyl(2',6'-dimethoxybiphenyl-2-yl)phosphine (S-Phos) (41 mg) and tris-(dibenzylidenacetone)-dipalladium-(0) (26 mg) are added, the vial is sealed and the mixture is stirred at 100°C for 12 hours. After cooling to room temperature the mixture is partitioned between ethyl acetate and saturated aqueous NH₄Cl solution. The organic phase is dried (MgSO₄) and concentrated. The residue is chromatographed on silica gel (cyclohexane/ethyl acetate 90:10→70:30) to give the title compound. Yield: 236 mg; LC (method 8): *t_R* = 1.00 min; Mass spectrum (ESI⁺): *m/z* = 563 [M+Na]⁺.

10 Intermediate 26

Methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-(tetrahydro-2H-pyran-4-yloxy)phenyl)-6,7-difluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate



Step 1: Methyl 3-(2-bromo-4,5-difluorophenyl)propanoate

15 The title compound is prepared from 1,2-dibromo-4,5-difluorobenzene following a procedure analogous to that described in Step 1 of Intermediate 17. The mixture is heated for 12 hours to 110°C. LC (method 4): *t_R* = 1.69 min.

Step 2: 3-(2-Bromo-4,5-difluorophenyl)propanoic acid

20 The title compound is prepared from methyl 3-(2-bromo-4,5-difluorophenyl)propanoate following a procedure analogous to that described in Step 2 of Intermediate 17. The mixture is stirred for 24 hours at room temperature. LC (method 4): *t_R* = 1.56 min; Mass spectrum (ESI⁻): *m/z* = 263 [M-H]⁻.

Step 3: 4-Bromo-6,7-difluoro-2,3-dihydro-1H-inden-1-one

The title compound is prepared from 3-(2-bromo-4,5-difluorophenyl)propanoic acid following a procedure analogous to that described in Step 4 of Intermediate 25. The mixture is heated for 1 hour to reflux and stirred for 12 hours at room temperature. LC (method 4): $t_R = 1.44$ min; Mass spectrum (ESI⁺): $m/z = 247$ [M+H]⁺.

5 Step 4: (S)-4-Bromo-6,7-difluoro-2,3-dihydro-1H-inden-1-ol

The title compound is prepared from 4-bromo-6,7-difluoro-2,3-dihydro-1H-inden-1-one following a procedure analogous to that described in Step 1 of Intermediate 1. LC (method 4): $t_R = 1.51$ min.

10 Step 5: Methyl 2-((S)-6-((R)-4-bromo-6,7-difluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

The title compound is prepared from (S)-4-bromo-6,7-difluoro-2,3-dihydro-1H-inden-1-ol and (S)-methyl 2-(6-hydroxy-2,3-dihydrobenzofuran-3-yl)acetate following a procedure analogous to that described in Step 3 of Intermediate 12. LC (method 4): $t_R = 1.98$ min; Mass spectrum (ESI⁺): $m/z = 439$ [M+H]⁺.

15 Step 6: Methyl 2-((S)-6-((R)-6,7-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

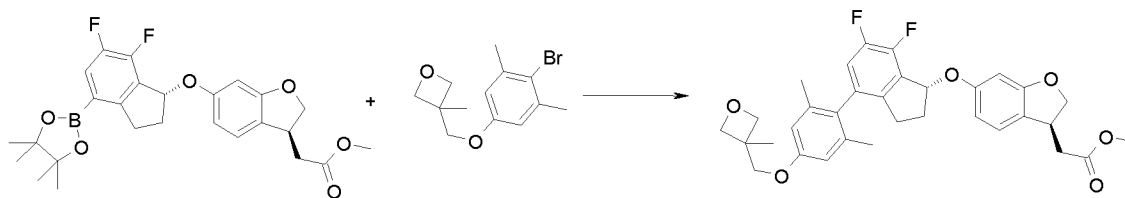
20 The title compound is prepared from methyl 2-((S)-6-((R)-4-bromo-6,7-difluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate following a procedure analogous to that described in Step 7 of Intermediate 1. LC (method 4): $t_R = 1.96$ min; Mass spectrum (ESI⁺): $m/z = 487$ [M+H]⁺.

Step 7: Methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-(tetrahydro-2H-pyran-4-yloxy)phenyl)-6,7-difluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

25 The title compound is prepared from methyl 2-((S)-6-((R)-6,7-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate and 4-(4-bromo-3,5-dimethylphenoxy)tetrahydro-2H-pyran following a procedure analogous to that described in Step 5 of Intermediate 12. LC (method 4): $t_R = 1.94$ min; Mass spectrum (ESI⁺): $m/z = 587$ [M+H]⁺.

Intermediate 27

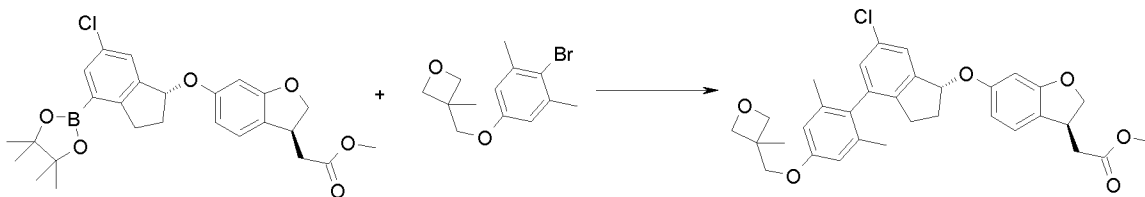
30 Methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-((3-methyloxetan-3-yl)methoxy)phenyl)-6,7-difluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate



The title compound is prepared from methyl 2-((S)-6-((R)-6,7-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate and 3-((4-bromo-3,5-dimethylphenoxy)methyl)-3-methyloxetane following a procedure analogous to that described in Step 5 of Intermediate 12. LC (method 4): $t_R = 1.94$ min; Mass spectrum (ESI^+): $m/z = 587$ $[M+H]^+$.

Intermediate 28

10 Methyl 2-((S)-6-((R)-6-chloro-4-(2,6-dimethyl-4-((3-methyloxetan-3-yl)methoxy)phenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

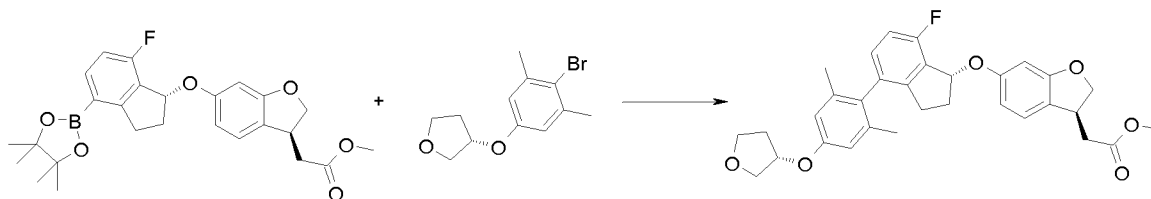


The title compound is prepared from methyl 2-((S)-6-((R)-6-chloro-4-(2,6-dimethyl-4-((3-methyloxetan-3-yl)methoxy)phenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate and 3-((4-bromo-3,5-dimethylphenoxy)methyl)-3-methyloxetane following a procedure analogous to that described in Step 8 of Intermediate 25. The mixture is heated for 4 hours to 100°C. LC (method 8): $t_R = 1.00$ min; Mass spectrum (ESI^+): $m/z = 563$ $[M+H]^+$.

20

Intermediate 29

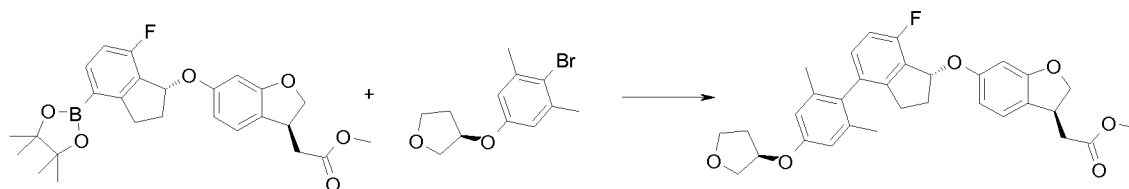
Methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-((S)-tetrahydrofuran-3-yloxy)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate



The title compound is prepared from methyl 2-((S)-6-((R)-7-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate and (S)-3-(4-bromo-3,5-dimethylphenoxy)tetrahydrofuran following a procedure analogous to that described in Step 5 of Intermediate 12. LC (method 4): t_R = 1.89 min; Mass spectrum (ESI⁺): m/z = 555 [M+Na]⁺.

Intermediate 30

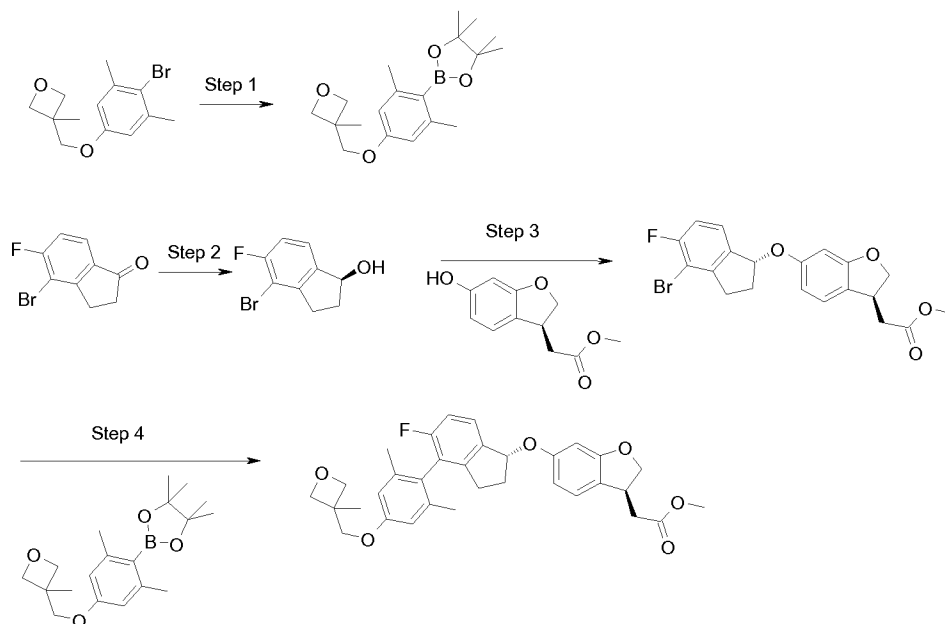
Methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-((R)-tetrahydrofuran-3-yloxy)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate



The title compound is prepared from methyl 2-((S)-6-((R)-7-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate and (R)-3-(4-bromo-3,5-dimethylphenoxy)tetrahydrofuran following a procedure analogous to that described in Step 5 of Intermediate 12. LC (method 4): t_R = 1.89 min; Mass spectrum (ESI⁺): m/z = 555 [M+Na]⁺.

Intermediate 31

Methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-((3-methyloxetan-3-yl)methoxy)phenyl)-5-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate



Step 1: 2-(2,6-Dimethyl-4-((3-methyloxetan-3-yl)methoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

The title compound is prepared from 3-((4-bromo-3,5-dimethylphenoxy)methyl)-3-methyloxetane following a procedure analogous to that described in Step 7 of Intermediate 1. The mixture is heated for 12 hours to 100°C. Mass spectrum (ESI⁺): m/z = 333 [M+H]⁺.

Step 2: (S)-4-Bromo-5-fluoro-2,3-dihydro-1H-inden-1-ol

The title compound is prepared from 4-bromo-5-fluoro-2,3-dihydro-1H-inden-1-one following a procedure analogous to that described in Step 1 of Intermediate 1. LC (method 4): t_R = 1.48 min.

Step 3: Methyl 2-((S)-6-((R)-4-bromo-5-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

The title compound is prepared from (S)-4-bromo-6,7-difluoro-2,3-dihydro-1H-inden-1-ol and (S)-methyl 2-(6-hydroxy-2,3-dihydrobenzofuran-3-yl)acetate following a procedure analogous to that described in Step 3 of Intermediate 12. LC (method 4): t_R = 1.89 min; Mass spectrum (ESI⁺): m/z = 421 [M+H]⁺.

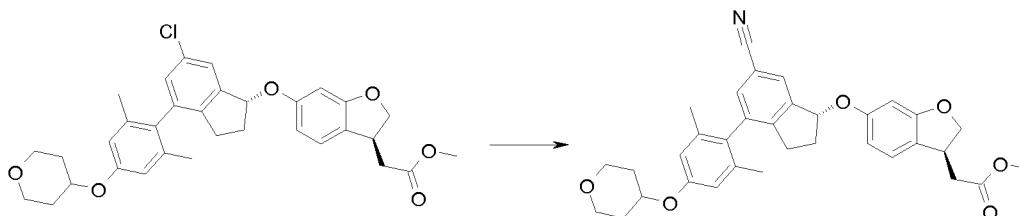
Step 4: Methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-((3-methyloxetan-3-yl)methoxy)phenyl)-5-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

The title compound is prepared from methyl 2-((S)-6-((R)-4-bromo-5-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate and 2-(2,6-dimethyl-4-((3-methyloxetan-3-yl)methoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

following a procedure analogous to that described in Step 5 of Intermediate 12. The reaction is run in the absence of water for 12 hours at 100°C. LC (method 7): t_R = 1.22 min; Mass spectrum (ESI⁺): m/z = 547 [M+H]⁺.

5 Intermediate 32

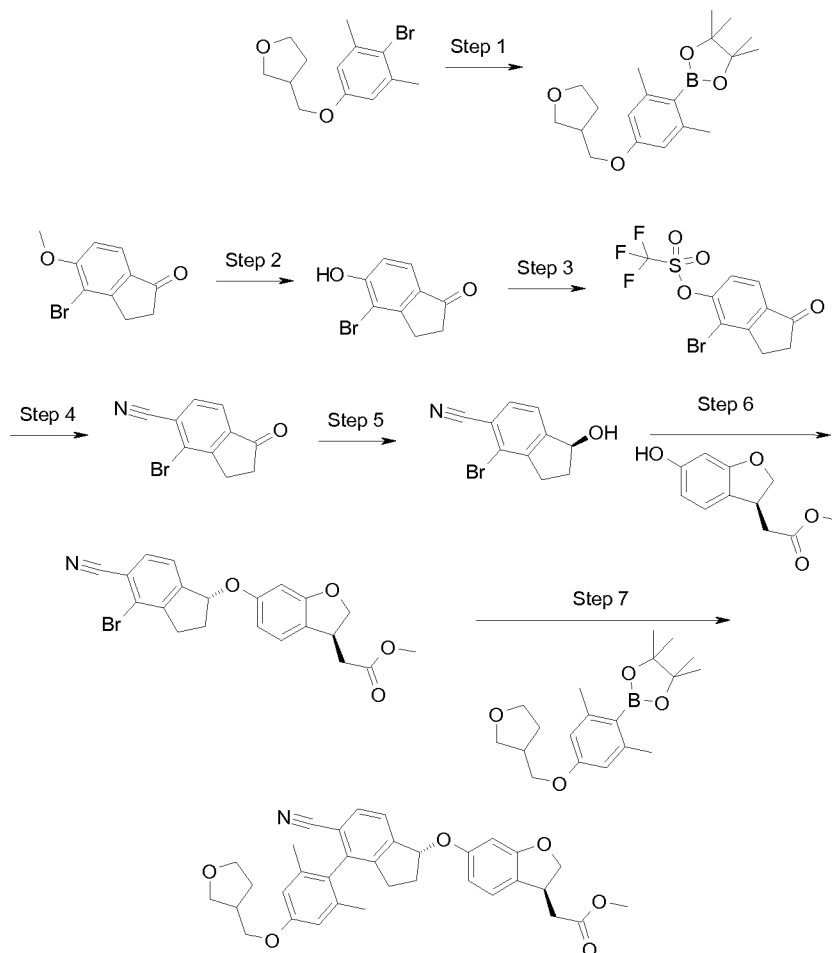
Methyl 2-((S)-6-((R)-6-cyano-4-(2,6-dimethyl-4-(tetrahydro-2H-pyran-4-yloxy)phenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate



In a microwave vial NaCN (16 mg) is added to a solution of methyl 2-((S)-6-((R)-6-chloro-4-(2,6-dimethyl-4-(tetrahydro-2H-pyran-4-yloxy)phenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate (90 mg) in N-methyl-2-pyrrolidinon (NMP) (2 mL) and the mixture is purged for 5 minutes with argon. NiBr₂ (35 mg) is added, the vial is sealed and the mixture is heated for 30 minutes to 180°C. The mixture is partitioned between water and ethyl acetate. The aqueous phase is extracted twice with ethyl acetate. The combined organic phases are washed with brine, dried (Na₂SO₄) and concentrated. The residue is chromatographed on silica gel (cyclohexane/ethyl acetate 90:10→70:30) to give the title compound. Yield: 34 mg; LC (method 7): t_R = 0.79 min.

20 Intermediate 33

Methyl 2-((3S)-6-((1R)-5-cyano-4-(2,6-dimethyl-4-((tetrahydrofuran-3-yl)methoxy)phenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate



Step 1: 2-(2,6-Dimethyl-4-((tetrahydrofuran-3-yl)methoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

The title compound is prepared from 3-((4-bromo-3,5-dimethylphenoxy)methyl)tetrahydrofuran following a procedure analogous to that described in Step 7 of Intermediate 1. The mixture is heated for 48 hours to 120°C. LC (method 1): $t_R = 1.48$ min; Mass spectrum (ESI⁺): $m/z = 333$ [M+H]⁺.

Step 2: 4-Bromo-5-hydroxy-2,3-dihydro-1H-inden-1-one

In a microwave vial sodium methanthiolate (2 g) is added to a solution of 4-bromo-5-methoxy-2,3-dihydro-1H-inden-1-one in N,N-dimethylformamide (10 mL). The vial is sealed and the mixture is heated for 2 hours to 130°C. The mixture is partitioned between ethyl acetate and 1 N aqueous HCl solution. The aqueous phase is extracted with ethyl acetate and the combined organic phases are washed with brine and dried (MgSO₄). The solvents are evaporated and the residue is triturated with diethylether. The precipitate is filtered off and dried in vacuo to give the title compound. Yield: 1.15 g; LC (method 1): $t_R = 0.84$ min; Mass spectrum (ESI⁺): $m/z = 227$ [M+H]⁺.

Step 3: 4-Bromo-1-oxo-2,3-dihydro-1H-inden-5-yl trifluoromethanesulfonate

4-Bromo-5-hydroxy-2,3-dihydro-1H-inden-1-one (5 g) and 2,6-dimethylpyridine (5.1 mL) are dissolved in dichloromethane (50 mL) cooled to 0°C and treated dropwise with trifluoromethanesulfonic anhydride (4 mL). The mixture is stirred for 2 hours at room temperature and then partitioned between saturated aqueous NH₄Cl solution and dichloromethane. The organic phase is washed with brine, dried (MgSO₄) and concentrated. The residue is chromatographed on silica gel (cyclohexane/ethyl acetate 99:1→50:50) to give the title compound. Yield: 5.9 g; LC (method 7): t_R = 1.08 min; Mass spectrum (ESI⁺): m/z = 359 [M+H]⁺.

Step 4: 4-Bromo-1-oxo-2,3-dihydro-1H-indene-5-carbonitrile

Zn(CN)₂ (600 mg) and 1,1'-bis(diphenylphosphino)-ferrocene (920 mg) are added to a solution of 4-bromo-1-oxo-2,3-dihydro-1H-inden-5-yl trifluoromethanesulfonate (5.9 g) in N,N-dimethylformamide (30 mL) and the mixture is purged for 5 minutes with argon. Tris-(dibenzylidenacetone)-dipalladium-(0) (760 mg) is added and the mixture is heated for 1 hour to 70°C. The mixture is diluted with ethyl acetate and washed with water and brine. The organic phase is dried (MgSO₄) and concentrated. The residue is chromatographed on silica gel (cyclohexane/ethyl acetate 99:1→50:50) to give the title compound. Yield: 1.5 g; LC (method 7): t_R = 0.88 min; Mass spectrum (ESI⁻): m/z = 234 [M-H]⁻.

Step 5: (S)-4-Bromo-1-hydroxy-2,3-dihydro-1H-indene-5-carbonitrile

The title compound is prepared from 4-bromo-1-oxo-2,3-dihydro-1H-indene-5-carbonitrile following a procedure analogous to that described in Step 1 of Intermediate 1. LC (method 7): t_R = 0.84 min; Mass spectrum (ESI⁺): m/z = 260 [M+Na]⁺.

Step 6: Methyl 2-((S)-6-((R)-4-bromo-5-cyano-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

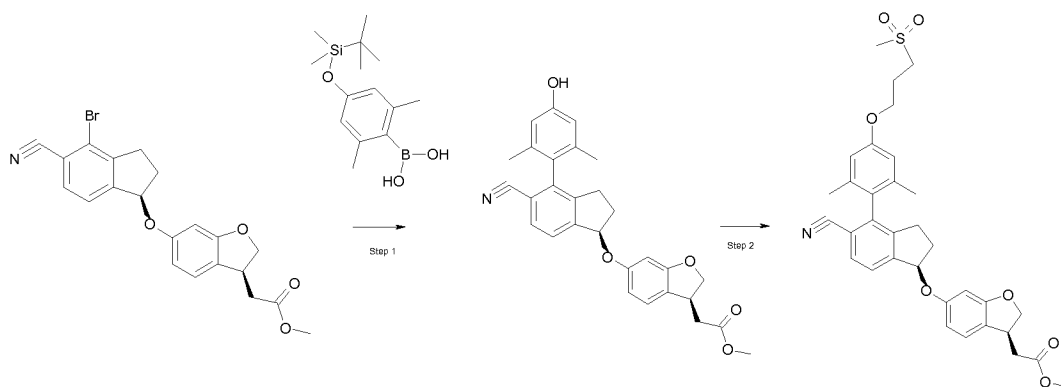
The title compound is prepared from (S)-4-bromo-1-hydroxy-2,3-dihydro-1H-indene-5-carbonitrile and (S)-methyl 2-(6-hydroxy-2,3-dihydrobenzofuran-3-yl)acetate following a procedure analogous to that described in Step 3 of Intermediate 12. LC (method 7): t_R = 1.15 min; Mass spectrum (ESI⁺): m/z = 428 [M+H]⁺.

Step 7: Methyl 2-((3S)-6-((1R)-5-cyano-4-(2,6-dimethyl-4-((tetrahydrofuran-3-yl)methoxy)phenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

The title compound is prepared from methyl 2-((S)-6-((R)-4-bromo-5-cyano-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate and 2-(2,6-dimethyl-4-((tetrahydrofuran-3-yl)methoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane following a procedure analogous to that described in Step 8 of Intermediate 25. The reaction is run for 48 hours at 100°C. LC (method 8): $t_R = 0.73$ min; Mass spectrum (ESI⁺): $m/z = 554$ [M+H]⁺.

Intermediate 33a

((S)-6-((R)-5-Cyano-4-[4-(3-methanesulfonyl-propoxy)-2,6-dimethyl-phenyl]-inden-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester



Step 1: ((S)-6-[(R)-5-Cyano-4-(4-hydroxy-2,6-dimethyl-phenyl)-inden-1-yloxy]-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester

Methyl 2-((S)-6-((R)-4-bromo-5-cyano-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate (1.7 g), 4-[[tert-butyl(dimethyl)silyl]oxy]-2,6-dimethylphenylboronic acid (EP1726580A1,2006) (2.22 g), 2-dicyclohexylphosphino-2'-(N,N-dimethylamino)biphenyl (85 mg), tris(dibenzylideneacetone)dipalladium(0) (36 mg) and sodium carbonate (120 mg) are stirred in toluene (40 mL) and water (5 mL) at 110 °C for 12 h. The reaction mixture is concentrated under vacuum and the crude product obtained is purified by flash chromatography (cyclohexane/ethyl acetate 100:0→50:50) to give the title compound. Yield: 450 mg.

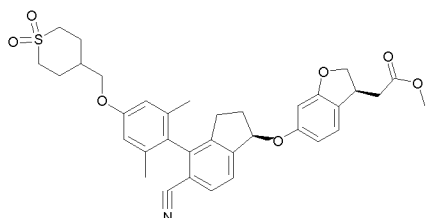
Step 2: ((S)-6-[(R)-5-Cyano-4-[4-(3-methanesulfonyl-propoxy)-2,6-dimethyl-phenyl]-inden-1-yloxy]-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester

((S)-6-[(R)-5-Cyano-4-(4-hydroxy-2,6-dimethyl-phenyl)-inden-1-yloxy]-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester (112 mg), methanesulfonic acid 3-methanesulfonyl-propyl ester (Moltzen, Ejner K et al. Journal of Medicinal Chemistry, 1995, vol. 38, # 11 p. 2009 – 2017) (73.5 mg)

and cesium carbonate (150 mg) are stirred in 2 mL of N,N-dimethylformamide for 3 h. The reaction mixture is concentrated under vacuum, the residue obtained is dissolved in dichloromethane and the organic phase is washed with water, dried over sodium sulfate and concentrated under vacuum. The residue is purified by flash chromatography (cyclohexane/ethyl acetate 100:0→70:30) to give the title compound. Yield: 45 mg.

Intermediate 33b

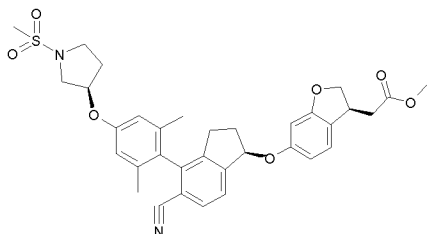
((S)-6-((R)-5-Cyano-4-[4-(1,1-dioxo-hexahydro-1-thiopyran-4-ylmethoxy)-2,6-dimethyl-phenyl]-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester



The title compound is prepared in analogy to Step 2 of Intermediate 33a starting from intermediate 49ga.

Intermediate 33c

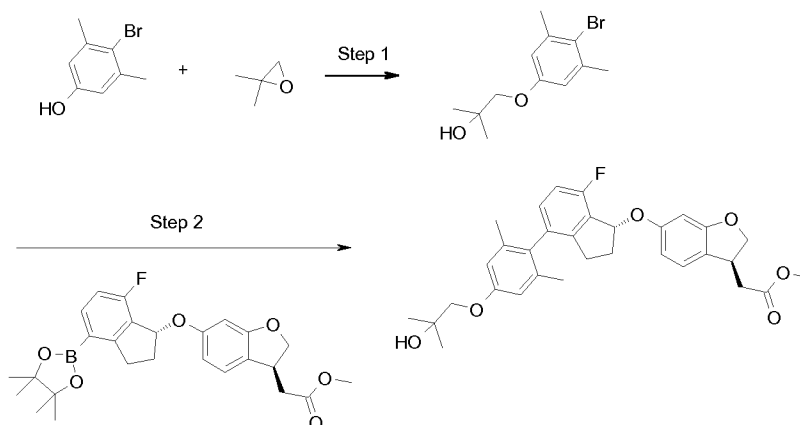
((S)-6-((R)-5-Cyano-4-[4-((R)-1-methanesulfonyl-pyrrolidin-3-yloxy)-2,6-dimethyl-phenyl]-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester



The title compound is prepared in analogy to Step 2 of Intermediate 33a starting from intermediate 49ea.

Intermediate 34

Methyl 2-((S)-6-((R)-7-fluoro-4-(4-(2-hydroxy-2-methylpropoxy)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate



Step 1: 1-(4-Bromo-3,5-dimethylphenoxy)-2-methylpropan-2-ol

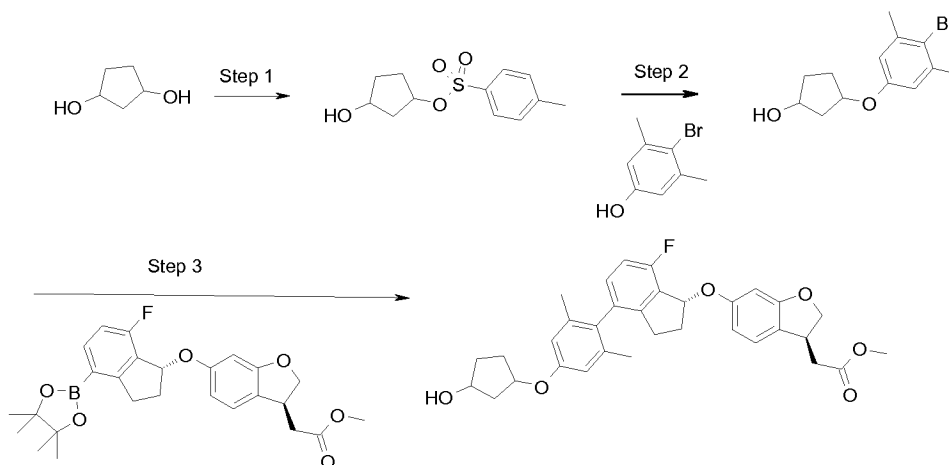
In a microwave vial 2,2-dimethyloxirane (2.2 g) is added to a suspension of 4-bromo-3,5-dimethylphenol and K_2CO_3 (11 g) in N,N-dimethylformamide (6 mL). The vial is sealed and the mixture is heated for 48 hours to 120°C. After cooling to room temperature the mixture is partitioned between saturated aqueous Na_2CO_3 solution and ethyl acetate. The aqueous phase is extracted twice with ethyl acetate and the combined organic phases are dried ($MgSO_4$) and concentrated. The residue is chromatographed on silica gel (cyclohexane/ethyl acetate 100:0→50:50) to give the title compound. Yield: 2.9 g; LC (method 4): t_R = 1.76 min; Mass spectrum (ESI^+): m/z = 273 $[M+H]^+$.

Step 2: Methyl 2-((S)-6-((R)-7-fluoro-4-(4-(2-hydroxy-2-methylpropoxy))-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

The title compound is prepared from methyl 2-((S)-6-((R)-7-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate and 1-(4-bromo-3,5-dimethylphenoxy)-2-methylpropan-2-ol following a procedure analogous to that described in Step 5 of Intermediate 12. LC (method 8): t_R = 0.77 min; Mass spectrum (ESI^+): m/z = 535 $[M+H]^+$.

Intermediate 35

Methyl 2-((3S)-6-((1R)-7-fluoro-4-(4-(3-hydroxycyclopentyloxy))-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate



Step 1: 3-Hydroxycyclopentyl 4-methylbenzenesulfonate

The title compound is prepared from cyclopentane-1,3-diol following a procedure analogous to that described in Step 4 of Intermediate 1. The product is purified by chromatography on silica gel (petrole ether/ethyl acetate 90:10→10:90) to give the title compound. LC (method 7): $t_R = 0.86$ min; Mass spectrum (ESI⁺): $m/z = 257$ [M+H]⁺.

Step 2: 3-(4-Bromo-3,5-dimethylphenoxy)cyclopentanol

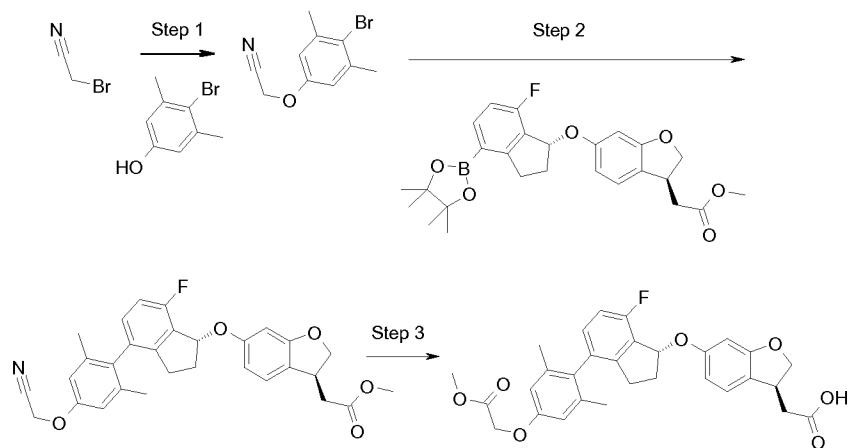
The title compound is prepared from 3-hydroxycyclopentyl 4-methylbenzenesulfonate and 4-bromo-3,5-dimethylphenol following a procedure analogous to that described in Step 5 of Intermediate 1. LC (method 7): $t_R = 1.07$ min; Mass spectrum (ESI⁺): $m/z = 285$ [M+H]⁺.

Step 3: Methyl 2-((3S)-6-((1R)-7-fluoro-4-(4-(3-hydroxycyclopentyl)oxy)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

The title compound is prepared from methyl 2-((S)-6-((R)-7-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate and 3-(4-bromo-3,5-dimethylphenoxy)cyclopentanol following a procedure analogous to that described in Step 5 of Intermediate 12. Mass spectrum (ESI⁺): $m/z = 547$ [M+H]⁺.

Intermediate 36

2-((S)-6-((R)-7-Fluoro-4-(4-(2-methoxy-2-oxoethoxy)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



Step 1: 2-(4-Bromo-3,5-dimethylphenoxy)acetonitrile

To a solution of 4-bromo-3,5-dimethylphenol (500 mg) and Cs_2CO_3 (1.3 g) in N,N-dimethylformamide (5 mL) is added 2-bromoacetonitrile (290 μL) and the mixture is stirred for 2 hours at 35°C . The mixture is poured on water and stirred for 15 minutes. The precipitate is filtered off and dried to give the title compound. Yield: 535 mg; Mass spectrum (EI): $m/z = 239$ $[\text{M}]^+$.

Step 2: Methyl 2-((S)-6-((R)-4-(4-(cyanomethoxy)-2,6-dimethylphenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

The title compound is prepared from methyl 2-((S)-6-((R)-7-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate and 2-(4-bromo-3,5-dimethylphenoxy)acetonitrile following a procedure analogous to that described in Step 5 of Intermediate 12. LC (method 8): $t_R = 0.71$ min; Mass spectrum (ESI^+): $m/z = 502$ $[\text{M}+\text{H}]^+$.

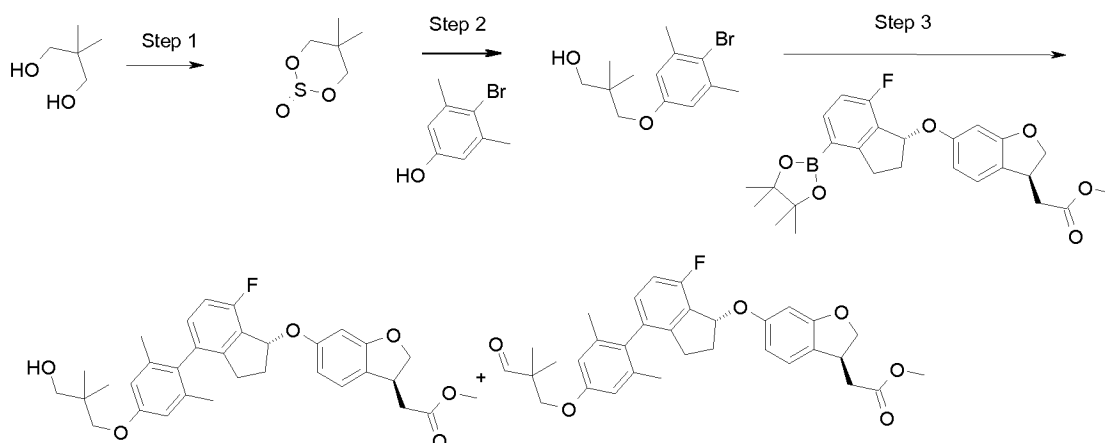
Step 3: 2-((S)-6-((R)-7-Fluoro-4-(4-(2-methoxy-2-oxoethoxy)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid

A 1 M aqueous NaOH solution (400 μL) is added to a solution of methyl 2-((S)-6-((R)-4-(4-(cyanomethoxy)-2,6-dimethylphenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate (120 mg) in methanol (4 mL). The mixture is stirred for 12 hours at room temperature. Methanol is evaporated off in vacuo and the residue is diluted with water. 1 M hydrochloric acid (400 μL) is added and the aqueous phase is extracted twice with dichloromethane. The combined organic phases are dried (MgSO_4) and concentrated. The residue is chromatographed on silica gel (petrole ether/ethyl acetate 60:40 $\rightarrow$ 0:100). The product thus obtained is

crystallized from n-hexane to give the title compound. Yield: 75 mg; LC (method 7): t_R = 0.99 min; Mass spectrum (ESI⁺): m/z = 521 [M+H]⁺.

Intermediate 37

5 Methyl 2-((S)-6-((R)-7-fluoro-4-(4-(3-hydroxy-2,2-dimethylpropoxy)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate



Step 1: 5,5-Dimethyl-[1,3,2]dioxathiane 2-oxide

Thionylchloride (735 mL) is added to a solution of 2,2-dimethylpropane-1,3-diol (1 g) in dichloromethane (10 mL) chilled in an ice bath. The mixture is heated to 40°C for 3 hours and partitioned between saturated aqueous NaHCO₃ solution and dichloromethane. The organic phase is washed with brine, dried (MgSO₄) and concentrated to give the title compound. Yield: 535 mg; TLC: r_f = 0.65 (silicagel, cyclohexane/ethyl acetate 3:1).

15 Step 2: 3-(4-Bromo-3,5-dimethylphenoxy)-2,2-dimethylpropan-1-ol

In a microwave vial Cs₂CO₃ (5.4 g) is added to a solution of 5,5-dimethyl-[1,3,2]dioxathiane 2-oxide (500 mg) and 4-bromo-3,5-dimethylphenol (670 mg) in N,N-dimethylformamide (5 mL). The vial is sealed and the mixture is heated to 120°C for 12 hours. The mixture is partitioned between ethyl acetate and water. The organic phase is washed three times with 2 M aqueous NaOH and with brine. After drying (MgSO₄) and concentration the residue is chromatographed on silica gel (cyclohexane/ethyl acetate 99:1→50:50) to give the title compound. Yield: 372 mg; LC (method 7): t_R = 1.17 min; Mass spectrum (ESI⁺): m/z = 287 [M+H]⁺.

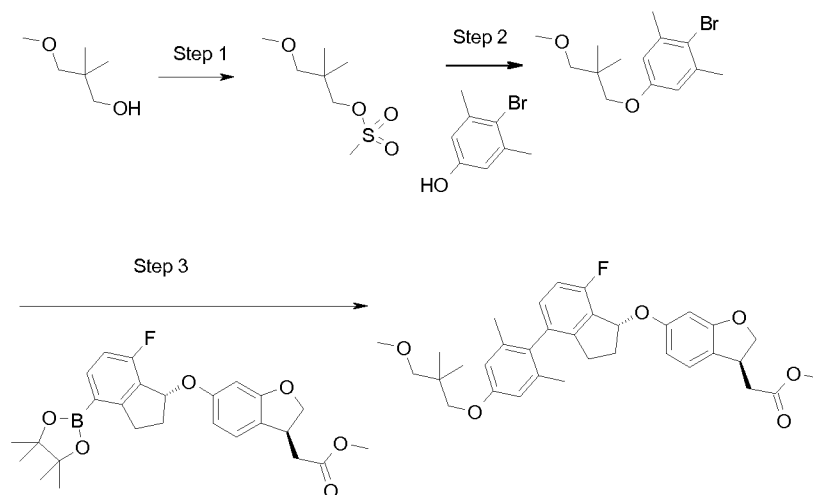
25 Step 3: Methyl 2-((S)-6-((R)-7-fluoro-4-(4-(3-hydroxy-2,2-dimethylpropoxy)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

In a microwave vial methyl 2-((S)-6-((R)-7-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate (250 mg), 3-(4-bromo-3,5-dimethylphenoxy)-2,2-dimethylpropan-1-ol (226 mg), K_3PO_4 (230 mg) are suspended in toluene (2 mL) and water (200 μ L) and purged for 10 minutes with argon. Palladium-(II)-acetate (12 mg) and dicyclohexyl(2',6'-dimethoxybiphenyl-2-yl)phosphine (S-Phos) (44 mg) are added, the vial is sealed and the mixture is stirred at 100°C for 12 hours. After cooling to room temperature the mixture is partitioned between ethyl acetate and water. The organic phase is washed with brine, dried ($MgSO_4$) and concentrated. The residue is chromatographed on silica gel (cyclohexane/ethyl acetate 99:1→60:40) to give the title compound. Yield: 99 mg; LC (method 8): t_R = 0.87 min; Mass spectrum (ESI^+): m/z = 549 $[M+H]^+$.

Additionally methyl 2-((S)-6-((R)-4-(4-(2,2-dimethyl-3-oxopropoxy)-2,6-dimethylphenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate is isolated. Yield: 83 mg; LC (method 8): t_R = 0.95 min; Mass spectrum (ESI^+): m/z = 547 $[M+H]^+$.

Intermediate 38

Methyl 2-((S)-6-((R)-7-fluoro-4-(4-(3-methoxy-2,2-dimethylpropoxy)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate



Step 1: 3-Methoxy-2,2-dimethylpropyl methanesulfonate

Methanesulfonyl chloride (330 mL) is added dropwise to a solution of 3-methoxy-2,2-dimethylpropan-1-ol (250 mg) and N,N-diisopropylethylamine (1.1 mL) in dichloromethane (3 mL) chilled in an ice bath. The mixture is stirred at room

temperature for 12 hours and partitioned between saturated aqueous NaHCO₃ solution and dichloromethane. The organic phase is washed twice with 1 N hydrochloric acid, saturated aqueous NaHCO₃ solution and brine. Then the organic phase is dried (MgSO₄) and concentrated to give the title compound. Yield: 407 mg;

5 TLC: r_f = 0.75 (silicagel, cyclohexane/ethyl acetate 3:1).

Step 2: 2-Bromo-5-(3-methoxy-2,2-dimethylpropoxy)-1,3-dimethylbenzene

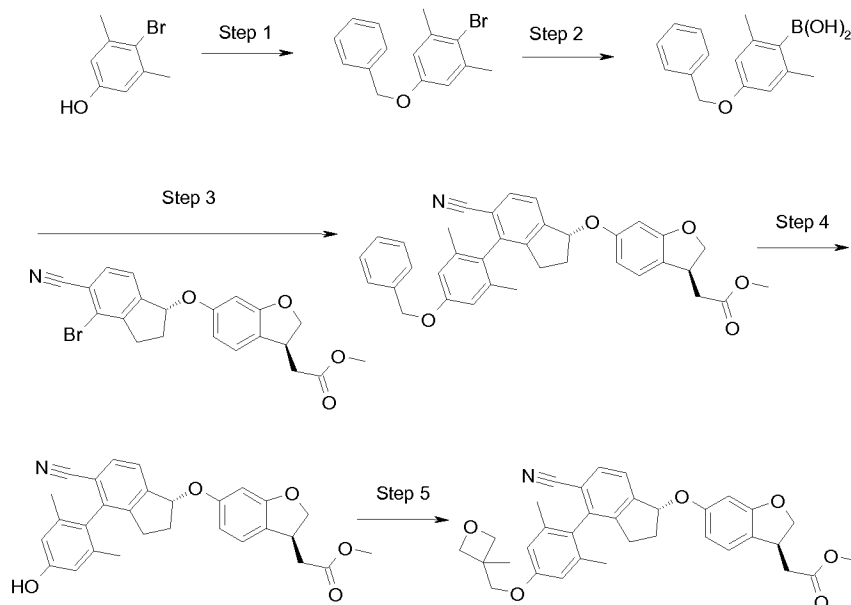
In a microwave vial Cs₂CO₃ (3.3 g) and KI (50 mg) are added to a solution of 3-methoxy-2,2-dimethylpropyl methanesulfonate (407 mg) and 4-bromo-3,5-dimethylphenol (415 mg) in N,N-dimethylformamide (5 mL). The vial is sealed and
10 the mixture is heated to 120°C for 12 hours. The mixture is partitioned between ethyl acetate and water. The organic phase is washed with water and brine and is dried (MgSO₄). The solvents are evaporated and the residue is chromatographed on silica gel (cyclohexane/ethyl acetate 99:1→80:20). The product thus obtained is purified by HPLC on reversed phase to give the title compound. Yield: 171 mg; LC (method 8):
15 t_R = 1.02 min; Mass spectrum (ESI⁺): m/z = 301 [M+H]⁺.

Step 3: Methyl 2-((S)-6-((R)-7-fluoro-4-(4-(3-methoxy-2,2-dimethylpropoxy)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

The title compound is prepared from methyl 2-((S)-6-((R)-7-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-
20 dihydrobenzofuran-3-yl)acetate and 2-bromo-5-(3-methoxy-2,2-dimethylpropoxy)-1,3-dimethylbenzene following a procedure analogous to that described in Step 5 of Intermediate 12. LC (method 8): t_R = 1.12 min; Mass spectrum (ESI⁺): m/z = 563 [M+H]⁺.

25 **Intermediate 39**

Methyl 2-((S)-6-((R)-5-cyano-4-(2,6-dimethyl-4-((3-methyloxetan-3-yl)methoxy)phenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate



Step 1: 5-(Benzyloxy)-2-bromo-1,3-dimethylbenzene

K_2CO_3 (1,75 g) is added to a solution of 4-bromo-3,5-dimethylphenol (2 g) and benzylbromide (1.43 mL) in N,N-dimethylformamide (3 mL) and the mixture is heated to 80°C for 12 hours. The mixture is diluted with ethyl acetate, washed with water and dried ($MgSO_4$). The solvents are evaporated and the residue is chromatographed on silica gel (petrole ether/ethyl acetate 98:2→80:20) to give the title compound. Yield: 2.38 g; TLC: r_f = 0.50 (silicagel, petrole ether/ethyl acetate 9:1); Mass spectrum (ESI^+): m/z = 291 $[M+H]^+$.

Step 2: 4-(Benzyloxy)-2,6-dimethylphenylboronic acid

Under argon 5-(benzyloxy)-2-bromo-1,3-dimethylbenzene (2,38 g) is dissolved in tetrahydrofuran (30 mL) and cooled to -78°C. n-Butyllithium (6.2 mL of a 1.6 M solution in tetrahydrofuran) is added dropwise, the mixture is stirred for 4 hours followed by dropwise addition of triisopropylborate (5.7 mL). The mixture is stirred for 12 hours while warming to room temperature. Then the mixture is poured on 2 N hydrochloric acid and stirred vigorously for 30 minutes. The phases are separated and the aqueous phase is extracted with ethyl acetate. The combined organic phases are washed with brine and dried ($MgSO_4$). The solvents are evaporated and the residue is crystallized from n-hexane. The precipitate is filtered off and dried to give the title compound. Yield: 1.38 g; LC (method 7): t_R = 0.94 min; Mass spectrum (ESI^-): m/z = 255 $[M-H]^-$.

Step 3: Methyl 2-((S)-6-((R)-4-(4-(benzyloxy)-2,6-dimethylphenyl)-5-cyano-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

In a microwave vial methyl 2-((S)-6-((R)-4-bromo-5-cyano-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate (130 mg), 4-(benzyloxy)-2,6-dimethylphenylboronic acid (120 mg), dicyclohexyl(2',6'-dimethoxybiphenyl-2-yl)phosphine (S-Phos) (18 mg) and K₃PO₄ (200 mg) are suspended in toluene (2 mL) and purged for 10 minutes with argon. Palladium-(II)-acetate (5 mg) is added, the vial is sealed and the mixture is stirred at 100°C for 12 hours. After cooling to room temperature the mixture is partitioned between diethylether and saturated aqueous NH₄Cl solution. The organic phase is dried (MgSO₄) and concentrated. The residue is chromatographed on silica gel (cyclohexane/ethyl acetate 90:10→40:60) to give the title compound. Yield: 125 mg; LC (method 10): t_R = 1.15 min; Mass spectrum (ESI⁺): m/z = 560 [M+H]⁺.

Step 4: Methyl 2-((S)-6-((R)-5-cyano-4-(4-hydroxy-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

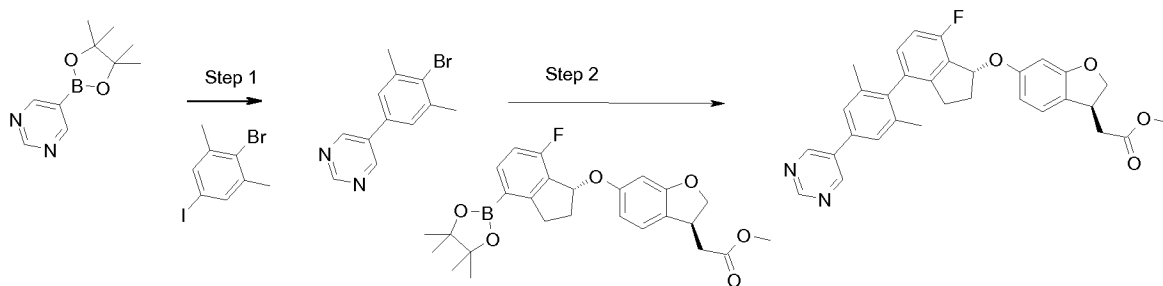
To a solution of methyl 2-((S)-6-((R)-4-(4-(benzyloxy)-2,6-dimethylphenyl)-5-cyano-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate (120 mg) in methanol (10 mL) is added 10% palladium on activated carbon (20 mg) and the mixture is hydrogenated at a pressure of 2 bar for 2 hours. The catalyst is filtered off and washed with methanol. The combined mother liquors are concentrated to give the title compound. Yield: 84 mg; Mass spectrum (ESI⁺): m/z = 470 [M+H]⁺.

Step 5: Methyl 2-((S)-6-((R)-5-cyano-4-(2,6-dimethyl-4-((3-methyloxetan-3-yl)methoxy)phenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

To a solution of methyl 2-((S)-6-((R)-5-cyano-4-(4-hydroxy-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate (80 mg) and Cs₂CO₃ (120 mg) in N,N-dimethylformamide (2 mL) is added 3-(bromomethyl)-3-methyloxetane (30 µL). The mixture is stirred for 12 hours at room temperature and then partitioned between saturated aqueous NH₄Cl solution and diethylether. The organic phase is dried (MgSO₄) and concentrated. The residue is chromatographed on silica gel (cyclohexane/ethyl acetate 90:10→10:90) to give the title compound. Yield: 50 mg; LC (method 9): t_R = 1.21 min; Mass spectrum (ESI⁺): m/z = 554 [M+H]⁺.

Intermediate 40

Methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-(pyrimidin-5-yl)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate



Step 1: 5-(4-Bromo-3,5-dimethylphenyl)pyrimidine

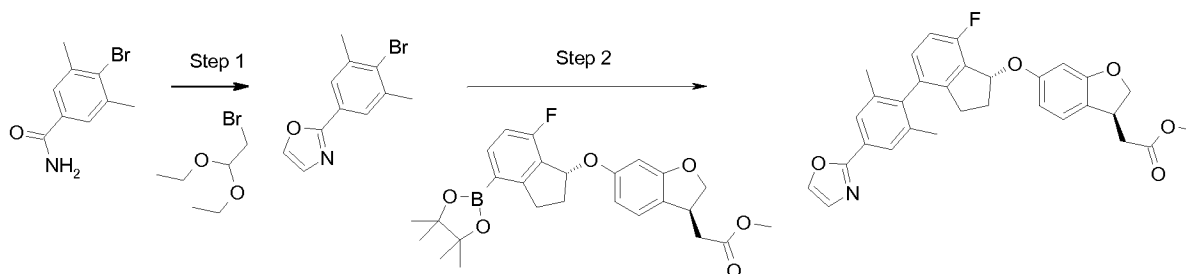
In a microwave vial 2-bromo-5-iodo-1,3-dimethylbenzene (1 g) and 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidine (665 mg) are suspended in N,N-dimethylformamide (15 mL) and Na₂CO₃ (4 mL of a 2 M aqueous solution). The mixture is purged for 5 minutes with argon. [1,1'-Bis(diphenylphosphino)-ferrocene]-dichloropalladium dichloromethane complex (85 mg) is added, the vial is sealed and the mixture is stirred at 60°C for 3 hours. After cooling to room temperature the mixture is Partitioned between water and ethyl acetate. The aqueous phase is extracted with ethyl acetate and the combined organic phases are washed with brine. Then the organic phase is dried (MgSO₄) and concentrated. The residue is chromatographed on silica gel (cyclohexane/ethyl acetate 80:20→50:50) to give the title compound. Yield: 446 mg; LC (method 9): t_R = 1.05 min; Mass spectrum (ESI⁺): m/z = 263 [M+H]⁺.

Step 2: Methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-(pyrimidin-5-yl)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

In a microwave vial methyl 2-((S)-6-((R)-7-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate (100 mg), 5-(4-bromo-3,5-dimethylphenyl)pyrimidine (85 mg), K₃PO₄ (90 mg) are suspended in toluene (1 mL) and water (100 µL) and purged for 10 minutes with argon. Palladium-(II)-acetate (2.4 mg) and dicyclohexyl(2',6'-dimethoxybiphenyl-2-yl)phosphine (S-Phos) (8.8 mg) are added, the vial is sealed and the mixture is stirred at 100°C for 12 hours. The mixture is diluted with tetrahydrofuran and purified by HPLC on reversed phase to give the title compound. Yield: 40 mg; Mass spectrum (ESI⁺): m/z = 525 [M+H]⁺.

Intermediate 41

Methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-(oxazol-2-yl)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate



Step 1: 2-(4-Bromo-3,5-dimethylphenyl)oxazole

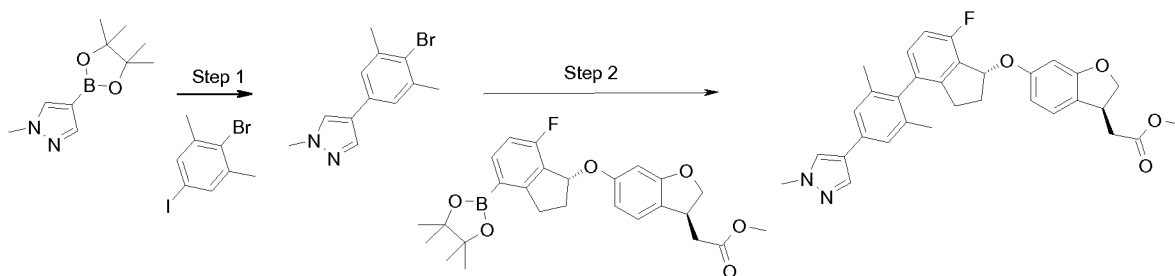
In a microwave vial 4-bromo-3,5-dimethylbenzamide (200 mg) is mixed with 2-bromo-1,1-diethoxyethane (1 mL), the vial is sealed and the mixture is heated to 150°C for 30 minutes. The mixture is diluted with acetonitrile (2 mL) and purified by HPLC on reversed phase to give the title compound. Yield: 125 mg; LC (method 7): t_R = 1.13 min; Mass spectrum (ESI⁺): m/z = 252 [M+H]⁺.

Step 2: Methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-(oxazol-2-yl)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

The title compound is prepared from methyl 2-((S)-6-((R)-7-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate and 2-(4-bromo-3,5-dimethylphenyl)oxazole following a procedure analogous to that described in Step 2 of Intermediate 40. LC (method 11): t_R = 1.27 min; Mass spectrum (ESI⁺): m/z = 514 [M+H]⁺.

Intermediate 42

Methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-(1-methyl-1H-pyrazol-4-yl)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate



Step 1: 4-(4-Bromo-3,5-dimethylphenyl)-1-methyl-1H-pyrazole

The title compound is prepared from 2-bromo-5-iodo-1,3-dimethylbenzene and 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole following a procedure analogous to that described in Step 1 of Intermediate 40. LC (method 9): t_R = 1.09 min; Mass spectrum (ESI⁺): m/z = 265 [M+H]⁺.

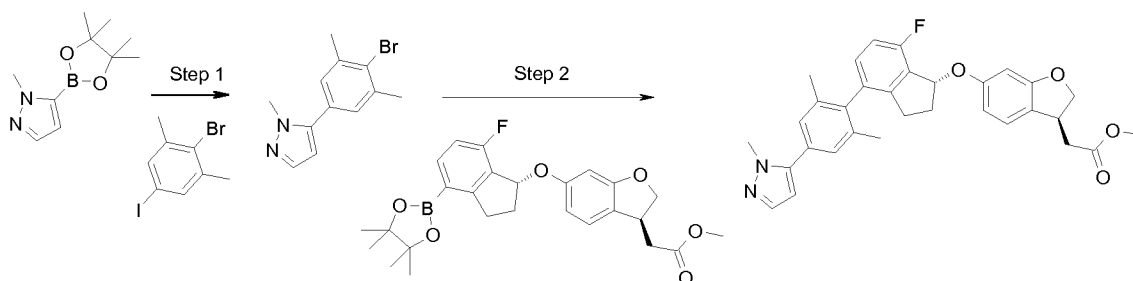
Step 2: Methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-(1-methyl-1H-pyrazol-4-yl)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

The title compound is prepared from methyl 2-((S)-6-((R)-7-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-

- 5 dihydrobenzofuran-3-yl)acetate and 4-(4-bromo-3,5-dimethylphenyl)-1-methyl-1H-pyrazole following a procedure analogous to that described in Step 2 of Intermediate 40. Mass spectrum (ESI⁺): m/z = 527 [M+H]⁺.

Intermediate 43

- 10 Methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-(1-methyl-1H-pyrazol-5-yl)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate



Step 1: 5-(4-Bromo-3,5-dimethylphenyl)-1-methyl-1H-pyrazole

The title compound is prepared from 2-bromo-5-iodo-1,3-dimethylbenzene and 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole following a procedure analogous to that described in Step 1 of Intermediate 40. LC (method 9): t_R = 1.11 min; Mass spectrum (ESI⁺): m/z = 265 [M+H]⁺.

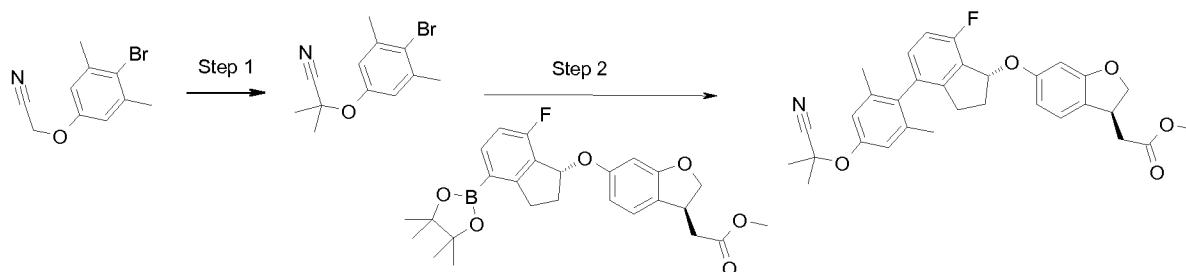
Step 2: Methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-(1-methyl-1H-pyrazol-5-yl)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

- 20 The title compound is prepared from methyl 2-((S)-6-((R)-7-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate and 5-(4-bromo-3,5-dimethylphenyl)-1-methyl-1H-pyrazole following a procedure analogous to that described in Step 2 of Intermediate 40. Mass spectrum (ESI⁺): m/z = 527 [M+H]⁺.

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Intermediate 44

Methyl 2-((S)-6-((R)-4-(4-(2-cyanopropan-2-yloxy)-2,6-dimethylphenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate



Step 1: 2-(4-Bromo-3,5-dimethylphenoxy)-2-methylpropanenitrile

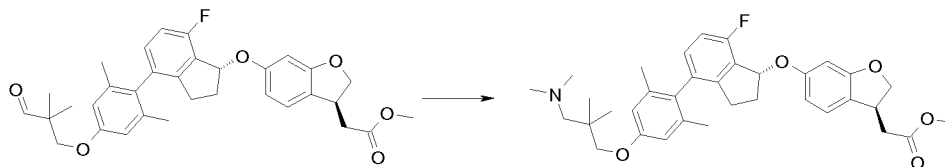
Under argon diisopropylamin (650 μ L) is dissolved in tetrahydrofuran (6 mL), cooled to -30°C and treated dropwise with n-butyllithium (2.75 mL of a 1.6 M solution in n-hexane). The mixture is stirred for 30 minutes, cooled to -78°C and then treated dropwise with a solution of 2-(4-bromo-3,5-dimethylphenoxy)acetonitrile (350 mg) and methyl iodide (549 μ L) in tetrahydrofuran (6 mL). The mixture is stirred for 2 hours warmed to 0°C and stirred for 1 hour. The reaction is quenched by addition of saturated aqueous NH_4Cl solution, the aqueous phase is extracted with diethylether and the organic phase is dried (MgSO_4). The solvents are evaporated and the residue is chromatographed on silica gel (petrole ether/ethyl acetate 95:5 $\rightarrow$ 60:40) to give the title compound. Yield: 120 mg; Mass spectrum (EI): $m/z = 267$ $[\text{M}]^+$.

Step 2: Methyl 2-((S)-6-((R)-4-(4-(2-cyanopropan-2-yloxy)-2,6-dimethylphenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

The title compound is prepared from methyl 2-((S)-6-((R)-7-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate and 2-(4-bromo-3,5-dimethylphenoxy)-2-methylpropanenitrile following a procedure analogous to that described in Step 5 of Intermediate 12. LC (method 7): $t_R = 1.25$ min; Mass spectrum (ESI^+): $m/z = 530$ $[\text{M}+\text{H}]^+$.

Intermediate 45

Methyl 2-((S)-6-((R)-4-(4-(3-(dimethylamino)-2,2-dimethylpropoxy)-2,6-dimethylphenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

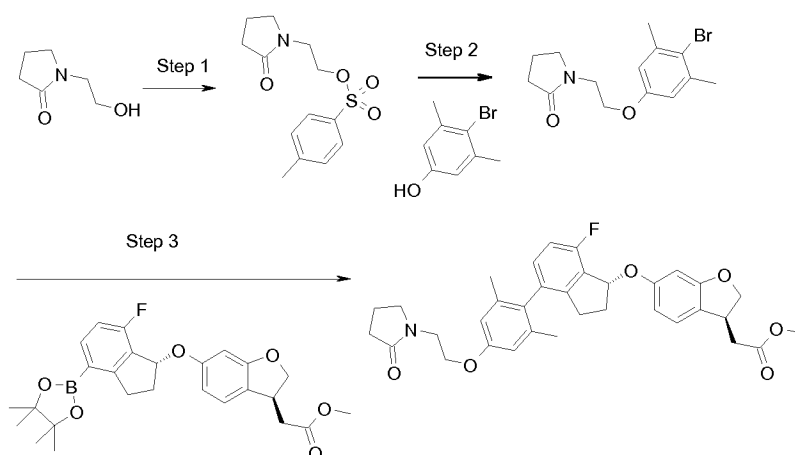


Dimethylamine (95 μ L of a 2 M solution in tetrahydrofuran) is added to a solution of methyl 2-((S)-6-((R)-4-(4-(2,2-dimethyl-3-oxopropoxy)-2,6-dimethylphenyl)-7-fluoro-

2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate (83 mg) and acetic acid (13 μ L) in 1,2-dichloroethane (2 mL). The mixture is stirred for 20 minutes and then treated with sodium triacetoxyborohydride (130 mg). After stirring for 12 hours the mixture is diluted with dichloromethane, washed with water and brine, dried (MgSO₄) and concentrated. The residue is purified by HPLC on reversed phase to give the title compound. Yield: 20 mg; LC (method 13): t_R = 1.18 min; Mass spectrum (ESI⁺): m/z = 576 [M+H]⁺.

Intermediate 46

10 Methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-(2-(2-oxopyrrolidin-1-yl)ethoxy)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate



Step 1: 2-(2-Oxopyrrolidin-1-yl)ethyl 4-methylbenzenesulfonate

p-Toluenesulfonylchloride (1 g) is added portionwise to a solution of 1-(2-hydroxyethyl)pyrrolidin-2-one (500 μ L) and pyridine (1.5 mL) in dichloromethane (8 mL) chilled in an ice bath. The mixture is stirred at room temperature for 12 hours and partitioned between 1 M hydrochloric acid and diethylether. The organic phase is dried (MgSO₄) and concentrated. The residue is chromatographed on silica gel (ethyl acetate) to give the title compound. Yield: 390 mg; Mass spectrum (ESI⁺): m/z = 284 [M+H]⁺.

Step 2: 1-(2-(4-Bromo-3,5-dimethylphenoxy)ethyl)pyrrolidin-2-one

Cs₂CO₃ (850 mg) is added to a solution of 2-(2-oxopyrrolidin-1-yl)ethyl 4-methylbenzenesulfonate (390 mg) and 4-bromo-3,5-dimethylphenol (200 mg) in N,N-dimethylformamide (4 mL). The mixture is heated to 50°C for 12 hours and partitioned between diethylether and saturated aqueous NH₄Cl solution. The organic phase is dried (MgSO₄) and concentrated. The residue is chromatographed on silica

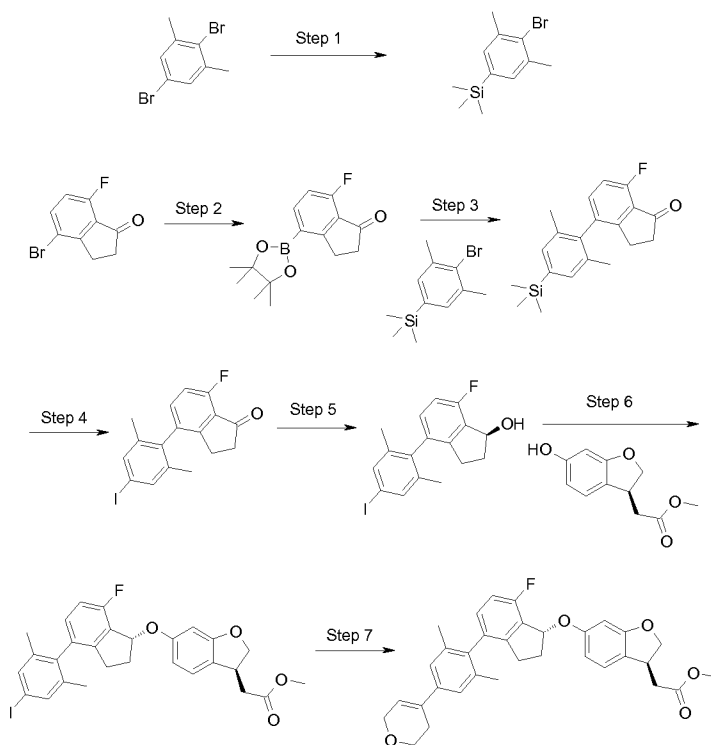
gel (ethyl acetate) to give the title compound. Yield: 210 mg; Mass spectrum (ESI⁺): m/z = 312 [M+H]⁺.

Step 3: Methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-(2-(2-oxopyrrolidin-1-yl)ethoxy)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

- 5 The title compound is prepared from methyl 2-((S)-6-((R)-7-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate and 1-(2-(4-bromo-3,5-dimethylphenoxy)ethyl)pyrrolidin-2-one following a procedure analogous to that described in Step 5 of Intermediate 12. The product is purified by HPLC on reversed phase. LC (method 8): t_R = 0.68 min; Mass spectrum (ESI⁺): m/z = 574 [M+H]⁺.
- 10

Intermediate 47

Methyl 2-((S)-6-((R)-4-(4-(3,6-dihydro-2H-pyran-4-yl)-2,6-dimethylphenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate



15

Step 1: (4-Bromo-3,5-dimethylphenyl)trimethylsilane

- A solution of 2,5-dibromo-1,3-dimethylbenzene (500 mg) in diethylether (3 mL) and tetrahydrofuran (2.5 mL) is cooled to -78°C and treated dropwise with n-butyllithium (200 µL of a 10 M solution in n-hexane). The mixture is stirred for 1 hour and treated dropwise with chloro-trimethyl-silane (275 µL). After stirring for 2 hours the reaction is quenched by addition of saturated aqueous NH₄Cl solution. The mixture is extracted
- 20

with diethylether. The organic phase is dried (MgSO_4) and concentrated. The residue is chromatographed on silica gel (cyclohexane/ethyl acetate 99:1→90:10) to give the title compound. Yield: 260 mg; Mass spectrum (ESI^+): $m/z = 279$ $[\text{M}+\text{Na}]^+$.

Step 2: 7-Fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-one

The title compound is prepared from 4-bromo-7-fluoro-2,3-dihydro-1H-inden-1-one following a procedure analogous to that described in Step 4 of Intermediate 12. LC (method 8): $t_R = 0.36$ min; Mass spectrum (ESI^+): $m/z = 277$ $[\text{M}+\text{H}]^+$.

Step 3: 4-(2,6-Dimethyl-4-(trimethylsilyl)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-one

The title compound is prepared from 7-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-one and (4-bromo-3,5-dimethylphenyl)trimethylsilane following a procedure analogous to that described in Step 5 of Intermediate 12. LC (method 8): $t_R = 0.89$ min; Mass spectrum (ESI^+): $m/z = 327$ $[\text{M}+\text{H}]^+$.

Step 4: 7-Fluoro-4-(4-iodo-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-one

4-(2,6-Dimethyl-4-(trimethylsilyl)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-one (110 mg) is dissolved in dichloromethane (2 mL), cooled to -30°C and treated dropwise with ICl (355 μL of a 1 M solution in dichloromethane). The mixture is stirred for 1 hour and then partitioned between saturated aqueous NaHCO_3 solution and dichloromethane. The organic phase is washed with a 10% aqueous solution of $\text{Na}_2\text{S}_2\text{O}_3$ and brine. After drying (MgSO_4) the solvents are evaporated off to give the title compound. Yield: 160 mg; LC (method 8): $t_R = 0.66$ min; Mass spectrum (ESI^+): $m/z = 381$ $[\text{M}+\text{H}]^+$.

Step 5: (S)-7-Fluoro-4-(4-iodo-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-ol

The title compound is prepared from 7-fluoro-4-(4-iodo-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-one following a procedure analogous to that described in Step 1 of Intermediate 1. LC (method 8): $t_R = 0.65$ min; Mass spectrum (ESI^-): $m/z = 381$ $[\text{M}-\text{H}]^-$.

Step 6: Methyl 2-((S)-6-((R)-7-fluoro-4-(4-iodo-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

The title compound is prepared from (S)-7-fluoro-4-(4-iodo-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-ol and (S)-methyl 2-(6-hydroxy-2,3-dihydrobenzofuran-3-yl)acetate following a procedure analogous to that described in Step 3 of

Intermediate 12. LC (method 8): $t_R = 1.08$ min; Mass spectrum (ESI^+): $m/z = 595$ $[M+Na]^+$.

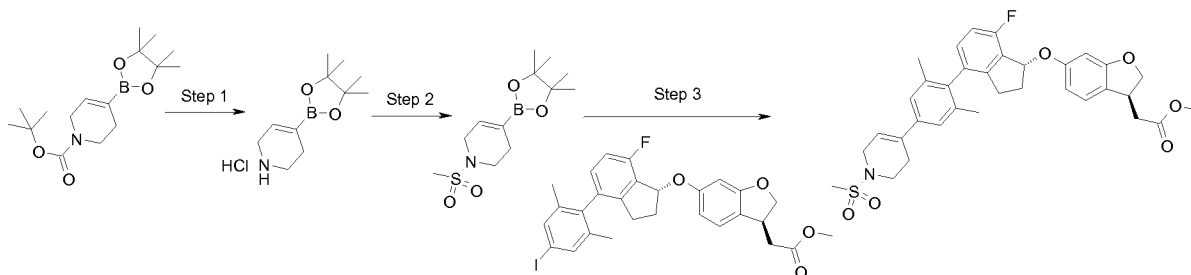
Step 7: Methyl 2-((S)-6-((R)-4-(4-(3,6-dihydro-2H-pyran-4-yl)-2,6-dimethylphenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

- 5 The title compound is prepared from methyl 2-((S)-6-((R)-7-fluoro-4-(4-iodo-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate and 2-(3,6-dihydro-2H-pyran-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane following a procedure analogous to that described in Step 4 of Intermediate 13. LC (method 8): $t_R = 0.92$ min; Mass spectrum (ESI^+): $m/z = 551$ $[M+Na]^+$.

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Intermediate 48

Methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-(1-(methanesulfonyl)-1,2,3,6-tetrahydropyridin-4-yl)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate



15

Step 1: 4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,6-tetrahydropyridinium chloride

- Tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydropyridine-1(2H)-carboxylate (10 g) is dissolved in dichloromethane (100 mL) and 5 M HCl in isopropanol (120 mL) and stirred for 12 hours. The solvents are evaporated, the residue is redissolved in toluene and the solvent is again evaporated to give the title compound. Yield: 8 g; LC (method 11): $t_R = 0.68$ min; Mass spectrum (ESI^+): $m/z = 210$ $[M+H]^+$.

- Step 2:** 1-(Methanesulfonyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,6-tetrahydropyridine

- To a cooled (0°C) solution of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,6-tetrahydropyridinium chloride (8 g) and N-ethyldiisopropylamine (12 mL) in dichloromethane (100 mL) is added dropwise methanesulfonyl chloride (3 mL). The mixture is stirred for 12 hours at room temperature. The mixture is partitioned between dichloromethane and 0.1 M hydrochloric acid. The organic phase is

30

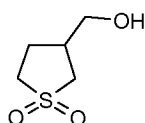
separated, washed with brine and dried (MgSO₄). The solvent is evaporated and the residue is crystallized from diethylether to give the title compound. Yield: 7.4 g; LC (method 15): t_R = 0.98 min; Mass spectrum (ESI⁺): m/z = 288 [M+H]⁺.

Step 3: Methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-(1-(methylsulfonyl)-1,2,3,6-tetrahydropyridin-4-yl)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

The title compound is prepared from methyl 2-((S)-6-((R)-7-fluoro-4-(4-iodo-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate and 1-(methylsulfonyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,6-tetrahydropyridine following a procedure analogous to that described in Step 4 of Intermediate 13. LC (method 8): t_R = 0.79 min; Mass spectrum (ESI⁺): m/z = 628 [M+Na]⁺.

Intermediate 49a

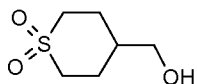
(1,1-Dioxo-tetrahydrothiophen-3-yl)methanol



1,1-Dioxo-tetrahydrothiophene-3-carboxylic acid (300 mg) is dissolved in dry tetrahydrofuran (10 mL). The reaction mixture is cooled to 0°C and borane tetrahydrofuran complex (2 mL) is added dropwise. After stirring for 1 hour at 0°C, the mixture is concentrated under vacuum, partitioned between dichloromethane and water. The organic phase is dried (MgSO₄) and concentrated to give the title compound. Yield: 250 mg.

Intermediate 49b

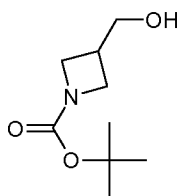
(1,1-Dioxo-tetrahydro-2H-thiopyran-4-yl)methanol



The title compound is prepared in analogy to Intermediate 49a starting from 1,1-dioxo-tetrahydro-2H-thiopyran-4-carboxylic acid.

Intermediate 49c

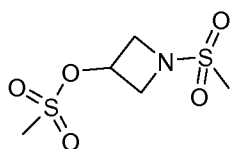
tert-Butyl 3-(hydroxymethyl)azetidine-1-carboxylate



The title compound is prepared in analogy to Intermediate 49a starting from 1-(tert-butoxycarbonyl)azetidine-3-carboxylic acid.

5 Intermediate 49d

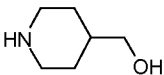
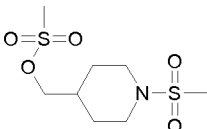
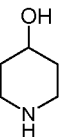
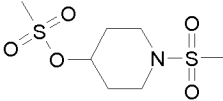
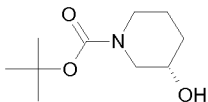
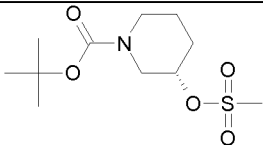
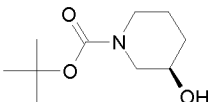
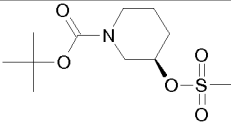
1-(Methylsulfonyl)azetidin-3-yl methanesulfonate

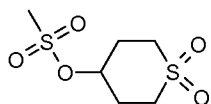


Azetidin-3-ol (3.3 g) and DIPEA (20 mL) are dissolved in dry tetrahydrofuran (40 mL). After 30 min the reaction mixture is cooled to 0°C and methanesulfonyl chloride (10.9 g) is added dropwise. After stirring for 2 hours at ambient temperature, the mixture is concentrated under vacuum, partitioned between ethyl acetate and water. The organic phase is dried (MgSO₄) and concentrated. Chromatography of the residue on silica gel (cyclohexane/ethyl acetate 70:30) gives the title compound. Yield: 5 g.

15 The intermediates in the following table are prepared following a procedure analogous to that described for Intermediate 49d.

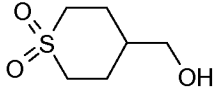
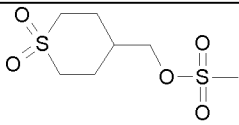
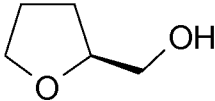
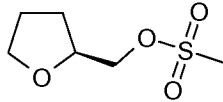
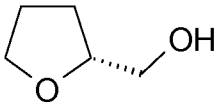
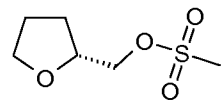
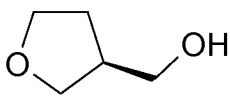
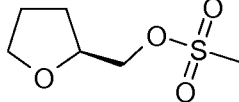
starting amino-alcohol	Intermediate	Molecular structure and name
 (R)-(+)-3-pyrrolidinol	49e	 (R)-1-(Methylsulfonyl)pyrrolidin-3-yl methanesulfonate
 (S)-(+)-3-pyrrolidinol	49ea	 (S)-1-(Methylsulfonyl)pyrrolidin-3-yl methanesulfonate

 Piperidin-4-yl-methanol	49f	 (1-(Methylsulfonyl)piperidin-4-yl)methyl methanesulfonate
 Piperidin-4-ol	49fa	 Methanesulfonic acid methanesulfonyl-piperidin-4-yl ester
	49fb	 (S)-3-Methanesulfonyloxy-piperidine-1-carboxylic acid tert-butyl ester
	49fc	 (R)-3-Methanesulfonyloxy-piperidine-1-carboxylic acid tert-butyl ester

Intermediate 49g1,1-Dioxo-tetrahydro-2H-thiopyran-4-yl methanesulfonate

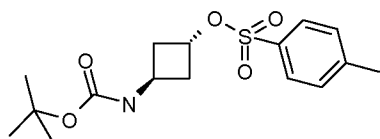
- 5 Methanesulfonyl chloride (0.15 mL), (1,1-dioxo-tetrahydro-2H-thiopyran-4-yl)methanol (150 mg) and triethylamine (0.3 mL) are stirred at 0°C in dry dichloromethane (2 mL). After 30 min, the reaction mixture is warmed to ambient temperature. After stirring for 3 hours, the mixture is diluted with dichloromethane, washed with 10% aqueous solution of KHSO₄, then with 10% aqueous solution
- 10 of K₂CO₃. The organic phase is collected by passing through a phase separator cartridge and concentrated. The residue is chromatographed on silica gel (dichloromethane/methanol 100:0→95:5) to give the title compound. Yield: 197 mg.

The following intermediates are prepared in analogy to Intermediate 49g starting from the corresponding alcohols.

starting alcohol	Intermediate	Molecular structure and name
 49b	49ga	 Methanesulfonic acid 1,1-dioxohexahydro-1-thiopyran-4-ylmethyl ester
 (S)-1-(Tetrahydro-furan-2-yl)-methanol	49gb	 Methanesulfonic acid (S)-1-(tetrahydro-furan-2-yl)methyl ester
 (R)-1-(Tetrahydro-furan-2-yl)-methanol	49gc	 Methanesulfonic acid (R)-1-(tetrahydro-furan-2-yl)methyl ester
 (S)-1-(Tetrahydro-furan-3-yl)-methanol	49gd	 Methanesulfonic acid (R)-1-(tetrahydro-furan-3-yl)methyl ester

Intermediate 49h

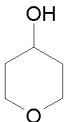
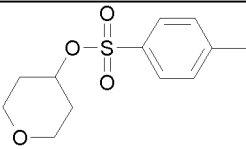
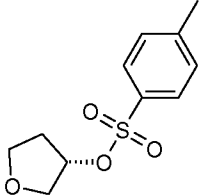
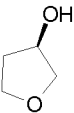
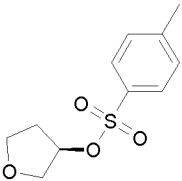
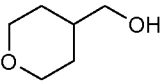
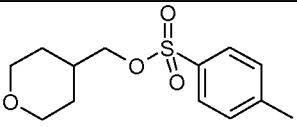
5 Trans-3-(tert-butoxycarbonylamino)cyclobutyl 4-methylbenzenesulfonate



Trans-tert-butyl-3-hydroxycyclobutylcarbamate (440 mg), p-toluenesulfonyl chloride (498 mg) and pyridine (0.74 mL) are dissolved in dichloromethane (7 mL) and a catalytic amount of 4-(dimethylamino)pyridine is added. The reaction mixture is stirred at ambient temperature overnight, concentrated, partitioned between ethyl

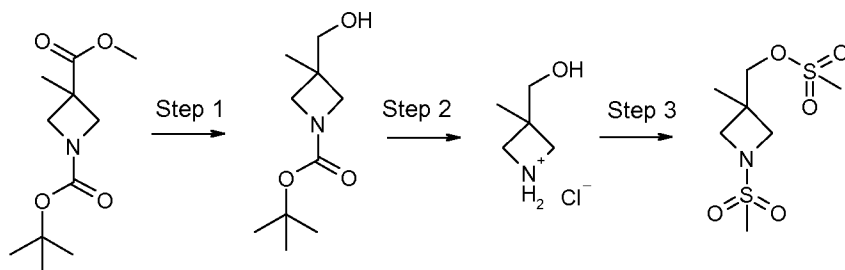
acetate and water. The organic phase is washed with a 20% aqueous solution of citric acid, dried (MgSO_4) and concentrated to give the title compound. Yield: 806 mg.

- The following intermediates are prepared in analogy to Intermediate 49h starting from
- 5 the corresponding alcohols.

starting alcohol	Intermediate	Molecular structure and name
 Tetrahydro-pyran-4-ol	49ha	 Toluene-4-sulfonic acid tetrahydro-pyran-4-yl ester
 (S)-Tetrahydro-furan-3-ol	49hb	 Toluene-4-sulfonic acid (S)-(tetrahydro-furan-3-yl) ester
 (R)-Tetrahydro-furan-3-ol	49hc	 Toluene-4-sulfonic acid (R)-(tetrahydro-furan-3-yl) ester
 (Tetrahydro-pyran-4-yl)-methanol	49hd	 Toluene-4-sulfonic acid tetrahydro-pyran-4-ylmethyl ester

Intermediate 49i

Methanesulfonic acid 1-methanesulfonyl-3-methyl-azetidin-3-ylmethyl ester



Step 1: 3-Hydroxymethyl-3-methyl-azetidine-1-carboxylic acid tert-butyl ester

3-Methyl-azetidine-1,3-dicarboxylic acid 1-tert-butyl ester 3-methyl ester (WO2006/73361 A1, 2006) (1.1 g) is dissolved in 20 mL of tetrahydrofuran.

- 5 Lithiumborohydride (16.8 mL of a 2 M solution in tetrahydrofuran) is added dropwise and the reaction mixture is stirred at room temperature overnight. The reaction mixture is diluted with water, washed with a saturated ammonium chloride water solution and the organic phase is separated, dried over sodium sulfate and concentrated under vacuum. The residue is chromatographed on silica gel
 10 (hexane/ethyl acetate 100:0→50:50) to give the title compound. Yield: 970 mg.

Step 2: 3-Hydroxymethyl-3-methyl-azetidine hydrochloride

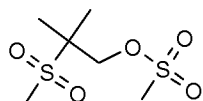
3-Hydroxymethyl-3-methyl-azetidine-1-carboxylic acid tert-butyl ester (1 g) is dissolved in 5 mL of ethyl ether. A 2 M aqueous solution of hydrochloric acid (4 mL) is added, the reaction mixture is stirred overnight and then concentrated under
 15 vacuum to give the title compound. Yield: 600 mg.

Step 3: Methanesulfonic acid 1-methanesulfonyl-3-methyl-azetidin-3-ylmethyl ester

The title compound is prepared following a procedure analogous to that described for Intermediate 49d.

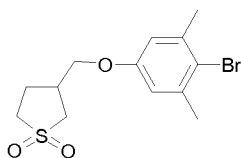
20 **Intermediate 49j**

Methanesulfonic acid 2-methanesulfonyl-2-methyl-propyl ester

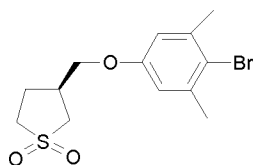


- The title compound is prepared following a procedure analogous to that described for Intermediate 49g starting from 2-methanesulfonyl-2-methyl-propan-1-ol (Rouchard,
 25 Jean; Moons, Chantal; Meyer, Joseph Bulletin de la Societe Chimique de France, 1980, vol. 2, # 9-10 p. 441 – 443).

Intermediate 50a

1,1-Dioxo-3-((4-bromo-3,5-dimethylphenoxy)methyl)tetrahydrothiophene

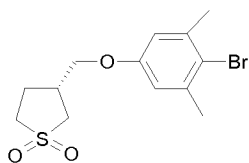
Intermediate 49a (235 mg), 4-bromo-3,5-dimethylphenol (318 mg), di-tert-butyl azodicarboxylate (396 mg) and triphenylphosphine (451 mg) are dissolved in dichloromethane (100 mL). The mixture is stirred at ambient temperature for 2 hours, diluted with dichloromethane and washed with water and brine. The organic phase is dried (MgSO₄) and concentrated. The residue is chromatographed on silica gel (cyclohexane/ethyl acetate 100:0→50:50) to give the title compound. Yield: 260 mg.

10 Intermediate 50aa(S)-3-(4-Bromo-3,5-dimethyl-phenoxy)methyl)-tetrahydro-thiophene 1,1-dioxide

The title compound is obtained by chiral HPLC chromatographic separation of the racemate 1,1-dioxo-3-((4-bromo-3,5-dimethylphenoxy)methyl)tetrahydrothiophene.

15 Chiral HPLC (method 1a): t_R = 18.85 min.

Absolute configuration unknown.

Intermediate 50ab(R)-3-(4-Bromo-3,5-dimethyl-phenoxy)methyl)-tetrahydro-t h i o p h e n e 1 , 1-dioxide

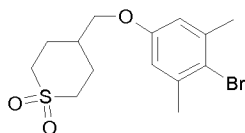
20

Further elution from the chiral column gives the title compound.

Chiral HPLC (method 1a): t_R = 23,57 min

Absolute configuration unknown.

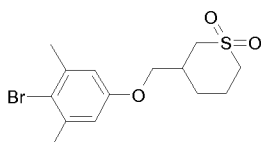
25 Intermediate 50b1,1-Dioxo-4-((4-bromo-3,5-dimethylphenoxy)methyl)tetrahydro-2H-thiopyran



The title compound is prepared in analogy to Intermediate 50a, starting from Intermediate 49b.

5 Intermediate 50ba

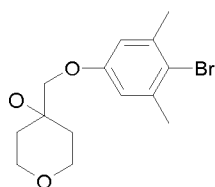
3-(4-Bromo-3,5-dimethyl-phenoxy)methyl)-tetrahydro-thiopyran 1,1-dioxide



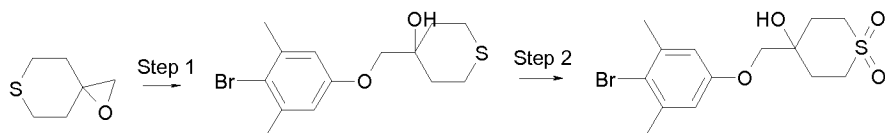
3-(Bromomethyl)tetrahydro-2H-thiopyrane 1,1-dioxide (1 g) is dissolved in 40 mL of
10 N,N-dimethylformamide. 4-Bromo-3,5-dimethylphenol (885 mg) and cesium carbonate (2.85 g) are added and the reaction mixture is stirred at 130°C overnight. The reaction mixture is concentrated under vacuum. Water is added and the mixture is extracted with ethyl acetate, The organic phase is separated, dried over sodium sulfate and concentrated under vacuum. The residue is chromatographed on silica
15 gel (cyclohexane/ethyl acetate 100:0→80:20) to give the title compound. Yield: 800 mg

Intermediate 50bb

4-(4-Bromo-3,5-dimethyl-phenoxy)methyl)-tetrahydro-pyran-4-ol



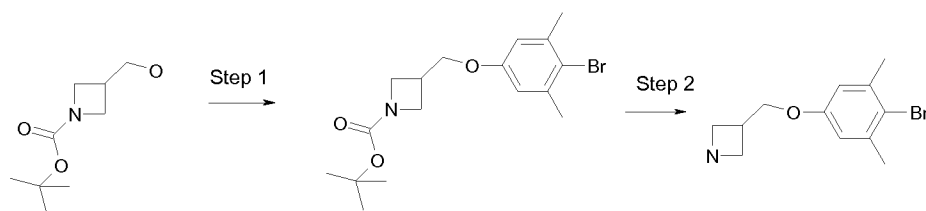
20 4-Bromo-3,5-dimethylphenol (1 g) and cesium carbonate (5.7 g) are suspended in 30 mL of N,N-dimethylacetamide, 1,6-dioxaspiro[2.5]octane (US2012/46304 A1, 2012) (1.78 g) is added and the reaction mixture is stirred at 110 °C overnight. Water is added and the mixture is extracted with ethyl acetate, the organic phase is
25 separated, dried over sodium sulfate and concentrated under vacuum. The residue is chromatographed on silica gel (cyclohexane/ethyl acetate 95:5) to give the title compound. Yield: 400 mg

Intermediate 50bc4-(4-Bromo-3,5-dimethyl-phenoxy)methyl)-1,1-dioxo-hexahydro-1-thiopyran-4-ol5 Step 1: 4-(4-Bromo-3,5-dimethyl-phenoxy)methyl)-tetrahydro-thiopyran-4-ol

The title compound is prepared in analogy to intermediate 50bb starting from 1-oxa-6-thia-spiro[2.5]octane (EP1726580 A1, 2006).

Step 2: 4-(4-Bromo-3,5-dimethyl-phenoxy)methyl)-1,1-dioxo-hexahydro-1-thiopyran-4-ol.

- 10 4-(4-Bromo-3,5-dimethyl-phenoxy)methyl)-tetrahydro-thiopyran-4-ol (820 mg) is stirred in 20 mL of tetrahydrofuran. A solution of potassium peroxomonosulfate (4.33 g) in 5 mL of water is added dropwise and the reaction mixture is stirred at room temperature for 2 h. Water is added and the reaction mixture is extracted with dichloromethane, the organic phase is separated, dried over sodium sulfate and
- 15 concentrated under vacuum. The residue is chromatographed on silica gel (cyclohexane/ethyl acetate 80:20→0:100) to give the title compound. Yield: 850 mg.

Intermediate 50c3-((4-Bromo-3,5-dimethylphenoxy)methyl)azetidine

20

Step 1: tert-Butyl 3-((4-bromo-3,5-dimethylphenoxy)methyl)azetidine-1-carboxylate

the title compound is prepared starting from Intermediate 49c and 4-bromo-3,5-dimethylphenol as described in the preparation of Intermediate 50a.

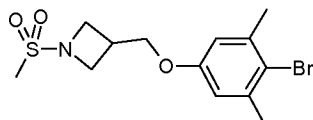
Step 2: 3-((4-Bromo-3,5-dimethylphenoxy)methyl)azetidine

- 25 tert-Butyl 3-((4-bromo-3,5-dimethylphenoxy)methyl)azetidine-1-carboxylate (900 mg) and trifluoroacetic acid (0.3 mL) are dissolved in dichloromethane (40 mL). The reaction mixture is stirred at 0°C for 6 hours, diluted with a saturated aqueous

solution of NaHCO₃, dried (MgSO₄) and concentrated to give the title compound.
Yield: 400 mg

Intermediate 50d

5 3-((4-Bromo-3,5-dimethylphenoxy)methyl)-1-(methylsulfonyl)azetidine



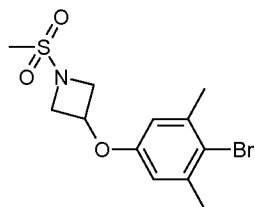
Intermediate 50c (400 mg) and N-ethyldiisopropylamine (0.48 mL) are dissolved in dry dichloromethane (26 mL). The reaction mixture is cooled to 0°C and methanesulfonyl chloride (0.1 mL) is added dropwise. After stirring for 0.5 hours at
10 ambient temperature, the mixture is partitioned between dichloromethane and water. The organic phase is dried (MgSO₄) and concentrated. The residue is chromatographed on silica gel (cyclohexane/ethyl acetate 100:0→50:50) to give the title compound. Yield: 330 mg.

15 The bromo-aryl intermediates in the following table are prepared starting from Intermediate 50c and the corresponding sulfonyl chlorides following a procedure analogous to that described for Intermediate 50d.

Sulfonyl chloride	Intermediate	Molecular structure and name
Ethanesulfonyl chloride	50e	3-((4-bromo-3,5-dimethylphenoxy)methyl)-1-(ethanesulfonyl)azetidine
Isopropylsulfonyl chloride	50f	3-((4-bromo-3,5-dimethylphenoxy)methyl)-1-(isopropylsulfonyl)azetidine

Intermediate 50g

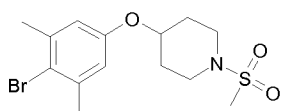
20 3-(4-Bromo-3,5-dimethylphenoxy)-1-(methylsulfonyl)azetidine



In a microwave vial 4-bromo-3,5-dimethylphenol (1 g) and sodium hydride (100 mg) are stirred in dry N,N-dimethylacetamide (25 mL) for 30 minutes. Intermediate 49d (1 g) is added, the vial is sealed and the mixture is stirred at 140°C for 1.5 hours (100 W). After cooling to ambient temperature, the mixture is concentrated, partitioned between ethyl acetate and water. The organic phase is dried (MgSO₄) and concentrated. The residue is chromatographed on silica gel (cyclohexane/ethyl acetate 100:0→70:30) to give the title compound. Yield: 500 mg.

10 Intermediate 50ga

4-(4-Bromo-3,5-dimethyl-phenoxy)-1-methanesulfonyl-piperidine

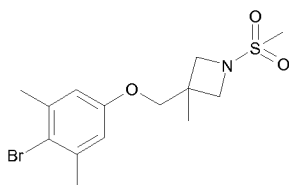


The title compound is prepared in analogy to Intermediate 50g, starting from Intermediate 49fa.

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Intermediate 50gb

3-(4-Bromo-3,5-dimethyl-phenoxy)-1-methanesulfonyl-3-methyl-azetidine

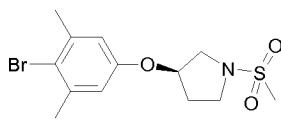


The title compound is prepared in analogy to Intermediate 50g, starting from Intermediate 49i.

20

Intermediate 50gc

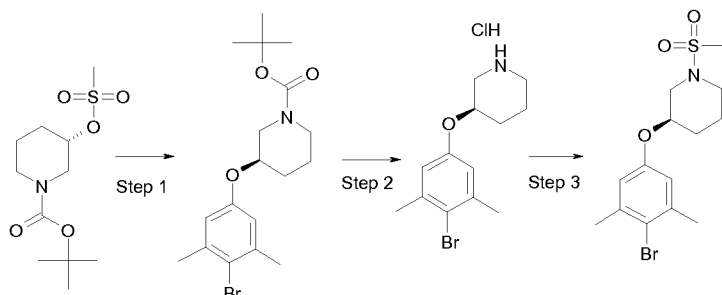
(R)-3-(4-Bromo-3,5-dimethyl-phenoxy)-1-methanesulfonyl-pyrrolidine



The title compound is prepared in analogy to Intermediate 50g, starting from intermediate 49ea.

Intermediate 50gd

5 (R)-3-(4-Bromo-3,5-dimethyl-phenoxy)-1-methanesulfonyl-piperidine



Step 1: (R)-3-(4-Bromo-3,5-dimethyl-phenoxy)-piperidine-1-carboxylic acid tert-butyl ester.

The title compound is prepared in analogy to Intermediate 50g, starting from intermediate 49fb.

Step 2: (R)-3-(4-Bromo-3,5-dimethyl-phenoxy)-piperidine hydrochloride

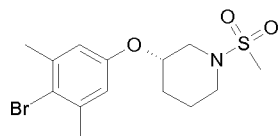
The title compound is prepared in analogy to Step 2 in the preparation of Intermediate 49i, starting from (R)-3-(4-Bromo-3,5-dimethyl-phenoxy)-piperidine-1-carboxylic acid tert-butyl ester

15 Step 3: (R)-3-(4-Bromo-3,5-dimethyl-phenoxy)-1-methanesulfonyl-piperidine

The title compound is prepared in analogy to Intermediate 50d starting from (R)-3-(4-bromo-3,5-dimethyl-phenoxy)-piperidine hydrochloride.

Intermediate 50ge

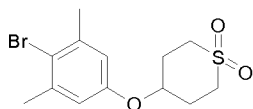
20 (S)-3-(4-Bromo-3,5-dimethyl-phenoxy)-1-methanesulfonyl-piperidine



The title compound is prepared in analogy to Intermediate 50gd, starting from intermediate 49fc.

25 **Intermediate 50h**

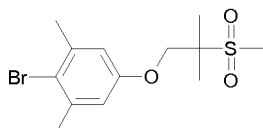
1,1-Dioxo-4-(4-bromo-3,5-dimethylphenoxy)tetrahydro-2H-thiopyran



The title compound is prepared in analogy to Intermediate 50g, starting from Intermediate 49g.

5 Intermediate 50ha

2-Bromo-5-(2-methanesulfonyl-2-methyl-propoxy)-1,3-dimethyl-benzene

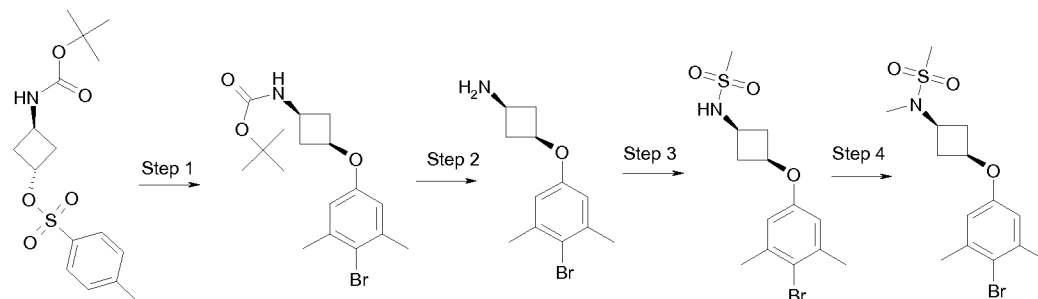


The title compound is prepared in analogy to Intermediate 50g, starting from Intermediate 49j.

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Intermediate 50i

N-((1s,3s)-3-(4-Bromo-3,5-dimethylphenoxy)cyclobutyl)-N-methylmethanesulfonamide



15 Step 1: tert-Butyl cis-3-(4-bromo-3,5-dimethylphenoxy)cyclobutylcarbamate

4-bromo-3,5-dimethylphenol (450 mg) and sodium hydride (60 mg) are stirred in N,N-dimethylacetamide (15 mL) for 30 minutes. Intermediate 49h (300 mg) is added and the mixture is stirred at 80°C for 3 hours. After cooling to ambient temperature, the mixture is concentrated, partitioned between ethyl acetate and water. The organic phase is dried (MgSO₄) and concentrated. The residue is chromatographed on silica gel (cyclohexane/ethyl acetate 90:10→40:60) to give the title compound. Yield: 200 mg.

Step 2: cis-3-(4-Bromo-3,5-dimethylphenoxy)cyclobutanamine

tert-Butyl cis-3-(4-bromo-3,5-dimethylphenoxy)cyclobutylcarbamate (200 mg) and trifluoroacetic acid (0.13 mL) are dissolved in dichloromethane (6 mL). The reaction

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mixture is stirred at 0°C for 5 hours, diluted with a saturated aqueous solution of NaHCO₃, dried (MgSO₄) and concentrated to give the title compound. Yield: 400 mg.

Step 3: N-(cis-3-(4-bromo-3,5-dimethylphenoxy)cyclobutyl)methanesulfonamide

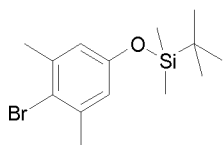
Methanesulfonyl chloride (0.16 mL), cis-3-(4-Bromo-3,5-dimethylphenoxy)cyclobutanamine (300 mg) and triethylamine (0.3 mL) are stirred at 0°C in dry dichloromethane (25 mL). After 10 min, the reaction mixture is warmed to ambient temperature. After stirring for 3 hours, the mixture is diluted with dichloromethane, washed with 10% aqueous solution of KHSO₄, then with 10% aqueous solution of K₂CO₃. The organic phase was passed through a phase separator and concentrated. The residue is chromatographed on silica gel (cyclohexane/ethyl acetate 90:10→50:50) to give the title compound. Yield: 200 mg.

Step 4: N-(cis-3-(4-bromo-3,5-dimethylphenoxy)cyclobutyl)-N-methylmethanesulfonamide

N-(cis-3-(4-bromo-3,5-dimethylphenoxy)cyclobutyl)methanesulfonamide (130 mg) and sodium hydride (16 mg) are stirred in N,N-dimethylacetamide (2 mL) for 10 minutes. Iodomethane (0.1 mL) is added and the mixture is stirred at ambient temperature overnight. After cooling to ambient temperature, the mixture is concentrated, partitioned between ethyl acetate and water. The organic phase is dried (MgSO₄) and concentrated. The residue is chromatographed on silica gel (cyclohexane/ethyl acetate gradient of increasing polarity) to give the title compound. Yield: 110 mg.

Intermediate 50j

(4-Bromo-3,5-dimethylphenoxy)(tert-butyl)dimethylsilane

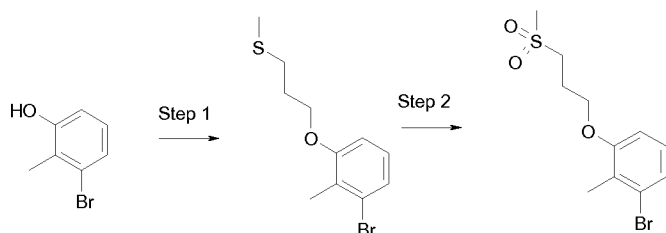


4-Bromo-3,5-dimethylphenol (3.5 g), 4-(dimethylamino)pyridine (212 mg) and triethylamine (2.7 mL) are stirred in dichloromethane (25 mL) at 0°C, then tert-butyldimethylchlorosilane (19 mL) is added dropwise. The reaction mixture is warmed to ambient temperature and stirred overnight. The reaction mixture is diluted with dichloromethane, washed with aqueous HCl (1 M, 25 mL) and then with saturated

aqueous NaHCO_3 (25 mL). The organic phase is dried (MgSO_4) and concentrated to give the title compound. Yield: 5.4 g

Intermediate 50k

5 1-Bromo-2-methyl-3-(3-(methylsulfonyl)propoxy)benzene



Step 1: (3-(3-Bromo-2-methylphenoxy)propyl)(methyl)sulfane

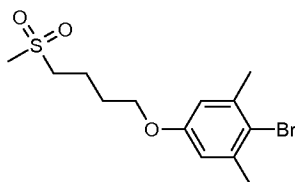
3-Bromo-2-methylphenol (0.10 g), 3-(methylthio)propanol (0.055 mL), tri-n-butyl phosphine (0.12 g) and 1,1'-(azodicarbonyl)dipiperidine (0.15 g) are stirred in tetrahydrofuran for 16 hours. Water is added and the mixture extracted with diethyl ether. The organic layer is washed with brine, dried (Na_2SO_4) and volatiles removed under reduced pressure. The product (80 mg) is obtained after column chromatography (silica gel, n-hexane/ethyl acetate gradient 100:0 to 50:50).

Step 2: 1-Bromo-2-methyl-3-(3-(methylsulfonyl)propoxy)benzene

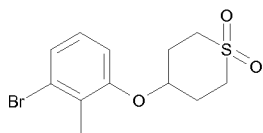
(3-(3-Bromo-2-methylphenoxy)propyl)(methyl)sulfane (0.90 g) and 3-chloroperbenzoic acid (1.7 g) are allowed to react in dichloromethane (15 mL) for 16 h. A saturated solution of K_2CO_3 is added with vigorous stirring, the organic layer collected, washed (brine), dried (Na_2SO_4) and volatiles removed under reduced pressure. The product (0.91 g) is obtained after column chromatography (silica gel, n-hexane/ethyl acetate gradient 100:0 to 70:30).

Intermediate 50ka

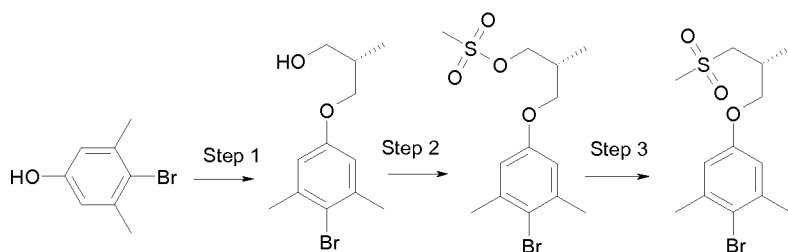
2-Bromo-5-(4-methanesulfonyl-butoxy)-1,3-dimethyl-benzene



The title compound is prepared in analogy to Intermediate 50k, starting from 4-methylsulfonylbutan-1-ol and from 4-bromo-3,5-dimethylphenol.

Intermediate 50l4-(3-Bromo-2-methyl-phenoxy)-tetrahydro-thiopyran 1,1-dioxide

The title compound is prepared in analogy to Intermediate 50g, starting from
 5 Intermediate 49g and from 3-bromo-2-methyl-phenol.

Intermediate 50m2-Bromo-5-((R)-3-methanesulfonyl-2-methyl-propoxy)-1,3-dimethyl-benzene**Step 1:** (S)-3-(4-Bromo-3,5-dimethyl-phenoxy)-2-methyl-propan-1-ol

(S)-3-Bromo-2-methyl-1-propanol (150 mg), 4-bromo-3,5-dimethylphenol (98.5 mg) and potassium carbonate are stirred in 5 mL of acetonitrile at 80 °C for 4 h. The reaction mixture is cooled to room temperature, water is added and the reaction mixture is extracted with diethyl ether. The organic phase is separated, dried over
 15 sodium sulfate and concentrated under vacuum to give a solid, used in the next step without further purification. Yield: 130 mg.

Step 2: Methanesulfonic acid (R)-3-(4-bromo-3,5-dimethyl-phenoxy)-2-methyl-propyl ester

(S)-3-(4-Bromo-3,5-dimethyl-phenoxy)-2-methyl-propan-1-ol (130 mg),
 20 methanesulfonyl chloride (0.073 mL) and triethylamine (0.264 mL) are stirred in 5 mL of dichloromethane at room temperature overnight. The reaction mixture is washed with citric acid saturated aqueous solution and with brine. The organic phase is separated, dried over sodium sulfate and concentrated under vacuum to give the title compound, used in the next step without further purification. Yield: 148 mg.

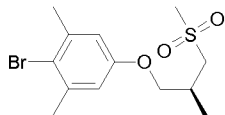
Step 3: 2-Bromo-5-((R)-3-methanesulfonyl-2-methyl-propoxy)-1,3-dimethyl-benzene

Methanesulfonic acid (R)-3-(4-bromo-3,5-dimethyl-phenoxy)-2-methyl-propyl ester (148 mg) and sodium methanesulfinate (215 mg) are stirred in 3 mL of N,N-dimethylformamide at 80 °C for 4 h. The reaction mixture is cooled to room

temperature, water is added and the reaction mixture is extracted with diethyl ether. The organic phase is separated, dried over sodium sulfate and concentrated under vacuum to give the title compound. Yield: 118 mg.

5 Intermediate 50n

2-Bromo-5-((S)-3-methanesulfonyl-2-methyl-propoxy)-1,3-dimethyl-benzene

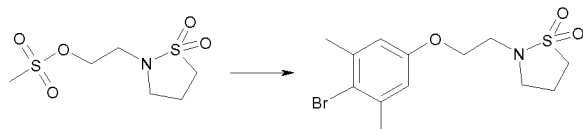


The title compound is prepared in analogy to Intermediate 50m, starting from (R)-3-bromo-2-methyl-1-propanol.

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Intermediate 50o

2-[2-(4-Bromo-3,5-dimethyl-phenoxy)-ethyl]-isothiazolidine 1,1-dioxide

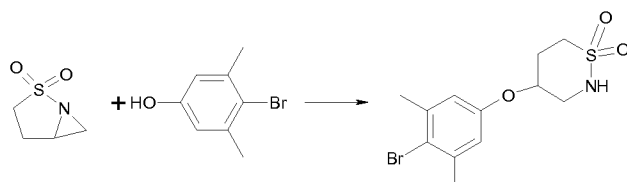


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The title compound is prepared in analogy to Intermediate 50g, starting from methanesulfonic acid 2-(1,1-dioxo-1-isothiazolidin-2-yl)-ethyl ester (EP1479684 A1, 2004).

Intermediate 50p

4-(4-Bromo-3,5-dimethyl-phenoxy)-[1,2]thiazinane 1,1-dioxide



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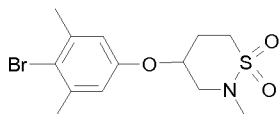
2-Thia-1-aza-bicyclo[3.1.0]hexane 2,2-dioxide (Liang, Jiang-Lin et al., Organic Letters, 2002, vol. 4, # 25 p. 4507 – 4510) (300 mg) is added to a suspension of 4-bromo-3,5-dimethylphenol (1.14 g) and sodium hydride (140 mg of a 60% mineral oil suspension) in 25 mL of N,N-dimethylacetamide. The reaction mixture is stirred at 130 °C for 5 h. Water is added and the reaction mixture is extracted with ethyl acetate. The organic phase is separated, dried over sodium sulfate and concentrated

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under vacuum. The residue is chromatographed on silica gel (cyclohexane/ethyl acetate 100:0→30:70) to give the title compound. Yield: 220 mg.

Intermediate 50q

5 4-(4-Bromo-3,5-dimethyl-phenoxy)-2-methyl-[1,2]thiazinane 1,1-dioxide

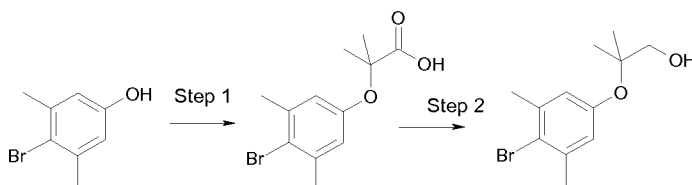


4-(4-Bromo-3,5-dimethyl-phenoxy)-[1,2]thiazinane 1,1-dioxide (110 mg) and sodium hydride (14,5 mg of a 60% mineral oil suspension) are suspended in 2 mL of N,N-dimethylformamide. Iodomethane (0.02 mL) is added and the reaction mixture is stirred at room temperature for 3 h. The solvent is removed, water is added and the reaction mixture is extracted with ethyl acetate. The organic phase is separated, dried over sodium sulfate and concentrated under vacuum. The residue is chromatographed on silica gel (cyclohexane/ethyl acetate 90:10→60:40) to give the title compound. Yield: 110 mg.

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Intermediate 50r

2-(4-Bromo-3,5-dimethyl-phenoxy)-2-methyl-propan-1-ol



Step 1: 2-(4-Bromo-3,5-dimethyl-phenoxy)-2-methyl-propionic acid.

To a solution of 4-bromo-3,5-dimethylphenol (5 g) in 100 mL of acetone stirred at -30 °C, sodium hydroxide (31 g) is added and the reaction mixture is allowed to reach room temperature in 30 min, then warmed to reflux for 3 h. The reaction mixture is concentrated under vacuum, iced-water is added and a 6 M solution of HCl is added up to acidic pH. The reaction mixture is extracted with ethyl acetate. The organic phase is separated, dried over sodium sulfate and concentrated under vacuum. The residue is chromatographed on silica gel (hexane/ethyl acetate:50/50) to give the title compound. Yield: 8 g.

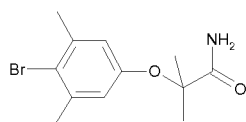
25

Step 2: 2-(4-Bromo-3,5-dimethyl-phenoxy)-2-methyl-propan-1-ol 2-(4-Bromo-3,5-dimethyl-phenoxy)-2-methyl-propionic acid (4.45 g) is dissolved in 50 mL of

tetrahydrofuran, borane methylsulfide complex (2.6 mL) is added and the reaction mixture is stirred at room temperature for 5 h. The reaction mixture is cooled to 0 °C, 10% HCl water solution is added dropwise and the reaction mixture is extracted with dichloromethane. The organic phase is separated, dried over sodium sulfate and concentrated under vacuum. The residue is chromatographed on silica gel (hexane/ethyl acetate 100:0→50:50) to give the title compound. Yield: 2.6 g.

Intermediate 50s

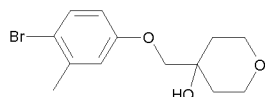
2-(4-Bromo-3,5-dimethyl-phenoxy)-2-methyl-propionamide



2-(4-Bromo-3,5-dimethyl-phenoxy)-2-methyl-propionic acid (500 mg) is dissolved in 10 mL of tetrahydrofuran, 1,1'-carbonyldimidazole (217 mg) and 30% ammonium hydroxide water solution are added and the reaction mixture is stirred at room temperature for 3h. The reaction mixture is concentrated under vacuum, ethyl acetate is added and the organic solution is washed with a 10% HCl water solution. The organic phase is separated, dried over sodium sulfate and concentrated under vacuum to give the title compound. Yield: 300 mg.

Intermediate 50ta

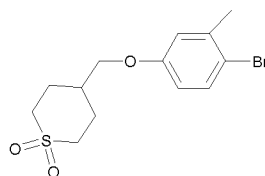
4-(4-Bromo-3-methyl-phenoxy)methyl)-tetrahydro-pyran-4-ol



The title compound is prepared in analogy to Intermediate 50bb, starting from 4-bromo-3-methylphenol.

Intermediate 50tb

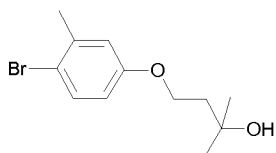
4-(4-Bromo-3-methyl-phenoxy)methyl)-tetrahydro-thiopyran 1,1-dioxide



Intermediate 49ga (400 mg) is dissolved in 10 mL of N,N-dimethylformamide, 4-bromo-3-methylphenol (309 mg) and cesium carbonate (1.08 g) are added and the reaction mixture is stirred at 130 °C for 12 h. The reaction mixture is concentrated under vacuum, water is added and the reaction mixture is extracted with dichloromethane, The organic phase is separated, dried over sodium sulfate and concentrated under vacuum. The residue is triturated with ethyl acetate to give the title compound. Yield: 250 g.

Intermediate 50tc

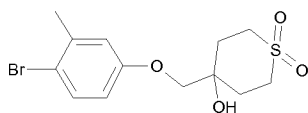
10 4-(4-Bromo-3-methyl-phenoxy)-2-methyl-butan-2-ol



Intermediate 7 Step 1 (440 mg) is dissolved in 5 mL of N,N-dimethylformamide, 4-Bromo-3-methylphenol (300 mg) and cesium carbonate (950 g) are added and the reaction mixture is stirred at 80 °C for 5 h. The reaction mixture is concentrated under vacuum, water is added and the reaction mixture is extracted with ethyl acetate, The organic phase is separated, dried over sodium sulfate and concentrated under vacuum. The residue is chromatographed on silica gel (cyclohexane/ethyl acetate 100:0→50:50) to give the title compound. Yield: 250 mg.

20 **Intermediate 50td**

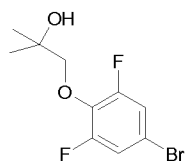
4-(4-Bromo-3-methyl-phenoxy)methyl)-1,1-dioxo-hexahydro-1-thiopyran-4-ol



The title compound is prepared in analogy to Intermediate 50bb, starting from 4-bromo-2,6-difluorophenol.

Intermediate 50ub

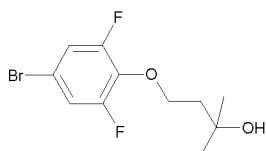
5 1-(4-Bromo-2,6-difluoro-phenoxy)-2-methyl-propan-2-ol



The title compound is prepared in analogy to Intermediate 50ua starting from 2,2-dimethyl-oxirane.

10 **Intermediate 50uc**

4-(4-Bromo-2,6-difluoro-phenoxy)-2-methyl-butan-2-ol

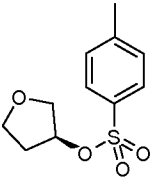
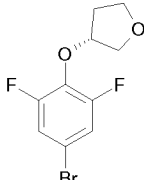
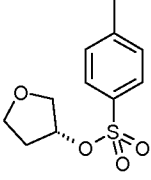
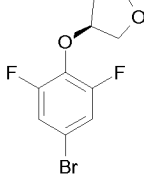


Intermediate 7 Step 1 (1 g) is dissolved in 10 mL of N,N'-dimethylacetamide, 4-bromo-2,6-difluorophenol (1 g) and cesium carbonate (2.5 g) are added and the reaction mixture is stirred at 80 °C for 5 h. The reaction mixture is concentrated under vacuum, water is added and the reaction mixture is extracted with ethyl acetate, The organic phase is separated, dried over sodium sulfate and concentrated under vacuum. The residue is chromatographed on silica gel (cyclohexane/ethyl acetate 100:0→80:20) to give the title compound. Yield: 640 mg.

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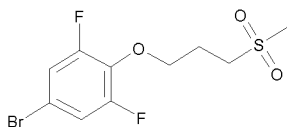
The following intermediates are prepared in analogy to Intermediate 50uc starting from the corresponding tosylate intermediate.

Starting tosylate Intermediate	Intermediate	Molecular structure and name
	50ud	

 49hb		 (R)-3-(4-Bromo-2,6-difluorophenoxy)- tetrahydro-furan
 49hc	50ue	 (S)-3-(4-Bromo-2,6-difluorophenoxy)- tetrahydro-furan

Intermediate 50uf

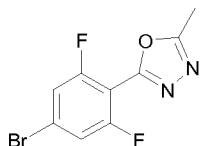
5-Bromo-1,3-difluoro-2-(3-methanesulfonyl-propoxy)-benzene



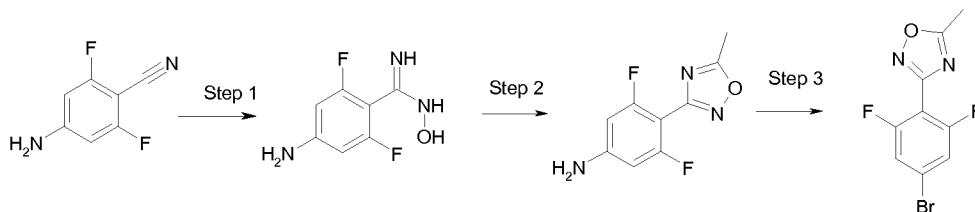
- 5 The title compound is prepared in analogy to Intermediate 50uc starting from methanesulfonic acid 3-methanesulfonyl-propyl ester

Intermediate 50ug

2-(4-Bromo-2,6-difluorophenyl)-5-methyl-[1,3,4]oxadiazole



- 10 Acetic acid hydrazide (340 mg) N,N,N',N'-tetramethyl-O-(benzotriazol-1-yl)uronium tetrafluoroborate (1.63 g) and di-isopropyl-ethyl amine (1.64 g) are stirred in 20 mL of acetonitrile at room temperature for 5 minutes. 4-Bromo-2,6-difluoro-benzoic acid (WO2005/12283 A1, 2005) (1 g) is added and the reaction mixture is stirred at room
- 15 temperature for 24 h, then at 70 °C for 3 h. The reaction mixture is concentrated under vacuum, The residue is chromatographed on silica gel (cyclohexane/ethyl acetate 100:0→60:40) to give the title compound. Yield: 300 mg.

Intermediate 50uh**3-(4-Bromo-2,6-difluoro-phenyl)-5-methyl-[1,2,4]oxadiazole****5 Step 1: 4-Amino-2,6-difluoro-N-hydroxy-benzamidine**

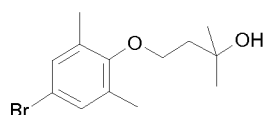
In a microwave vial, 4-amino-2,5-difluoro-benzonitrile (2 g) is dissolved in 10 mL of ethanol. Hydroxylamine (1,71 g) is added, the vial is sealed and the mixture is stirred at 100 °C for 1 h (100 W). The solvent is removed, the residue is washed with water. The precipitated solid is dried under vacuum and used in the next step without further purification. Yield: 2.4 g.

Step 2: 3,5-Difluoro-4-(5-methyl-[1,2,4]oxadiazol-3-yl)-phenylamine

4-Amino-2,6-difluoro-N-hydroxy-benzamidine (2.4 g) acetyl chloride (25,64 mL) and triethylamine (5.35 mL) are stirred in 10 mL of 1,4-dioxane at room temperature for 30 minutes, then at 120 °C for 2 h. the solvent is removed, the residue is partitioned between a bicarbonate saturated water solution and ethyl acetate. The organic phase is separated, dried over sodium sulfate and concentrated under vacuum. The residue is chromatographed on silica gel (cyclohexane/ethyl acetate 100:0→50:50) to give the title compound. Yield: 620 mg.

Step 3: 4-Amino-2,6-difluoro-N-hydroxy-benzamidine

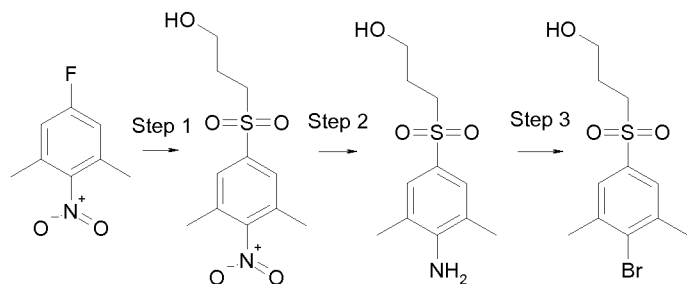
Copper bromide (790 mg) and tert-butyl nitrite (870 mL) are stirred in 15 mL of acetonitrile at 65 °C for 20 minutes, 3,5-Difluoro-4-(5-methyl-[1,2,4]oxadiazol-3-yl)-phenylamine (620 mg) is added and the reaction mixture is stirred at 65 °C for 4 h. The reaction mixture is concentrated under vacuum, The residue is chromatographed on silica gel (cyclohexane/ethyl acetate 100:0→80:20) to give the title compound. Yield: 700 mg.

Intermediate 50w**4-(4-Bromo-2,6-dimethyl-phenoxy)-2-methyl-butan-2-ol**

The title compound is prepared in analogy to Intermediate 7 starting from 4-bromo-2,6-dimethyl-phenol.

Intermediate 50x

5 3-(4-Bromo-3,5-dimethyl-benzenesulfonyl)-propan-1-ol



Step 1: 3-(3,5-Dimethyl-4-nitro-benzenesulfonyl)-propan-1-ol

5-Fluoro-1,3-dimethyl-2-nitrobenzene (2 g), 3-mercaptopropan-1-ol (1.5 mL) and potassium carbonate (2.4 g) are stirred in 20 mL of N,N-dimethylformamide at 60 °C for 4 h. The reaction mixture is cooled to 0 °C and 3-chloroperbenzoic acid (10 g) is added. The reaction mixture is stirred at room temperature for 1 h, water is added and the reaction mixture is extracted with ethyl acetate. The organic phase is washed with a bicarbonate saturated aqueous solution, with a 5% sodium sulfite water solution and with brine. The solvent is removed to give the title compound, used in the next step without further purification. Yield: 2.8 g.

Step 2: 3-(4-Amino-3,5-dimethyl-benzenesulfonyl)-propan-1-ol

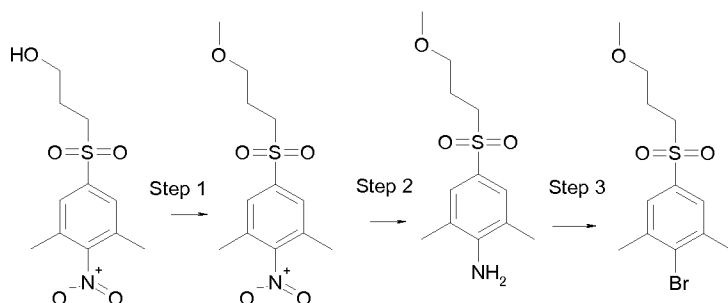
3-(3,5-Dimethyl-4-nitro-benzenesulfonyl)-propan-1-ol is dissolved in 15 mL of ethanol, Pd/C(5%) (55 mg) is added and the reaction mixture is stirred under hydrogen atmosphere (3 bar) for 3 h. The reaction mixture is filtered on a celite pad, the solvent is concentrated under vacuum to give the title compound. Yield: 1 g.

Step 3: 3-(4-Bromo-3,5-dimethyl-benzenesulfonyl)-propan-1-ol

The title compound is prepared following a procedure analogous to Step 3 in the preparation of Intermediate 50uh, starting from 2: 3-(4-Amino-3,5-dimethyl-benzenesulfonyl)-propan-1-ol. Yield: 740 mg.

Intermediate 50y

2-Bromo-5-(3-methoxy-propane-1-sulfonyl)-1,3-dimethyl-benzene



Step 1: 5-(3-Methoxy-propane-1-sulfonyl)-1,3-dimethyl-2-nitro-benzene

3-(3,5-Dimethyl-4-nitro-benzenesulfonyl)-propan-1-ol (1.4 g) is dissolved in 20 mL of acetonitrile, cesium carbonate (3.34 g) and iodometane (638 mL) are added and the reaction mixture is stirred at room temperature overnight. Water is added and the reaction mixture is extracted with ethyl ether. The organic phase is separated, dried over sodium sulfate and concentrated under vacuum. The residue is chromatographed on silica gel (hexane/ethyl acetate 100:0→50:50) to give the title compound. Yield: 1 g.

Step 2: 4-(3-Methoxy-propane-1-sulfonyl)-2,6-dimethyl-phenylamine

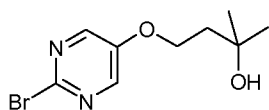
The title compound is prepared following a procedure analogous to Step 2 in the preparation of Intermediate 50x, starting from 5-(3-Methoxy-propane-1-sulfonyl)-1,3-dimethyl-2-nitro-benzene

Step 3: 2-Bromo-5-(3-methoxy-propane-1-sulfonyl)-1,3-dimethyl-benzene

The title compound is prepared following a procedure analogous to Step 3 in the preparation of Intermediate 50uh, starting from 4-(3-Methoxy-propane-1-sulfonyl)-2,6-dimethyl-phenylamine.

Intermediate 50z

4-(2-Bromo-pyrimidin-5-yloxy)-2-methyl-butan-2-ol

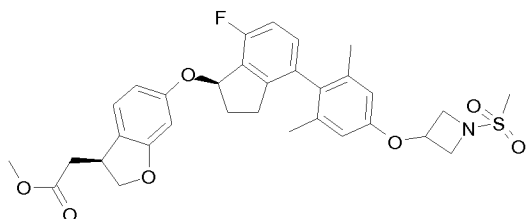


3-Methyl-1,3-butanediol (180 mg) is stirred in 5 mL of N,N-dimethylformamide at 0 °C, sodium hydride (6 mg of a 60% mineral oil suspension) is added and the reaction mixture is stirred for 2 h, then it is added dropwise to a solution of 2-bromo-4-fluoropyrimidine (300 mg) in 5 mL of N,N-dimethylformamide and the reaction mixture stirred at 0 °C for 2 h again. The solvent is removed and the residue is purified by

flash chromatography (hexane/ethyl acetate 90:10→70:30) to give the title compound. Yield: 20 mg.

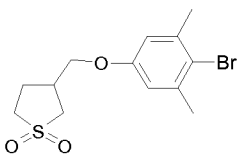
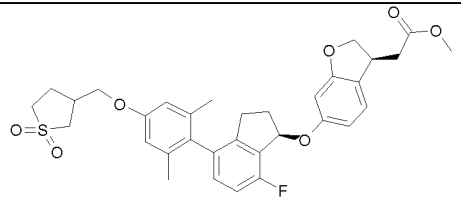
Intermediate 51a

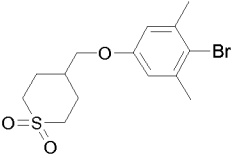
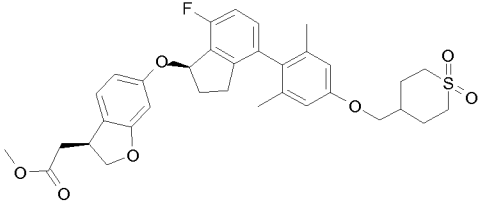
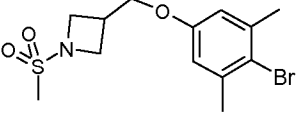
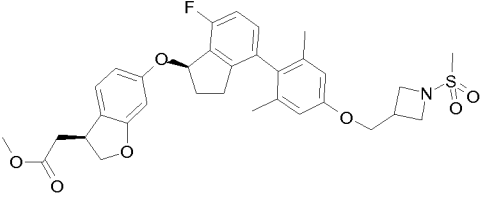
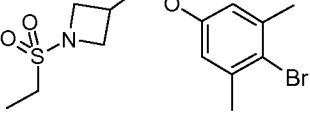
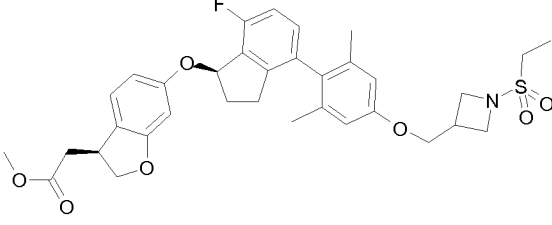
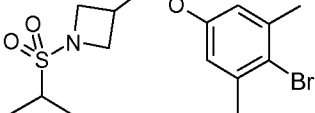
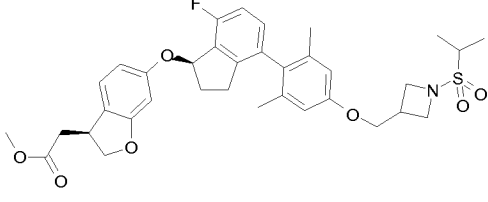
- 5 Methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-(1-(methylsulfonyl)azetidin-3-yloxy)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

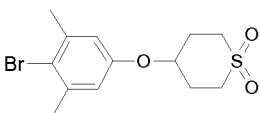
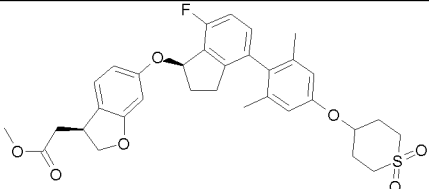
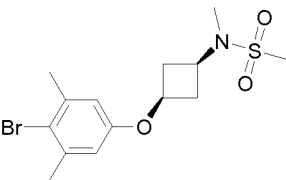
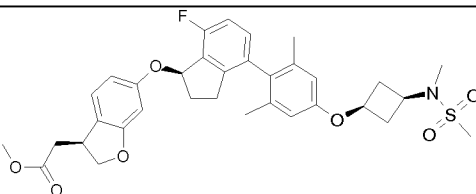
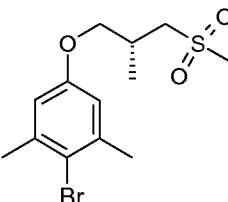
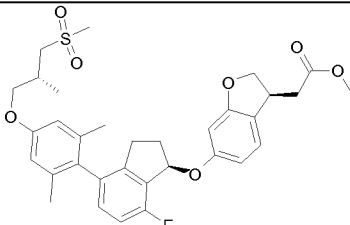
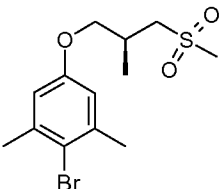
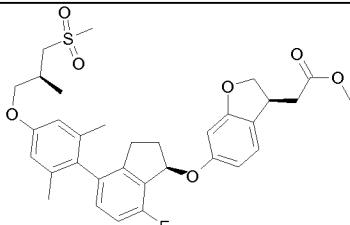


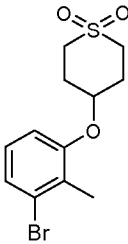
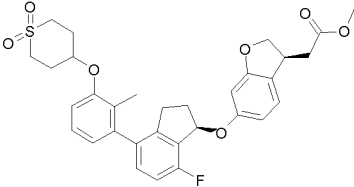
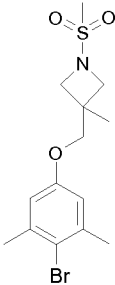
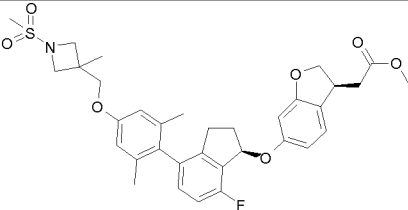
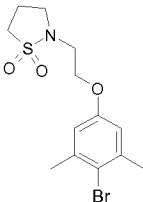
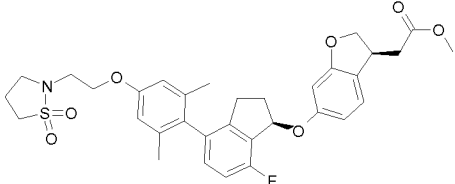
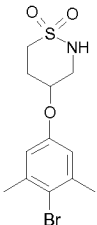
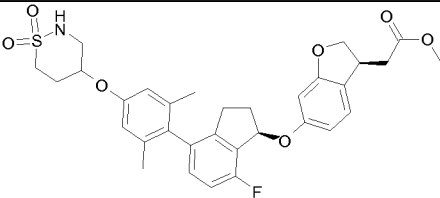
- In a microwave vial, methyl 2-((S)-6-((R)-7-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate (130 mg), intermediate 50g (104 mg), K₃PO₄ (133 mg) are suspended in toluene (2 mL) and water (200 µL) and purged for 10 minutes with nitrogen. Palladium-(II)-acetate (5 mg) and dicyclohexyl(2',6'-dimethoxybiphenyl-2-yl)phosphine (S-Phos) (8.5 mg) are added, the vial is sealed and the mixture is stirred at 120°C for 1 hours (100 W). After cooling to ambient temperature the mixture is partitioned between diethylether and saturated aqueous NH₄Cl solution. The organic phase is dried (MgSO₄) and concentrated. The residue is chromatographed on silica gel (cyclohexane/ethyl acetate 100:0→50:50) to give the title compound. Yield: 55 mg.

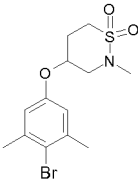
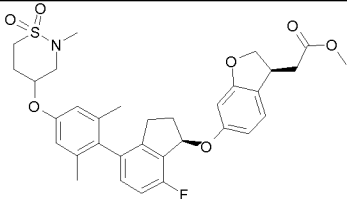
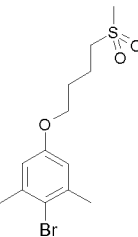
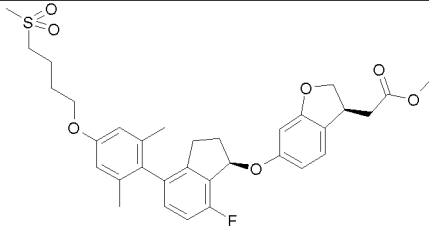
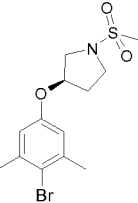
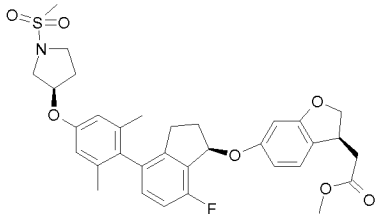
- The intermediates in the following table are prepared from methyl 2-((S)-6-((R)-7-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate and the corresponding starting bromo-aryl intermediates following a procedure analogous to that described for Intermediate 51a.

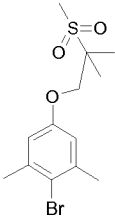
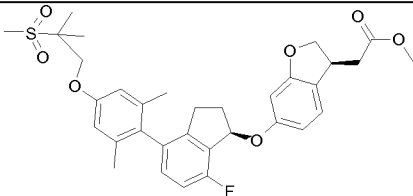
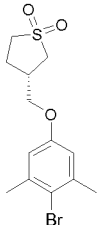
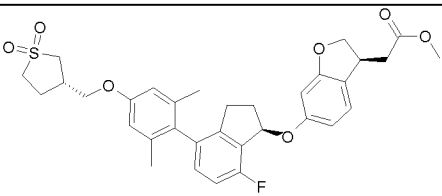
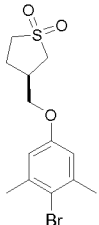
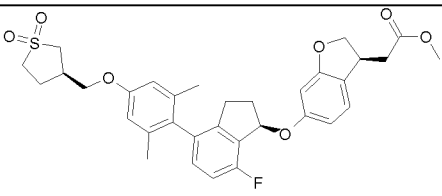
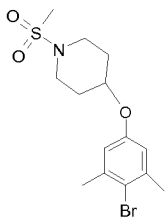
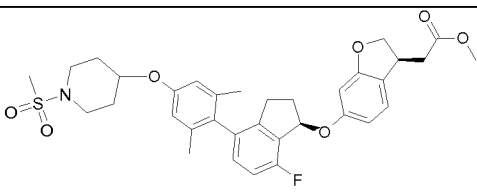
Starting bromoaryl Intermediate	Intermediate	Molecular structure and name
 50a	51b	 Methyl 2-((3S)-6-((1R)-4-(2,6-dimethyl-4-((1,1-

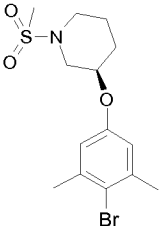
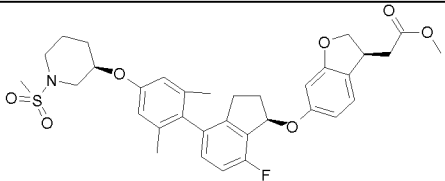
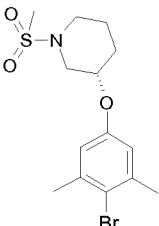
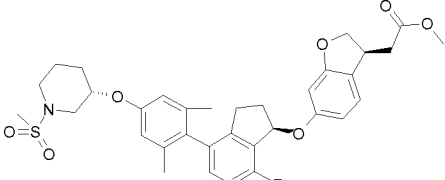
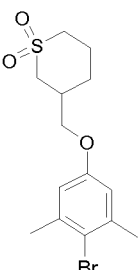
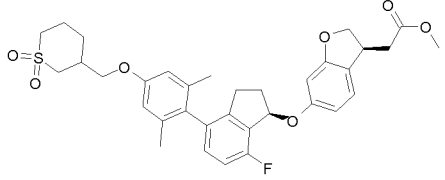
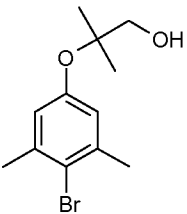
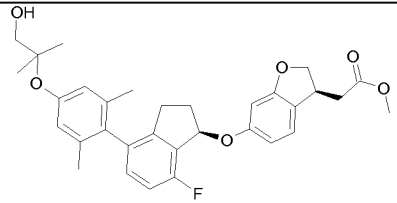
		dioxo-tetrahydrothiophen-3-yl)methoxy)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate
 50b	51c	 Methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-((1,1-dioxo-tetrahydro-2H-thiopyran-4-yl)methoxy)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate
 50d	51d	 Methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-((1-(methylsulfonyl)azetidin-3-yl)methoxy)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate
 50e	51e	 Methyl 2-((S)-6-((R)-4-(4-((1-(ethylsulfonyl)azetidin-3-yl)methoxy)-2,6-dimethylphenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate
 50f	51f	 Methyl 2-((S)-6-((R)-7-fluoro-4-(4-((1-(isopropylsulfonyl)azetidin-3-yl)methoxy)-2,6-dimethylphenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

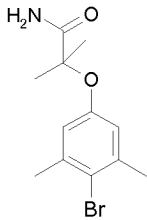
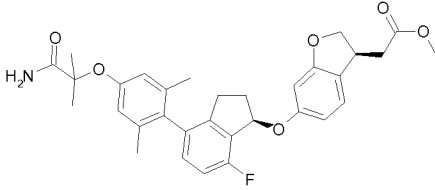
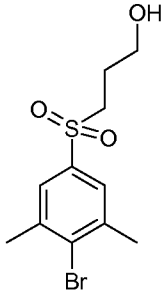
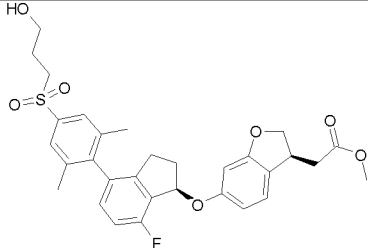
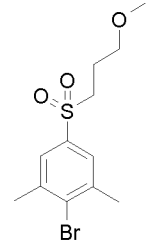
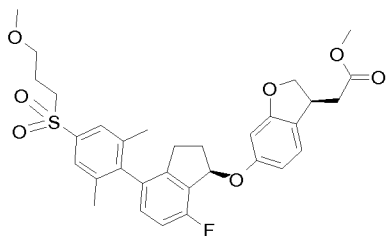
		dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)- 2,3-dihydrobenzofuran-3-yl)acetate
 50h	51g	 Methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-(1,1-dioxo-tetrahydro-2H-thiopyran-4-yloxy)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate
 50i	51h	 Methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-((1s,3S)-3-(N-methylmethylsulfonamido)cyclobutoxy)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate
 50m	51n	 ((S)-6-((R)-7-Fluoro-4-[4-((R)-3-methanesulfonyl-2-methyl-propoxy)-2,6-dimethyl-phenyl]-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester
 50n	51o	 ((S)-6-((R)-7-Fluoro-4-[4-((S)-3-methanesulfonyl-2-methyl-propoxy)-2,6-dimethyl-phenyl]-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester

		-dimethyl-phenyl]-indan-1-yloxy}-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester
 50l	51p	 ((S)-6-((R)-4-[3-(1,1-Dioxo-hexahydro-1--thiopyran-4-yloxy)-2-methyl-phenyl]-7-fluoro-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester
 50gb	51q	 ((S)-6-((R)-7-Fluoro-4-[4-(1-methanesulfonyl-3-methyl-azetidin-3-ylmethoxy)-2,6-dimethyl-phenyl]-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester
 50o	51r	 [(S)-6-((R)-4-[4-[2-(1,1-Dioxo-1-isothiazolidin-2-yl)-ethoxy]-2,6-dimethyl-phenyl]-7-fluoro-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl]-acetic acid methyl ester
 50s	51s	 ((S)-6-((R)-4-[4-(1,1-Dioxo-1--[1,2]thiazinan-4-

50p		yl-oxy)-2,6-dimethyl-phenyl]-7-fluoro-indan-1-yloxy}-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester
 50q	51t	 ((S)-6-((R)-4-[2,6-Dimethyl-4-(2-methyl-1,1-dioxo-1,2-thiazinan-4-yloxy)-phenyl]-7-fluoro-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester
 50ka	51u	 ((S)-6-((R)-7-Fluoro-4-[4-(4-methanesulfonyl-butoxy)-2,6-dimethyl-phenyl]-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester
 50gc	51v	 ((S)-6-((R)-7-Fluoro-4-[4-((R)-1-methanesulfonyl-pyrrolidin-3-yloxy)-2,6-dimethyl-phenyl]-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester

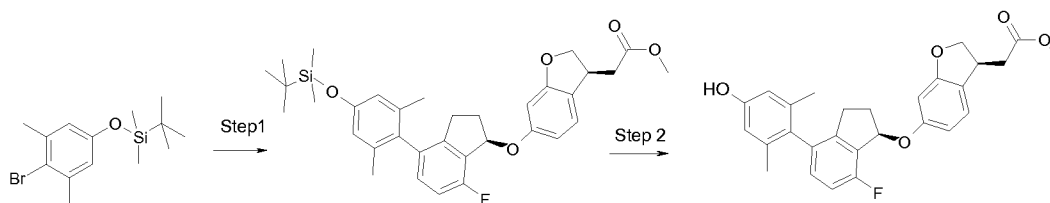
 50ha	51w	 ((S)-6-{(R)-7-Fluoro-4-[4-(2-methanesulfonyl-2-methyl-propoxy)-2,6-dimethyl-phenyl]-indan-1-yloxy}-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester
 50aa	51x	 ((S)-6-{(R)-4-[4-((S)-1,1-Dioxo-tetrahydro-1-thiophen-3-ylmethoxy)-2,6-dimethyl-phenyl]-7-fluoro-indan-1-yloxy}-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester Absolute configuration unknown.
 50aa	51y	 ((S)-6-{(R)-4-[4-((R)-1,1-Dioxo-tetrahydro-1-thiophen-3-ylmethoxy)-2,6-dimethyl-phenyl]-7-fluoro-indan-1-yloxy}-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester. Absolute configuration unknown.
 50ga	51z	 ((S)-6-{(R)-7-Fluoro-4-[4-(1-methanesulfonyl-piperidin-4-yloxy)-2,6-di

		methyl-phenyl]-indan-1-yloxy}-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester
 50gd	51za	 ((S)-6-{(R)-7-Fluoro-4-[4-((R)-1-methanesulfonyl-piperidin-3-yloxy)-2,6-dimethyl-phenyl]-indan-1-yloxy}-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester
 50ge	51zb	 ((S)-6-{(R)-7-Fluoro-4-[4-((S)-1-methanesulfonyl-piperidin-3-yloxy)-2,6-dimethyl-phenyl]-indan-1-yloxy}-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester
 50ba	51zc	 ((S)-6-{(R)-4-[4-(1,1-Dioxo-hexahydro-1-thiopyran-3-ylmethoxy)-2,6-dimethyl-phenyl]-7-fluoro-indan-1-yloxy}-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester
 50r	51zd	 ((S)-6-{(R)-7-Fluoro-4-[4-(2-hydroxy-1,1-dimethyl-ethoxy)-2,6-dimethyl

		-phenyl]-indan-1-yloxy}-2,3-dihydro -benzofuran-3-yl)-acetic acid methy l ester
 50s	51zeb	 ((S)-6-((R)-4-[4-(1-Carbamoyl-1-met hyl-ethoxy)-2,6-dimethyl-phenyl]-7- fluoro-indan-1-yloxy}-2,3-dihydro-b enzofuran-3-yl)-acetic acid methyl ester
 50x	51zf	 ((S)-6-((R)-7-Fluoro-4-[4-(3-hydrox y-propane-1-sulfonyl)-2,6-dimethyl- phenyl]-indan-1-yloxy}-2,3-dihydro- benzofuran-3-yl)-acetic acid methyl ester
 50y	51zg	 (6-{7-Fluoro-4-[4-(3-methoxy-propan e-1-sulfonyl)-2,6-dimethyl-phenyl]- indan-1-yloxy}-2,3-dihydro-benzofur an-3-yl)-acetic acid methyl ester

Intermediate 51i

Methyl 2-((S)-6-((R)-7-fluoro-4-(4-hydroxy-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate



Step 1: Methyl 2-((S)-6-((R)-4-(4-(tert-butyldimethylsilyloxy)-2,6-dimethylphenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

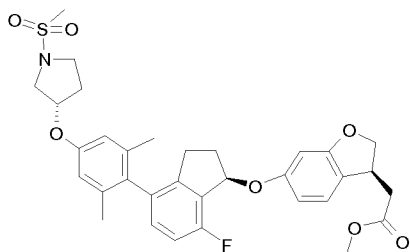
Methyl 2-((S)-6-((R)-7-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate (500 mg), Intermediate 50j (500 mg), K_3PO_4 (450 mg) are suspended in toluene (2.5 mL) and water (0.2 mL) and purged for 10 minutes with argon. Palladium-(II)-acetate (12 mg) and dicyclohexyl(2',6'-dimethoxybiphenyl-2-yl)phosphine (S-Phos) (44 mg) are added and the mixture is stirred at 100°C overnight. After cooling to ambient temperature the mixture is partitioned between diethylether and saturated aqueous NH_4Cl solution. The organic phase is dried ($MgSO_4$) and concentrated. The residue is chromatographed on silica gel (cyclohexane/ethyl acetate 99:1→70:30) to give the title compound. Yield: 440 mg.

Step 2: Methyl 2-((S)-6-((R)-7-fluoro-4-(4-hydroxy-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

Methyl 2-((S)-6-((R)-4-(4-(tert-butyldimethylsilyloxy)-2,6-dimethylphenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate (440 mg) and tetrabutylammonium fluoride in tetrahydrofuran (1 M; 3.1 mL) are stirred in tetrahydrofuran (5 mL) at ambient temperature overnight. The reaction mixture is partitioned between diethylether and saturated aqueous NH_4Cl solution. The organic phase is dried ($MgSO_4$) and concentrated. The residue is chromatographed on silica gel (cyclohexane/ethyl acetate 90:10→60:40) to give the title compound. Yield: 280 mg.

Intermediate 51j

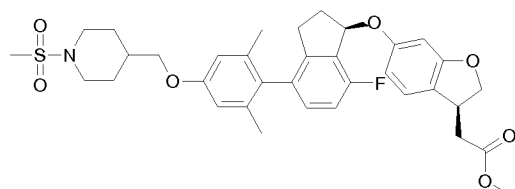
Methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-((S)-1-(methylsulfonyl)pyrrolidin-3-yloxy)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate



Methyl 2-((S)-6-((R)-7-fluoro-4-(4-hydroxy-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate (60 mg), Intermediate 49e and K_2CO_3 (34 mg) are suspended in N,N-dimethylformamide (5 mL) and stirred at 95°C for 72 hours. The reaction mixture is concentrated under vacuum, partitioned between ethyl acetate and water. The organic phase is dried ($MgSO_4$) and concentrated. The residue is chromatographed on silica gel (cyclohexane/ethyl acetate 100:0→75:25) to give the title compound. Yield: 29 mg.

10 Intermediate 51k

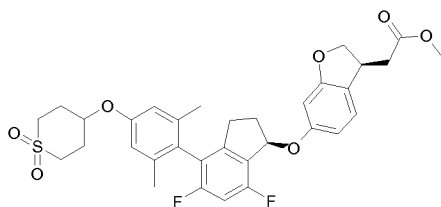
M e t h y l 2-((S)-6-((R)-4-(2,6-dimethyl-4-((1-(methylsulfonyl)piperidin-4-yl)methoxy)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate



15 The title compound is prepared in analogy to Intermediate 51j starting from Intermediate 49f and Intermediate 51i.

Intermediate 51l

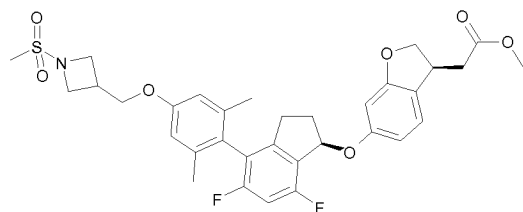
M e t h y l 2-((S)-6-((R)-4-(2,6-dimethyl-4-(1,1-dioxo-tetrahydro-2H-thiopyran-4-yloxy)phenyl)-5,7-difluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate



The title compound is prepared in analogy to Intermediate 51a, starting from Intermediate 50h and Intermediate 52.

Intermediate 51la

- 5 ((S)-6-((R)-5,7-Difluoro-4-[4-(1-methanesulfonyl-azetidin-3-ylmethoxy)-2,6-dimethyl-phenyl]-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester

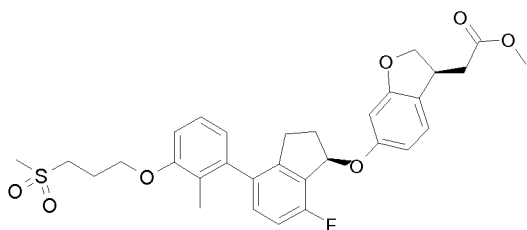


The title compound is prepared in analogy to Intermediate 51a starting from Intermediate 50d and Intermediate 52.

10

Intermediate 51m

- Methyl 2-((3S)-6-((1R)-7-fluoro-4-(2-methyl-3-(3-(methylsulfonyl)propoxy)phenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate



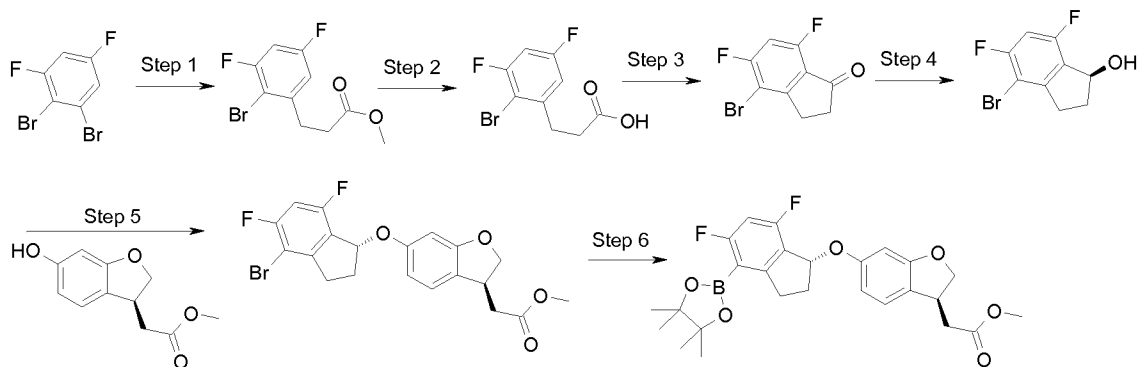
- 15 The title compound is prepared from methyl 2-((S)-6-((R)-7-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate and Intermediate 50k following a procedure analogous to that described for Intermediate 51a.

LC (method 17): t_R = 1.38 min.

20

Intermediate 52

- Methyl 2-((S)-6-((R)-5,7-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate



Step 1: Methyl 3-(2-bromo-3,5-difluorophenyl)propanoate

A mixture of 1,2-dibromo-3,5-difluorobenzene (4.5 g), 3,3-dimethoxyprop-1-ene (5.1 mL), tetrabutylammonium chloride (4.6 g) and triethylamine (3.5 mL) in N,N-dimethylformamide (50 mL) is purged with nitrogen for 20 minutes. Palladium-(II)-acetate (111 mg) is added and the mixture heated for 16 hours at 90°C. After cooling the mixture is partitioned between aqueous HCl (1 M) and diethyl ether, the organic layer dried (Na₂SO₄), volatiles evaporated under reduced pressure and the residue purified by column chromatography (silica gel; n-hexane/ethyl acetate 98:2→80:20) to give the title compound (3.6 g).

GC (method 1): t_R = 9.36 min.

Step 2: 3-(2-Bromo-3,5-difluorophenyl)propanoic acid

Methyl 3-(2-bromo-3,5-difluorophenyl)propanoate (4.3 g) in aqueous NaOH (4 M, 13.5 mL) and 2-propanol (30 mL) is heated at 50°C for 2 hours. Water is added, the mixture washed with diethyl ether, acidified to ca. pH 5 by adding concentrated aqueous HCl, and extracted twice with diethyl ether. The combined extracts of the acidified mixture are washed with brine and volatiles evaporated under reduced pressure. The resulting material (3.6 g) is used in the next step without further purification.

LC (method 16): t_R = 0.99 min.

Step 3: 4-Bromo-5,7-difluoro-2,3-dihydro-1H-inden-1-one

3-(2-Bromo-3,5-difluorophenyl)propanoic acid (3.0 g) is stirred with chlorosulfonic acid (10 mL) for 2 hours at ambient temperature. The mixture is then added dropwise to a vigorously stirred mixture of water and ice (200 mL) and further stirred for 15 minutes. Extraction with diethyl ether, subsequent washing of the organic layer with water, NaOH (0.2 M), and brine, drying (Na₂SO₄) and removal of the solvent under reduced pressure gives the crude product (2.7 g) that is used in the next step without further purification.

LC (method 16): t_R = 1.16 min.

Step 4: (S)-4-Bromo-5,7-difluoro-2,3-dihydro-1H-inden-1-ol

To triethylamine (3.7 mL) in dichloromethane is added dropwise with cooling in an ice bath formic acid (1.3 mL). 4-Bromo-5,7-difluoro-2,3-dihydro-1H-inden-1-one (2.9 g) is added and the mixture degassed with a stream of argon. Chloro[[[(1S,2S)-(-)-2-amino-1,2-diphenylethyl](4-toluenesulfonyl)amido](mesitylene)ruthenium(II) is added and the mixture stirred at ambient temperature for 16 hours. The mixture is washed with water, dried (Na_2SO_4) and the solvent removed under reduced pressure. Purification by column chromatography (silica gel; n-hexane/ethyl acetate 98:2→80:20) gives the title compound (2.5 g).

GC (method 1): t_R = 9.33 min. Chiral HPLC t_R = 9.33 min (Column Daicel Chiralcel OJ-H; 250 x 4.6 mm 5 μm ; n-hexane/EtOH 95:5; 1 mL/min; 25°C).

Step 5: Methyl 2-((S)-6-((R)-4-bromo-5,7-difluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

(S)-4-Bromo-5,7-difluoro-2,3-dihydro-1H-inden-1-ol (1.5 g), (S)-methyl 2-(6-hydroxy-2,3-dihydrobenzofuran-3-yl)acetate (1.4 g), triphenylphosphine (1.7 g) and di-tert-butyl azodicarboxylate (1.5 g) are stirred in tetrahydrofuran (50 mL) for 1 hour. Volatiles are evaporated under reduced pressure and the residue purified by column chromatography (silica gel; n-hexane/ethyl acetate 98:2→80:20) to give the title compound (1.5 g).

LC (method 16): t_R = 2.82 min.

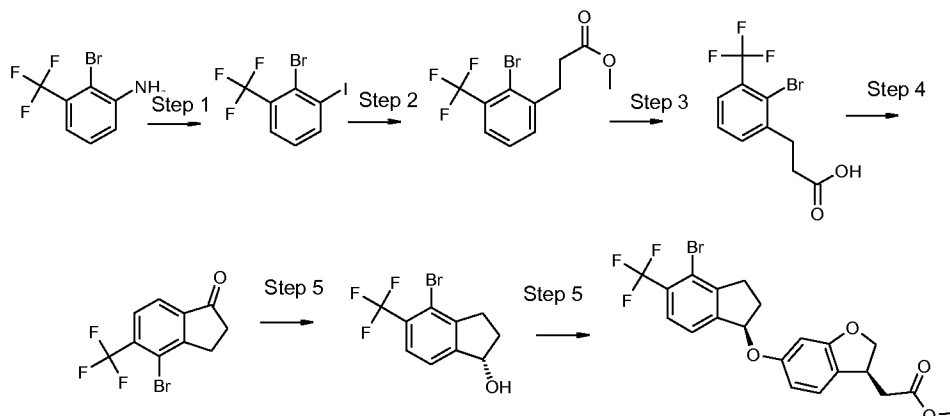
Step 6: Methyl 2-((S)-6-((R)-5,7-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

Methyl 2-((S)-6-((R)-4-bromo-5,7-difluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate (210 mg), bis(pinacolato)diboron (182 mg), [1,1'-bis(diphenylphosphino)-ferrocene]-dichloropalladium-(II) (35 mg) and potassium acetate (117 mg) are suspended in dry 1,4-dioxane (3 mL) in a microwave vial and degassed for 5 minutes with a flow of argon. The mixture is heated under microwave irradiation for 150 minutes at 120°C, then diluted with ethyl acetate, washed with water, the organic phase dried and the solvent removed under vacuum. The residue is purified by chromatography on silica gel (cyclohexane/ethyl acetate 100:0→80:20) to give the title compound (220 mg).

LC (method 18): t_R = 0.75 min; Mass spectrum: m/z = 487 $[\text{M}+\text{H}]^+$.

Intermediate 52a

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



5

Step 1: 2-Bromo-1-iodo-3-trifluoromethyl-benzene

2-Bromo-3-trifluoromethyl-phenylamine (8 g) is stirred in 90 mL of water at 0°C, sulfuric acid (96%) (27 mL) is added and the reaction mixture is stirred for 30 minutes. A solution of sodium nitrite (2.40 g) in 5 mL of water is added dropwise and after 30 minutes at 0 °C, potassium iodide (9.24 g) and iodine (9.31 g) are added. After completion of nitrogen evolution, the reaction mixture is warmed to 40 °C for 30 minutes. A saturated sodium sulfite water solution is added and the reaction mixture is extracted with ethyl acetate. The organic phase dried over sodium sulfate and concentrated under vacuum. The residue is purified by chromatography on silica gel (cyclohexane 100%) to give the title compound. Yield: 10 g.

Step 2: 3-(2-Bromo-3-trifluoromethyl-phenyl)-propionic acid methyl ester

The title compound is prepared following a procedure analogous to Step 1 in the preparation of Intermediate 17, starting from 2-bromo-1-iodo-3-trifluoromethyl-benzene.

Step 3: 3-(2-Bromo-3-trifluoromethyl-phenyl)-propionic acid

The title compound is prepared following a procedure analogous to Step 2 in the preparation of Intermediate 17, starting from 3-(2-bromo-3-trifluoromethyl-phenyl)-propionic acid methyl ester.

Step 4: 4-Bromo-5-trifluoromethyl-indan-1-one

3-(2-Bromo-3-trifluoromethyl-phenyl)-propionic acid (3 g), oxalyl chloride (1.8 mL) and few drops of N,N-dimethylformamide are stirred in 30 mL of dichloromethane under reflux for 1h. The solvent is removed, trifluoromethane sulfonic acid (20 mL) is

added and the reaction mixture is stirred at 60 °C for 3 h. The reaction mixture is slowly added dropwise to 300 mL of iced-water, then partitioned between bicarbonate saturated aqueous solution and ethyl acetate. The organic phase dried over sodium sulfate and concentrated under vacuum to give the title compound.

5 Yield: 2.5 g.

Step 5: (S)-4-Bromo-5-trifluoromethyl-indan-1-ol

The title compound is obtained following a procedure analogous to Step 1 in the preparation of Intermediate 1, starting from 4-bromo-5-trifluoromethyl-indan-1-one.

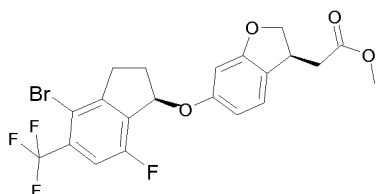
Step 6: [(S)-6-((R)-4-Bromo-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl]-acetic acid methyl ester

10

The title compound is obtained following a procedure analogous to Step 6 in the preparation of Intermediate 1, starting from (S)-4-bromo-5-trifluoromethyl-indan-1-ol.

Intermediate 52b

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

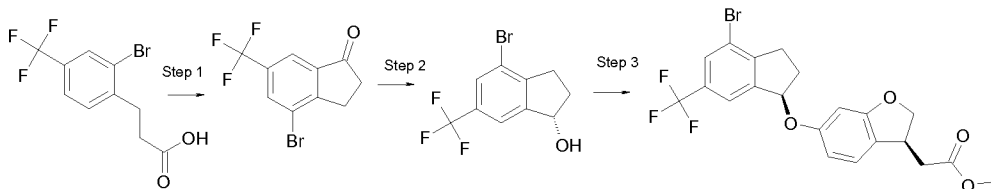


The title compound is prepared following a analogous procedure analogous to that described in the preparation of Intermediate 52a, starting in Step 2 with 2,3-dibromo-5-fluoro-benzotrifluoride as starting material.

20

Intermediate 52c

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



25

Step 1: 4-Bromo-6-trifluoromethyl-indan-1-one

3-(2-Bromo-4-trifluoromethyl-phenyl)-propionic acid (US2005/261310A1,2005) (1.45 g) is suspended in 15 mL of trifluoromethanesulfonic acid. The reaction mixture is

stirred at 85 °C for 4 h. Iced water and then a bicarbonate saturated aqueous solution are added. The reaction mixture is extracted with ethyl acetate. The organic phase is dried over sodium sulfate and concentrated under vacuum to give the title compound. Yield: 600 mg.

5 **Step 2: (S)-4-Bromo-6-trifluoromethyl-indan-1-ol**

The title compound is obtained following a procedure analogousous to Step 1 in the preparation of Intermediate 1, starting from 4-bromo-6-trifluoromethyl-indan-1-one.

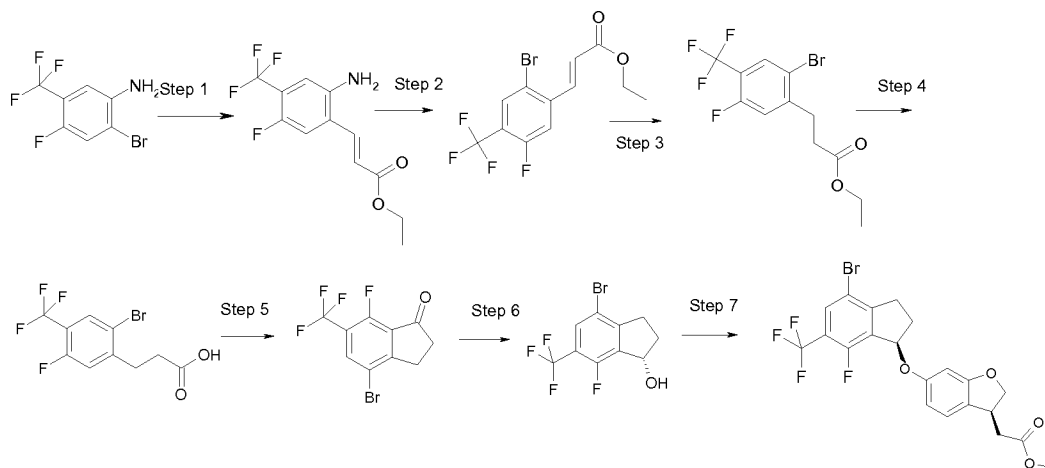
Step 3: [(S)-6-((R)-4-Bromo-6-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl]-acetic acid methyl ester

10 The title compound is obtained following a procedure analogous to Step 6 in the preparation of Intermediate 1, starting from (S)-4-bromo-6-trifluoromethyl-indan-1-ol.

Intermediate 52d

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

15



Step 1: (E)-3-(2-Amino-5-fluoro-4-trifluoromethyl-phenyl)-acrylic acid ethyl ester

2-Bromo-4-fluoro-5-(trifluoromethyl)aniline (15 g), ethylacrylate (17.45 g) tri-*o*-tolylphosphine (1.77 g), palladium(II) acetate (650 mg), and *N,N'*-diisopropylethylamine (15 g) are stirred in 100 mL of propionitrile at 100 °C for 12 h. The reaction mixture is concentrated under vacuum. The residue is purified by chromatography on silica gel (cyclohexane/ethyl acetate 100:0→80:20) to give the title compound. Yield: 10 g.

Step 2: (E)-3-(2-Bromo-5-fluoro-4-trifluoromethyl-phenyl)-acrylic acid ethyl ester

The title compound is prepared following a procedure analogous to Step 3 in the preparation of Intermediate 50uh, starting from (E)-3-(2-amino-5-fluoro-4-trifluoromethyl-phenyl)-acrylic acid ethyl ester.

25

Step 3: 3-(2-Bromo-5-fluoro-4-trifluoromethyl-phenyl)-propionic acid ethyl ester

(E)-3-(2-Bromo-5-fluoro-4-trifluoromethyl-phenyl)-acrylic acid ethyl ester (10 g) and hydrazine hydrate (5 mL) are dissolved in 180 mL of ethanol, the reaction mixture is cooled to 0 °C and hydrogen peroxide (12 mL) is added dropwise. After 10 minutes, the reaction mixture is warmed to 70 °C for 2h. The reaction mixture is concentrated under vacuum, the residue is partitioned between water and ethyl acetate. The organic phase dried over sodium sulfate and concentrated under vacuum to give the title compound. Yield: 10 g.

Step 4: 3-(2-Bromo-5-fluoro-4-trifluoromethyl-phenyl)-propionic acid

The title compound is prepared following a procedure analogous to Step 2 in the preparation of Intermediate 17, starting from 3-(2-bromo-5-fluoro-4-trifluoromethyl-phenyl)-propionic acid ethyl ester.

Step 5: 4-Bromo-7-fluoro-6-trifluoromethyl-indan-1-one

The title compound is prepared following a procedure analogous to Step 1 in the preparation of Intermediate 52c, starting from 3-(2-bromo-5-fluoro-4-trifluoromethyl-phenyl)-propionic acid.

Step 6: (S)-4-Bromo-7-fluoro-6-trifluoromethyl-indan-1-ol

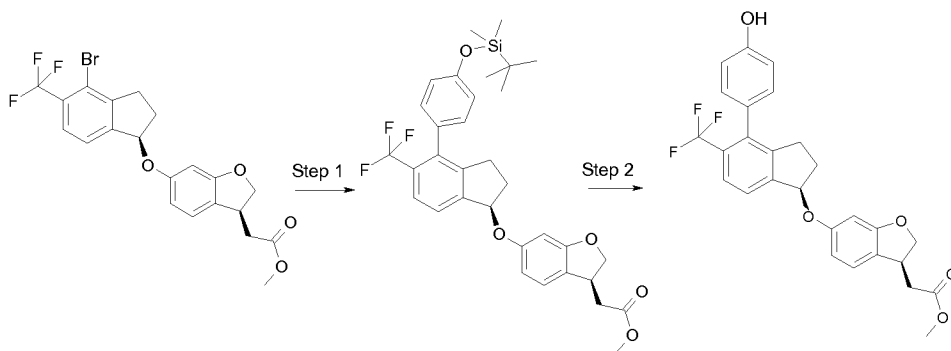
The title compound is obtained following a procedure analogous to Step 1 in the preparation of Intermediate 1, starting from 4-bromo-7-fluoro-6-trifluoromethyl-indan-1-one.

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

The title compound is obtained following a procedure analogous to Step 6 in the preparation of Intermediate 1, starting from (S)-4-bromo-7-fluoro-6-trifluoromethyl-indan-1-ol.

Intermediate 52aa

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



Step 1: ((S)-6-((R)-4-[4-(tert-Butyl-dimethyl-silanyloxy)-phenyl]-5-trifluoromethylindan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester

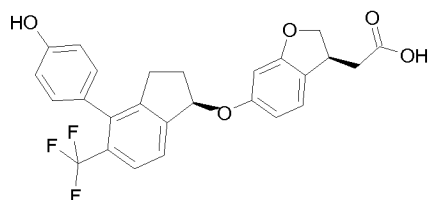
Intermediate 52a (1 g), 4-(tert-butyl-dimethylsilyloxy)phenylboronic acid (500 mg), potassium carbonate (822 mg) 2,6-di-tert-butyl-4-methylphenol (218 mg) and tricyclohexyl-phosphine (44 mg) are stirred in 15 mL of 1,4-dioxane and 3 mL of water, tris(dibenzylideneacetone)dipalladium(0) (73 mg) is added and the reaction mixture is stirred at 110 °C for 2 h. Ammonium chloride saturated aqueous solution is added and the reaction mixture is extracted with ethyl acetate. The organic phase is separated, dried over sodium sulfate and concentrated under vacuum. The residue is purified by chromatography on silica gel (cyclohexane/ethyl acetate 100:0→80:20) to give the title compound. Yield: 1 g.

Step 2: ((S)-6-[(R)-4-(4-Hydroxy-phenyl)-5-trifluoromethyl-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester

((S)-6-((R)-4-[4-(tert-Butyl-dimethyl-silanyloxy)-phenyl]-5-trifluoromethylindan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester (570 mg) is dissolved in 50 mL of tetrahydrofuran. Tetrabutylammonium fluoride (19 mL) is added and the reaction mixture is stirred at room temperature overnight. The reaction mixture is partitioned between ammonium chloride saturated aqueous solution and ethyl acetate. The organic phase is separated, dried over sodium sulfate and concentrated under vacuum. The residue is purified by chromatography on silica gel (cyclohexane/ethyl acetate 90:10→30:70) to give the title compound. Yield: 80 mg.

Intermediate 52aa'

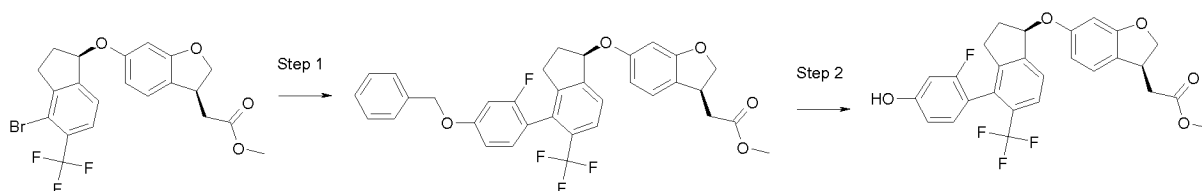
((S)-6-[(R)-4-(4-Hydroxy-phenyl)-5-trifluoromethyl-indan-1-yloxy]-2,3-dihydrobenzofuran-3-yl)-acetic acid



The title compound is obtained by further elution from the column with dichloromethane/methanol 80:20 in the preparation of intermediate 52aa.

5 Intermediate 52aa''

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



- 10 Step 1: {{(S)-6-[(R)-4-(4-Benzyloxy-2-fluoro-phenyl)-5-trifluoromethyl-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester

The title compound is prepared following a procedure analogous to Step 1 in the preparation of Intermediate 52aa, starting from 2-fluoro-4-(benzyloxy)phenylboronic acid.

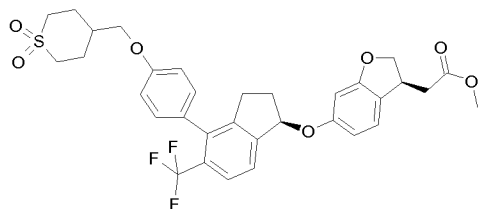
- 15 Step 2: {{(S)-6-[(R)-4-(2-Fluoro-4-hydroxy-phenyl)-5-trifluoromethyl-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester

- {{(S)-6-[(R)-4-(4-Benzyloxy-2-fluoro-phenyl)-5-trifluoromethyl-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester (500 mg) is dissolved in 10 mL of tetrahydrofurane and 20 mL of methanol, Pd/C(5%) (10 mg) is added and
20 the reaction mixture is stirred under hydrogen atmosphere (50 psi) for 2 h.

The reaction mixture is filtered on a celite pad and the solvent is concentrated under vacuum. The residue is purified by chromatography on silica gel (cyclohexane/ethyl acetate 100:0→75:25) to give the title compound. Yield: 300 mg.

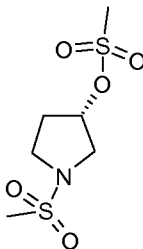
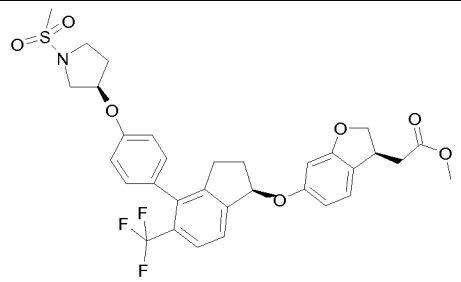
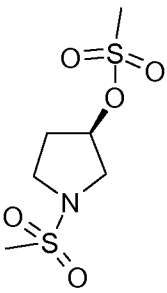
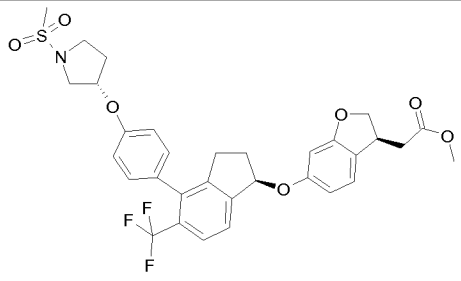
25 Intermediate 52aaa

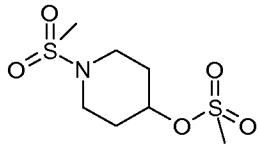
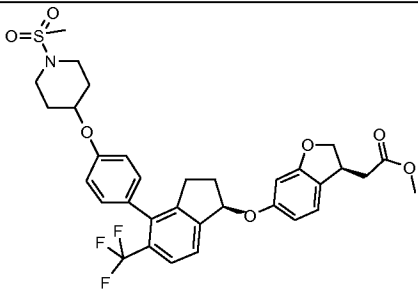
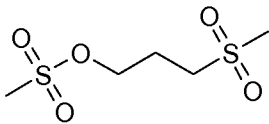
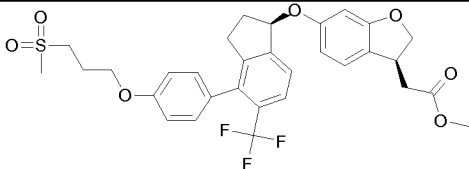
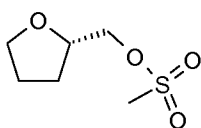
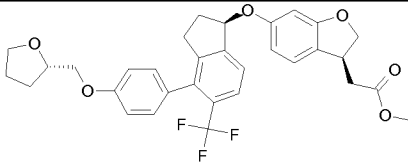
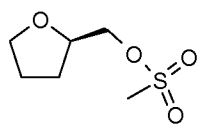
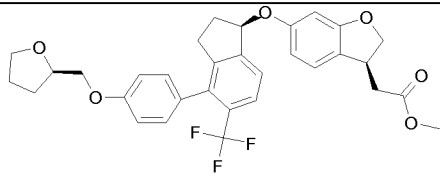
{{(S)-6-[(R)-4-[4-(1,1-Dioxo-hexahydro-1-thiopyran-4-ylmethoxy)-phenyl]-5-trifluoromethyl-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester

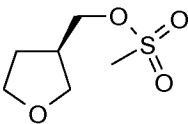
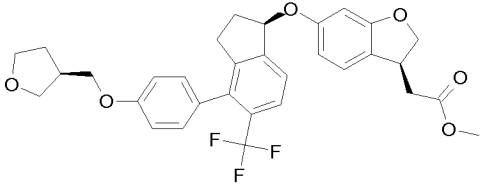


The title compound is prepared following a procedure analogous to the preparation of intermediate 50tb, starting from Intermediate 52aa and mesylate intermediate 49ga.

- 5 The following intermediates are prepared in analogy to Intermediate 52aaa starting from Intermediate 52aa and the corresponding mesylate intermediates.

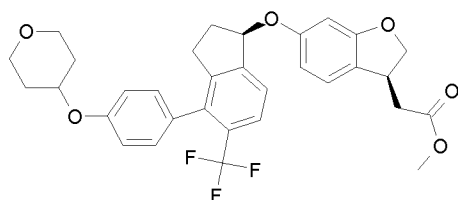
Starting mesylate Intermediate	Intermediate	Molecular structure and name
 49ea	52aab	 ((S)-6-((R)-4-[4-((R)-1-Methanesulfonylpyrrolidin-3-yloxy)-phenyl]-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester
 49e	52aac	 ((S)-6-((R)-4-[4-((S)-1-Methanesulfonylpyrrolidin-3-yloxy)-phenyl]-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester

 49fa	52aad	 ((S)-6-((R)-4-[4-(1-Methanesulfonyl-piperidin-4-yloxy)-phenyl]-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester
 US2011/130398 A1, 2011	52aae	 ((S)-6-((R)-4-[4-(3-Methanesulfonyl-propoxy)-phenyl]-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester
 49gb	52aaf	 [(S)-6-((R)-4-{4-[(S)-1-(Tetrahydro-furan-2-yl)methoxy]-phenyl}-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl]-acetic acid methyl ester
 49gb	52aag	 [(S)-6-((R)-4-{4-[(R)-1-(Tetrahydro-furan-2-yl)methoxy]-phenyl}-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl]-acetic acid methyl ester

 49gd	52aah	 [(S)-6-((R)-4-{4-[(R)-1-(Tetrahydro-furan-3-yl)methoxy]-phenyl}-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl]-acetic acid methyl ester

Intermediate 52aai

[(S)-6-{(R)-4-[4-(Tetrahydro-pyran-4-yloxy)-phenyl]-5-trifluoromethyl-indanyloxy}-2,3-dihydro-benzofuran-3-yl]-acetic acid methyl ester

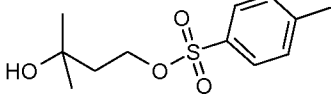
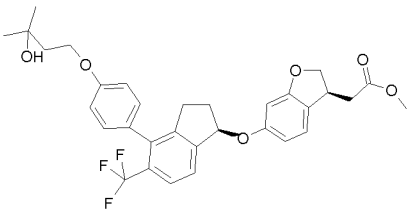


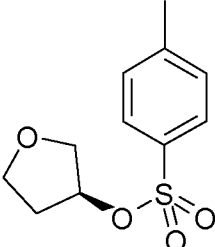
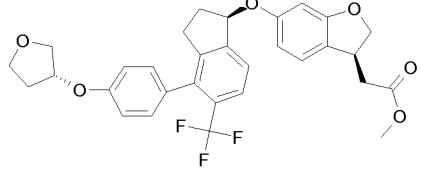
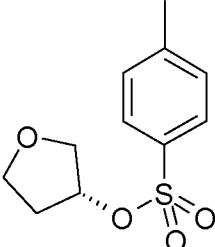
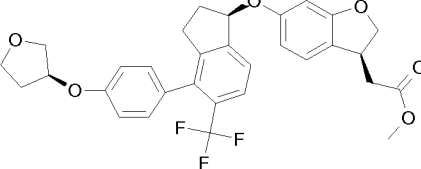
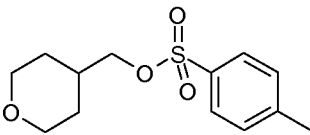
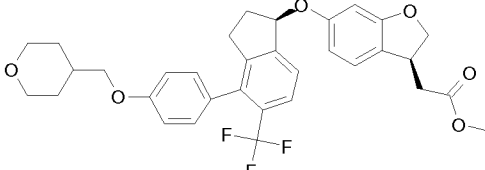
5

The title compound is prepared following a procedure analogous to the preparation of intermediate 50tc, starting from Intermediate 52aa and tosylate Intermediate 49ha.

The following intermediates are prepared in analogy to Intermediate 52aai starting from Intermediate 52aa and the corresponding tosylate intermediates.

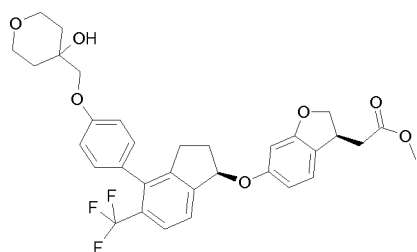
10

Starting tosylate Intermediate	Intermediate	Molecular structure and name
 Toluene-4-sulfonic acid 3-hydroxy-3-methyl-butyl ester (Intermediate 7; step 1)	52aaj	 ((S)-6-{(R)-4-[4-(3-Hydroxy-3-methyl-butoxy)-phenyl]-5-trifluoromethyl-indan-1-yloxy}-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester

 49hb	52aak	 [(S)-6-((R)-4-{4-[(R)-(Tetrahydro-furan-3-yl)oxy]-phenyl}-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl]-acetic acid methyl ester
 49hc	52aal	 [(S)-6-((R)-4-{4-[(S)-(Tetrahydro-furan-3-yl)oxy]-phenyl}-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl]-acetic acid methyl ester
 49hd	52aam	 ((S)-6-((R)-4-[4-(Tetrahydro-pyran-4-ylmethoxy)-phenyl]-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester

Intermediate 52aan

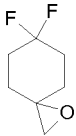
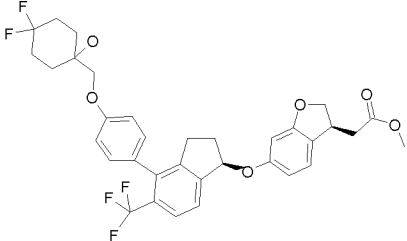
[(S)-6-((R)-4-[4-(4-Hydroxy-tetrahydro-pyran-4-ylmethoxy)-phenyl]-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl]-acetic acid methyl ester



5

The title compound is prepared following a procedure analogous to the preparation of intermediate 50bb, starting from Intermediate 52aa and the epoxide intermediate 1,6-dioxaspiro[2.5]octane (US2012/46304 A1, 2012)

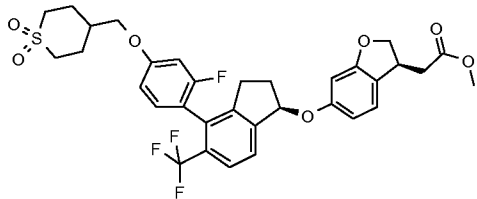
The following intermediate is prepared in analogy to Intermediate 52aan starting from Intermediate 52aa and the corresponding epoxide intermediates.

Starting epoxide	Intermediate	Molecular structure and name
 6,6-Difluoro-1-oxa-spiro[2.5]octane Prepared in analogy to 1,6-Dioxaspiro[2.5]octane starting from 4,4-difluoro-cyclohexanone	52aao	 ((S)-6-{(R)-4-[4-(4,4-Difluoro-1-hydroxy-cyclohexylmethoxy)-phenyl]-5-trifluoromethyl-indan-1-yloxy}-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester

5

Intermediate 52aap

((S)-6-{(R)-4-[4-(1,1-Dioxo-hexahydro-1-thiopyran-4-ylmethoxy)-2-fluoro-phenyl]-5-trifluoromethyl-indan-1-yloxy}-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester

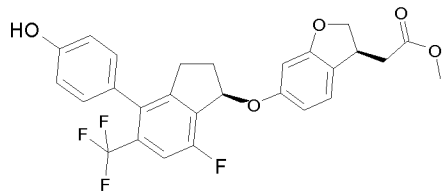


- 10 The title compound is prepared in analogy to intermediate 52aaa starting from Intermediate 52aa”.

Intermediate 52ba

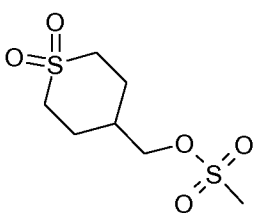
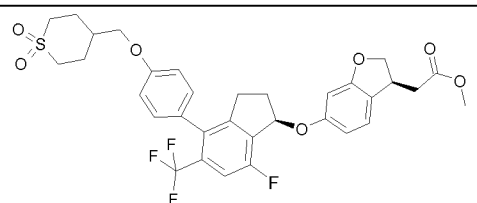
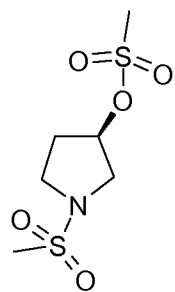
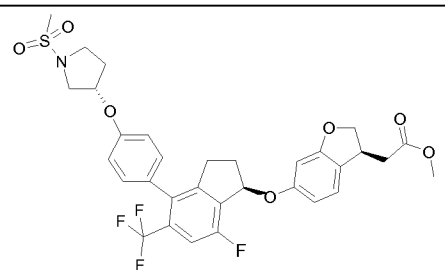
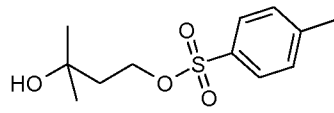
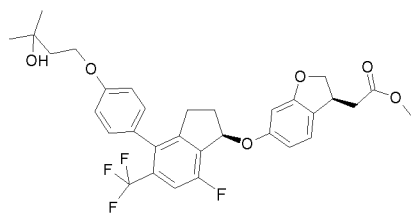
{(S)-6-[(R)-7-Fluoro-4-(4-hydroxy-phenyl)-5-trifluoromethyl-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester

15



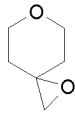
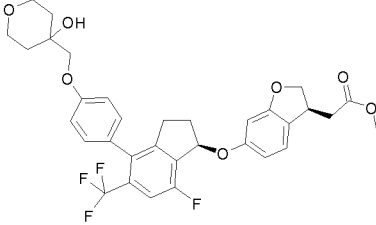
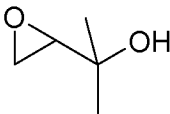
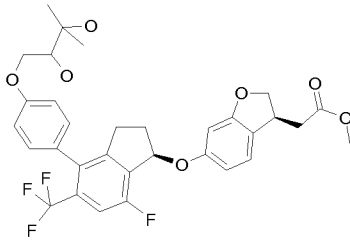
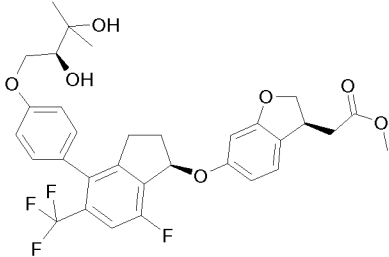
The title compound is prepared in analogy to Intermediate 52aa starting from Intermediate 52b.

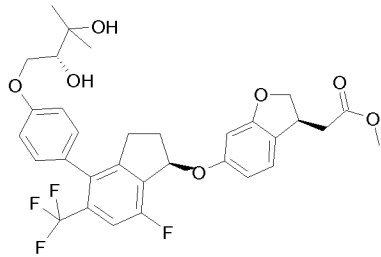
- The following intermediates are prepared in analogy to Intermediate 52aaa or 52aai
5 starting from Intermediate 52ba and the corresponding mesylate or tosylate intermediates.

Starting mesylate/tosylate Intermediate	Intermediate	Molecular structure and name
 49ga	52baa	 ((S)-6-((R)-4-[4-(1,1-Dioxo-hexahydro-1-thiopyran-4-ylmethoxy)-phenyl]-7-fluoro-5-trifluoromethyl-indan-1-yloxy}-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester
 49e	52bab	 ((S)-6-((R)-7-Fluoro-4-[4-((S)-1-methanesulfonyl-pyrrolidin-3-yloxy)-phenyl]-5-trifluoromethyl-indan-1-yloxy}-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester
 Toluene-4-sulfonic acid 3-hydroxy-3-methyl-butyl ester (Intermediate 7; step 1)	52bac	 ((S)-6-((R)-7-Fluoro-4-[4-(3-hydroxy-3-methyl-butoxy)-phenyl]-5-trifluoromethyl-indan-1-yloxy}-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester

		ester

The following intermediates are prepared in analogy to Intermediate 52aan starting from Intermediate 52ba and the corresponding epoxide intermediates.

Starting epoxide	Intermediate	Molecular structure and name
 1,6-Dioxaspiro[2.5]octane	52bad	 ((S)-6-[(R)-7-Fluoro-4-[4-(4-hydroxy-tetrahydropyran-4-ylmethoxy)-phenyl]-5-trifluoromethyl-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester
 Yamada, Sachiko et al. Chemical & Pharmaceutical Bulletin, 1981, vol. 29, # 4 p. 1187 - 1188	52bae	 ((S)-6-[(R)-4-[4-(2,3-Dihydroxy-3-methylbutoxy)-phenyl]-7-fluoro-5-trifluoromethyl-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester
	52baf*	 ((S)-6-[(R)-4-[4-((S)-2,3-Dihydroxy-3-methylbutoxy)-phenyl]-7-fluoro-5-trifluoromethyl-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester Absolute configuration unknown.

	52bag*	 ((S)-6-((R)-4-[4-((R)-2,3-Dihydroxy-3-methylbutoxy)-phenyl]-7-fluoro-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester Absolute configuration unknown.

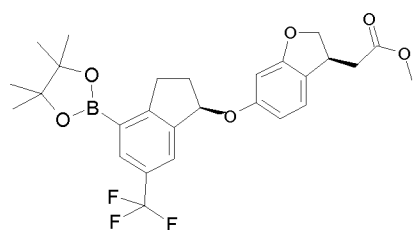
*Intermediate 52baf and intermediate 52bag are obtained from chiral HPLC separation of racemate Intermediate 52bae.

Intermediate 52baf: first eluted: Chiral HPLC (method 1b): t_R = 12.35 min. Absolute configuration unknown.

Intermediate 52bag: second eluted: Chiral HPLC (method 1b): t_R = 12.40 min. Absolute configuration unknown.

Intermediate 52ca

10 {((S)-6-[(R)-4-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-6-trifluoromethyl-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester

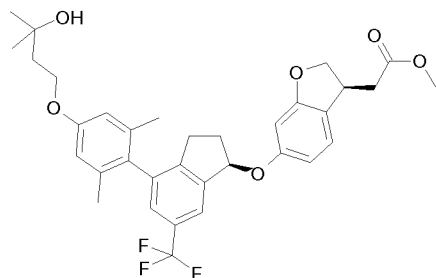


The title compound is prepared in analogy to Step 6 in the preparation of Intermediate 52 starting from Intermediate 52c.

15

Intermediate 52caa

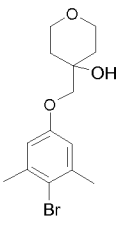
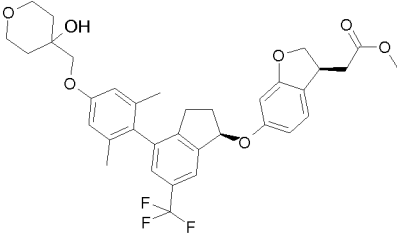
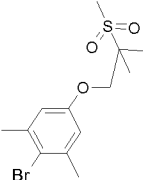
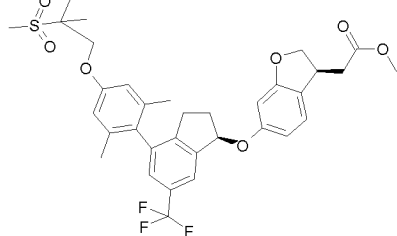
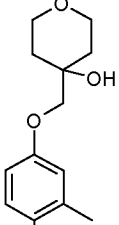
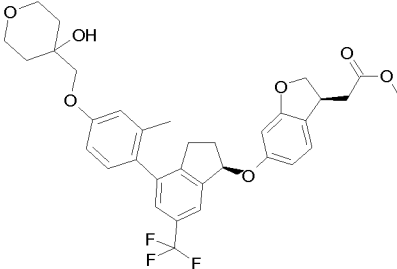
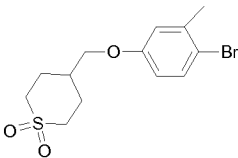
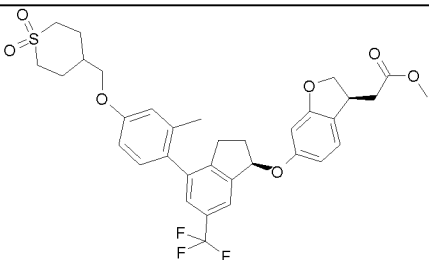
((S)-6-((R)-4-[4-(3-Hydroxy-3-methyl-butoxy)-2,6-dimethyl-phenyl]-6-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester

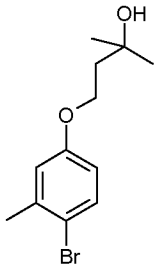
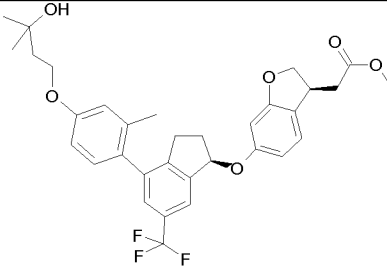
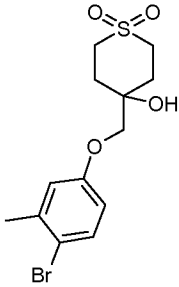
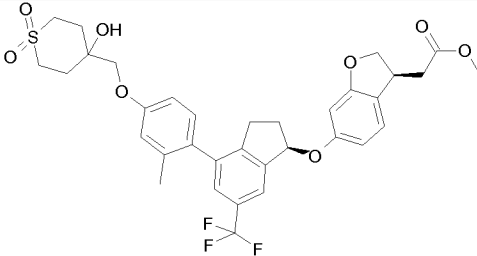


The title compound is prepared starting from Intermediate 52ca and intermediate 7 following a procedure analogous to that described for Intermediate 51a.

- 5 The intermediates in the following table are prepared from Intermediate 52ca and the corresponding starting bromo-aryl intermediates following a procedure analogous to that described for Intermediate 52caa.

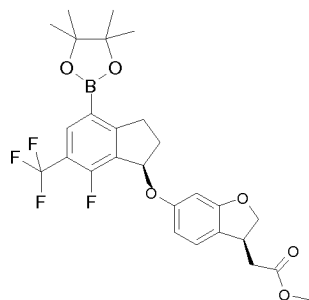
Starting bromo-aryl Intermediate	Intermediate	Molecular structure and name
50b	52cab	((S)-6-((R)-4-[4-(1,1-Dioxo-hexahydro-1-thiopyran-4-ylmethoxy)-2,6-dimethyl-phenyl]-6-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester
50bc	52cac	((S)-6-((R)-4-[4-(4-Hydroxy-1,1-dioxo-hexahydro-1-thiopyran-4-ylmethoxy)-2,6-dimethyl-phenyl]-6-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester

 50bb	52cad	 ((S)-6-((R)-4-[4-(4-Hydroxy-tetrahydro-pyran-4-ylmethoxy)-2,6-dimethyl-phenyl]-6-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester
 50ha	52cae	 ((S)-6-((R)-4-[4-(2-Methanesulfonyl-2-methyl-propoxy)-2,6-dimethyl-phenyl]-6-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester
 50ta	52caf	 ((S)-6-((R)-4-[4-(4-Hydroxy-tetrahydro-pyran-4-ylmethoxy)-2-methyl-phenyl]-6-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester
 50tb	52cag	 ((S)-6-((R)-4-[4-(1,1-Dioxo-hexahydro-1-thiopyran-4-ylmethoxy)-2-methyl-phenyl]-6-

		trifluoromethyl-indan-1-yloxy}-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester
 50tc	52cah	 ((S)-6-((R)-4-[4-(3-Hydroxy-3-methyl-butoxy)-2-methyl-phenyl]-6-trifluoromethyl-indan-1-yloxy}-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester
 50td	52cai	 ((S)-6-((R)-4-[4-(4-Hydroxy-1,1-dioxo-hexahydro-1-thiopyran-4-ylmethoxy)-2-methyl-phenyl]-6-trifluoromethyl-indan-1-yloxy}-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester

Intermediate 52da

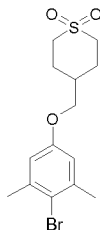
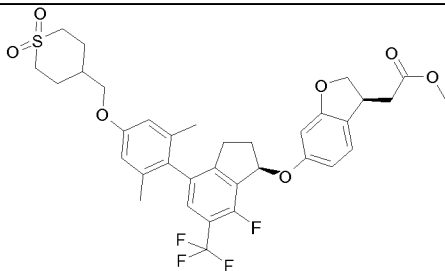
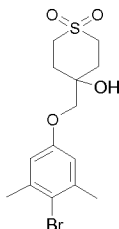
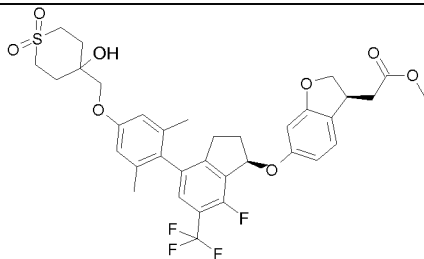
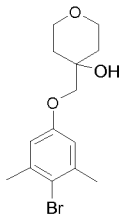
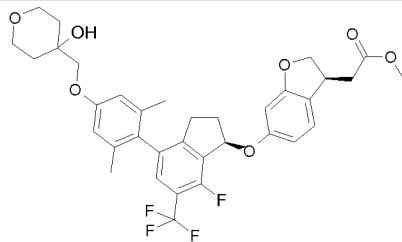
{{(S)-6-[(R)-7-Fluoro-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-6-trifluoromethyl-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester

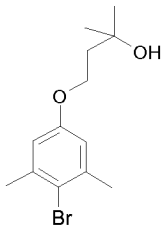
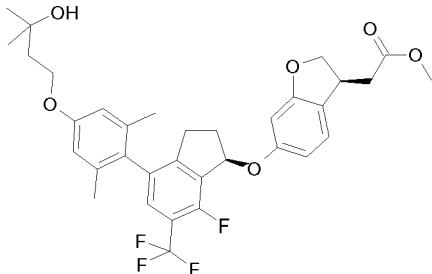


5

The title compound is prepared in analogy to Step 6 in the preparation of Intermediate 52 starting from Intermediate 52d.

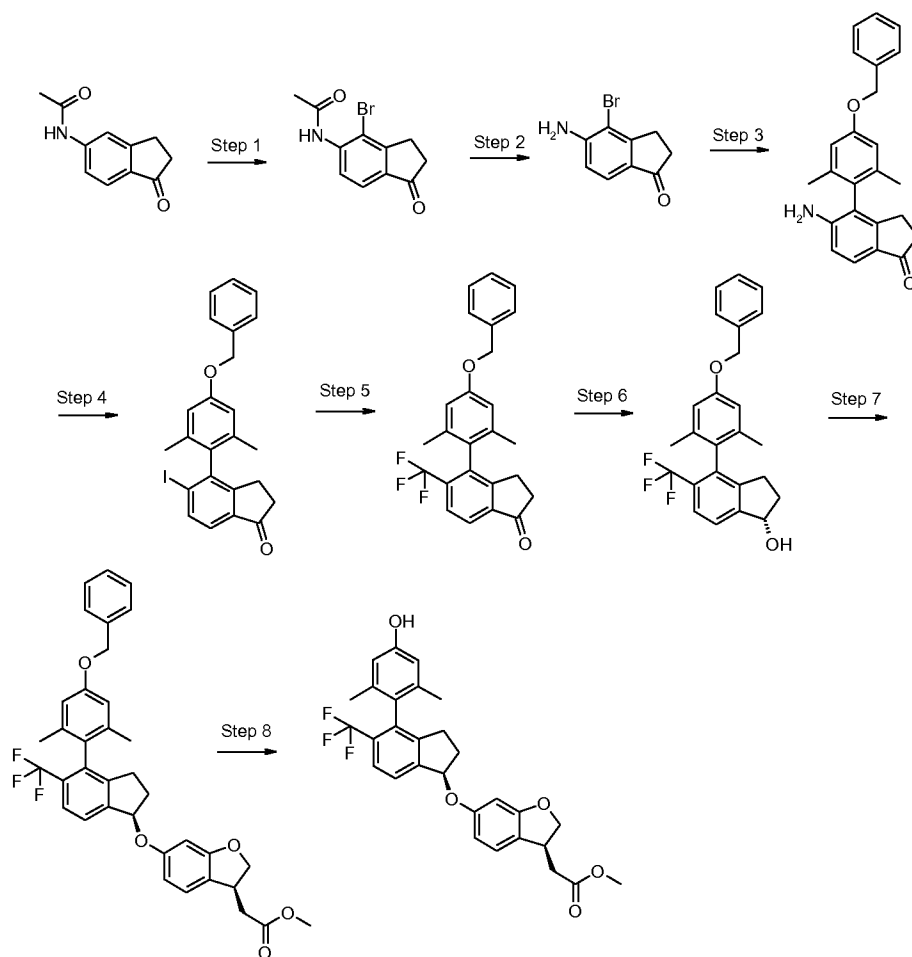
The intermediates in the following table are prepared from Intermediate 52da and the corresponding starting bromo-aryl intermediates following a procedure analogous to that described for Intermediate 52caa.

Starting bromo-aryl Intermediate	Intermediate	Molecular structure and name
 50b	52daa	 ((S)-6-((R)-4-[4-(1,1-Dioxo-hexahydro-1-thiopyran-4-ylmethoxy)-2,6-dimethyl-phenyl]-7-fluoro-6-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester
 50bc	52dab	 ((S)-6-((R)-7-Fluoro-4-[4-(4-hydroxy-1,1-dioxo-hexahydro-1-thiopyran-4-ylmethoxy)-2,6-dimethyl-phenyl]-6-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester
 50bb	52dac	 ((S)-6-((R)-7-Fluoro-4-[4-(4-hydroxy-tetrahydro-pyran-4-ylmethoxy)-2,6-dimethyl-phenyl]-6-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-

		benzofuran-3-yl)-acetic acid methyl ester
 7	52dad	 ((S)-6-((R)-7-Fluoro-4-[4-(3-hydroxy-3-methylbutoxy)-2,6-dimethyl-phenyl]-6-trifluoromethyl-indan-1-yloxy}-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester

Intermediate 52ea

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



5

Step 1: N-(4-Bromo-1-oxo-indan-5-yl)-acetamide

N-(1-Oxo-indan-5-yl)-acetamide (5.0 g) is suspended in a mixture of acetonitrile (40 mL), water (1 mL) and acetic acid (1 mL) and N-bromo succinimide (5.64 g) is added. The mixture is heated at reflux for 6 hours then allowed to cool to room temperature. The title compound is collected by filtration and dried under vacuum. Yield 3.14 g.

5 Step 2: 5-Amino-4-bromo-indan-1-one

N-(4-Bromo-1-oxo-indan-5-yl)-acetamide (1.81 g) is suspended in 2 M aqueous hydrochloric acid solution and heated at 100 °C for 2 hours then allowed to cool to room temperature. The title compound is collected by filtration and dried under vacuum. Yield 1.37 g.

10 Step 3: 5-Amino-4-(4-benzyloxy-2,6-dimethyl-phenyl)-indan-1-one

Toluene (80 mL) and water (40 mL) are degassed with a flow of nitrogen for 30 minutes and then added to 5-amino-4-bromo-indan-1-one (700 mg), 4-benzyloxy-2,6-dimethyl-phenyl-boronic acid (Example 39, step 2, 3.3 g), and sodium carbonate (1.15 g) in a nitrogen flushed flask. The mixture is heated at reflux overnight under a nitrogen atmosphere then allowed to cool to room temperature, diluted with ethyl acetate (100 mL) and the phases separated. The organic phase is washed with water and brine, dried over sodium sulfate and the solvent removed under vacuum. The residue is purified by flash chromatography (cyclohexane/ethyl acetate 100:0→70:30) to give the title compound. Yield 985 mg.

20 Step 4: 4-(4-Benzyloxy-2,6-dimethyl-phenyl)-5-iodo-indan-1-one

5-Amino-4-(4-benzyloxy-2,6-dimethyl-phenyl)-indan-1-one (985 mg) is suspended in diiodomethane and heated to 100 °C. Isoamyl nitrate (1.47 mL) is added and the mixture stirred at 100 °C for 30 minutes then allowed to cool to room temperature. The excess reagents are removed by distillation under vacuum (90 °C, 8 mbar) and the residue is purified by flash chromatography (cyclohexane/ethyl acetate 100:0→80:20) to give the title compound. Yield 776 mg.

Step 5: 4-(4-Benzyloxy-2,6-dimethyl-phenyl)-5-trifluoromethyl-indan-1-one

4-(4-Benzyloxy-2,6-dimethyl-phenyl)-5-iodo-indan-1-one (770 mg) is suspended in N-methylpyrrolidone (20 mL) in a flask equipped with an overhead mechanical stirrer and copper(I)iodide (9.39 g) is added followed by methyl 2,2-difluoro-2-(fluorosulfonyl)acetate (4 mL). The mixture is stirred for 30 minutes at 110 °C then further 2,2-difluoro-2-(fluorosulfonyl)acetate (4 mL) is added and the mixture stirred for 90 minutes at 100 °C. A further portion of 2,2-difluoro-2-(fluorosulfonyl)acetate (4 mL) is added and the mixture stirred for 30 minutes at 110 °C then allowed to cooled

to room temperature. The mixture is diluted with water (150 mL) and ethyl acetate (150 mL), shaken well and the phases separated. The organic phase is washed with brine and the solvent removed under vacuum. The residue is suspended in diethyl ether, washed with water and brine, dried over sodium sulfate and the solvent removed under vacuum. The residue is purified by flash chromatography (cyclohexane/ethyl acetate 100:0→80:20) to give the title compound (Yield 452 mg).

Step 6: (S)-4-(4-Benzyloxy-2,6-dimethyl-phenyl)-5-trifluoromethyl-indan-1-ol

Triethylamine 0.46 mL is suspended in dichloromethane (2 mL) and cooled to 0 °C. Formic acid (0.15 mL) is added and the mixture stirred for 5 minutes. 4-(4-Benzyloxy-2,6-dimethyl-phenyl)-5-trifluoromethyl-indan-1-one (452 mg) is added followed by chloro[[[(1S,2S)-(-)-2-amino-1,2-diphenylethyl](4

toluenesulfonyl)amido](mesitylene)ruthenium(II) (14 mg) and the mixture stirred overnight at room temperature. The solution is diluted with dichloromethane, washed with water, dried over sodium sulfate and the solvent removed under vacuum. The residue is purified by flash chromatography (cyclohexane/ethyl acetate 100:0→80:20) to give the title compound-Yield 494 mg.

Step 7: {(S)-6-[(R)-4-(4-Benzyloxy-2,6-dimethyl-phenyl)-5-trifluoromethyl-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester

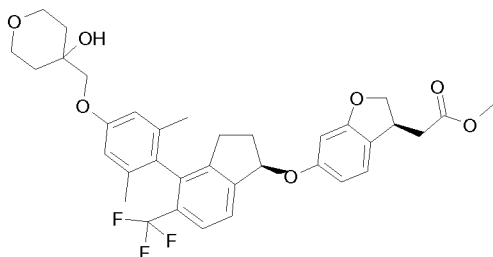
(S)-4-(4-Benzyloxy-2,6-dimethyl-phenyl)-5-trifluoromethyl-indan-1-ol (494 mg), (S)-(6-hydroxy-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester (275 mg), triphenylphosphine (345 mg) and di-*tert*-butylazodicarboxylate (303 mg) are combined in dry tetrahydrofuran (10 mL) at 0 °C. The mixture is allowed to warm to room temperature and stirred for 2 hours. The solvent is removed under vacuum and the residue is purified by flash chromatography (cyclohexane/ethyl acetate 100:0→80:20) to give the title compound.Yield 573 mg.

Step 8: {(S)-6-[(R)-4-(4-Hydroxy-2,6-dimethyl-phenyl)-5-trifluoromethyl-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester

{(S)-6-[(R)-4-(4-Benzyloxy-2,6-dimethyl-phenyl)-5-trifluoromethyl-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester (350 mg) is suspended in methanol (20 mL) and 10% palladium on carbon (35 mg) is added. The mixture is shaken under a hydrogen atmosphere at 2 Bar for one hour then filtered through celite and the solvent removed. The residue is purified by flash chromatography (cyclohexane/ethyl acetate 100:0→90:10) to give the title compound. Yield 213 mg.

Intermediate 52eaa

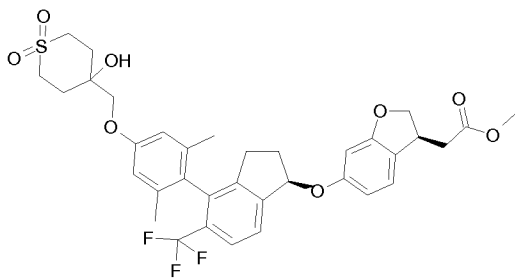
((S)-6-((R)-4-[4-(4-Hydroxy-tetrahydro-pyran-4-ylmethoxy)-2,6-dimethyl-phenyl]-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester



- 5 {((S)-6-((R)-4-(4-Hydroxy-2,6-dimethyl-phenyl)-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester (Intermediate 52ea, 79 mg), 1,6-dioxa-spiro[2.5]octane (30 mg) and cesium carbonate (134 mg) are suspended in dry N,N-dimethylformamide and stirred at 100 °C for 3 hours. An additional portion of 1,6-dioxa-spiro[2.5]octane (30 mg) are added and the mixture is stirred a further 2
- 10 hours at 100 °C. The mixture is diluted with ethyl acetate, washed with water, dried over sodium sulfate and the solvent removed under vacuum. The residue is purified by flash chromatography (cyclohexane/ethyl acetate 100:0→60:40) to give the title compound (Yield 35 mg).

Intermediate 52eab

((S)-6-((R)-4-[4-(4-Hydroxy-1,1-dioxo-hexahydro-1-thiopyran-4-ylmethoxy)-2,6-dimethyl-phenyl]-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester

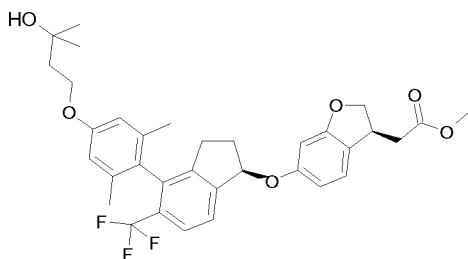


- 20 The title compound is prepared following a procedure analogous to that described in the preparation of Intermediate 50bc, starting from Intermediate 52ea.

Intermediate 52eac

((S)-6-((R)-4-[4-(3-Hydroxy-3-methyl-butoxy)-2,6-dimethyl-phenyl]-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester

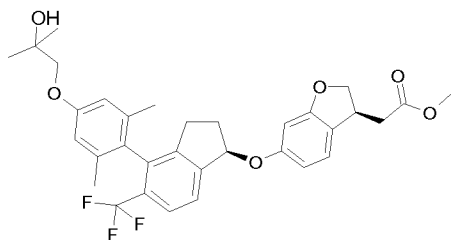
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Intermediate 52ea (78 mg), Intermediate 7 (67 mg) and cesium carbonate (133 mg) are suspended in dry N,N-dimethylformamide and stirred at 100 °C for 1 hour. The mixture is diluted with ethyl acetate, washed with water, dried over sodium sulfate and the solvent removed under vacuum. The residue is purified by flash chromatography (cyclohexane/ethyl acetate 100:0→60:40) to give the title compound. Yield 64 mg.

Intermediate 52ead

10 ((S)-6-((R)-4-[4-(2-Hydroxy-2-methyl-propoxy)-2,6-dimethyl-phenyl]-5-trifluoromethyl-indan-1-yloxy}-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester

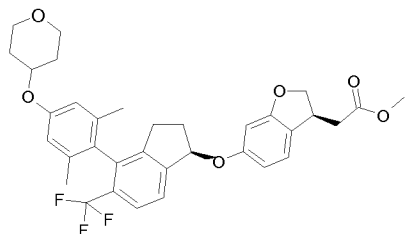


Intermediate 52ea (78 mg), isobutylene oxide (19 mg) and cesium carbonate (133 mg) are suspended in dry N,N-dimethylformamide and stirred at 100 °C for 1 hour. A further portion of isobutylene oxide (48 mg) are added and the mixture is stirred for 2 hours at 100 °C. The mixture is diluted with ethyl acetate, washed with water, dried over sodium sulfate and the solvent removed under vacuum. The residue is purified by flash chromatography (cyclohexane/ethyl acetate 100:0→60:40) to give the title compound. Yield 28 mg.

20

Intermediate 52eae

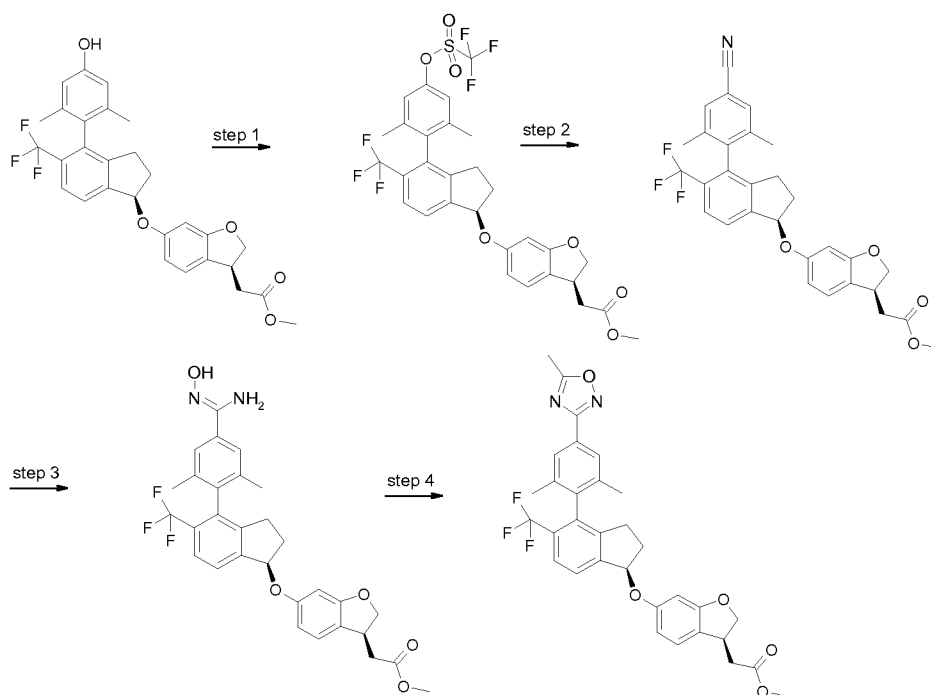
((S)-6-((R)-4-[2,6-Dimethyl-4-(tetrahydro-pyran-4-yloxy)-phenyl]-5-trifluoromethyl-indan-1-yloxy}-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester



Intermediate 52ea (78 mg), Intermediate 49ha (66 mg) and cesium carbonate (133 mg) are suspended in dry N,N-dimethylformamide and stirred at 100 °C for 1 hour. toluene-4-sulfonic acid tetrahydro-pyran-4-yl ester (66 mg) are added and the mixture is stirred for 2 hours at 100 °C. The mixture is diluted with ethyl acetate, washed with water, dried over sodium sulfate and the solvent removed under vacuum. The residue is purified by flash chromatography (cyclohexane/ethyl acetate 100:0→70:30) to give the title compound. Yield 50 mg.

10 Intermediate 52eaf

((S)-6-((R)-4-[2,6-Dimethyl-4-(5-methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-5-trifluoromethyl-indan-1-yloxy}-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester



Step 1: ((S)-6-((R)-4-(2,6-Dimethyl-4-trifluoromethanesulfonyloxy-phenyl)-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester
Intermediate 52ea (213 mg) and pyridine (74 µL) are suspended in dichloromethane (10 mL) and cooled to 0 °C. Trifluoromethane sulfonyl chloride (0.127 mL) is added, the mixture allowed to warm to room temperature and stirred for 30 minutes. The

mixture is washed with saturated aqueous sodium bicarbonate solution, 1 M aqueous hydrochloric acid, dried over sodium sulfate and the solvent removed under vacuum to give the crude title compound which is used without further purification. Yield 291 mg.

- 5 Step 2: {(S)-6-[(R)-4-(4-Cyano-2,6-dimethyl-phenyl)-5-trifluoromethyl-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester

{(S)-6-[(R)-4-(2,6-Dimethyl-4-trifluoromethanesulfonyloxy-phenyl)-5-trifluoromethyl-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester (291 mg), zinc cyanide (80 mg), tris(dibenzylideneacetone)dipalladium(0) (21 mg) and 1,1'-bis(diphenylphosphino)ferrocene (25 mg) are suspended in dry N,N-dimethylformamide (5 mL), degassed with a flow of argon and stirred for 1 hour at 70 °C. The mixture is diluted with ethylacetate, washed with water and brine, dried over sodium sulfate and the solvent removed under vacuum. The residue is purified by flash chromatography (cyclohexane/ethyl acetate 100:0→90:10) to give the title
15 compound. Yield 66 mg.

Step 3: ((S)-6-{(R)-4-[4-(N-Hydroxycarbamimidoyl)-2,6-dimethyl-phenyl]-5-trifluoromethylindan-1-yloxy}-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester

{(S)-6-[(R)-4-(4-Cyano-2,6-dimethyl-phenyl)-5-trifluoromethyl-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester (61 mg) is suspended in absolute
20 ethanol (7 mL) and hydroxylamine hydrochloride (12 mg) and triethylamine (24 µL,) are added. The mixture is refluxed for 2 hours then cooled, diluted with water and extracted with ethyl acetate. The extracts are dried over sodium sulfate and the solvent removed under vacuum to give the crude title compound which is used without further purification. Yield 64 mg.

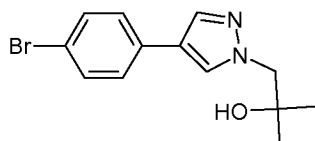
- 25 Step 4: ((S)-6-{(R)-4-[2,6-Dimethyl-4-(5-methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-5-trifluoromethyl-indan-1-yloxy}-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester

((S)-6-{(R)-4-[4-(N-Hydroxycarbamimidoyl)-2,6-dimethyl-phenyl]-5-trifluoromethyl-indan-1-yloxy}-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester (64 mg) is suspended in absolute ethanol (7 mL) and acetic anhydride (20 mg) and
30 triethylamine (46 µL) are added. The mixture is refluxed for 3 hours then cooled, and the solvent removed under vacuum. The residue is partitioned between dichloromethane and water, the organic phase is collected, dried over sodium sulfate and the solvent removed under vacuum. The residue is purified by flash

chromatography (cyclohexane/ethyl acetate 100:0→80:20) to give the title compound. Yield 41 mg.

Intermediate 52fa

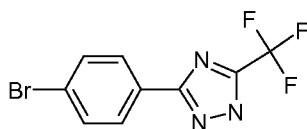
5 1-[4-(4-Bromo-phenyl)-pyrazol-1-yl]-2-methyl-propan-2-ol



1-Bromo-4-iodo-bromobenzene (780 mg) and 2-methyl-1-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-pyrazol-1-yl]-propan-2-ol (US2011/76291 A1, 2011) (832 mg) are stirred in 6 mL of 1,4-dioxane and 2 mL of water, 1,1'-bis(diphenylphosphino)ferrocenedichloropalladium(II) (100 mg) and cesium carbonate (1.8 g) are added and the reaction mixture is stirred under nitrogen atmosphere at 100 °C overnight. Water is added and the reaction mixture is extracted with ethyl acetate. The organic phase is collected, dried over sodium sulfate and the solvent removed under vacuum. The residue is purified by flash chromatography (cyclohexane/ethyl acetate 100:0→50:50) to give the title compound. Yield: 670 mg.

Intermediate 52fb

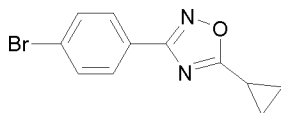
3-(4-Bromo-phenyl)-5-trifluoromethyl-1H-[1,2,4]triazole



4-Bromobenzimidazole hydrochloride (WO2010/62571 A1, 2010) (3 g), trifluoroacetic acid hydrazide (2.53 g) and triethylamine (2.55 g) are stirred in 1,4-dioxane at room temperature overnight. Solvent is concentrated under vacuum. The residue is purified by flash chromatography (cyclohexane/ethyl acetate 100:0→50:50) to give the title compound. Yield: 2.8 g.

Intermediate 52fc

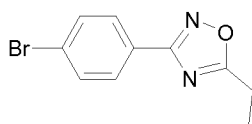
3-(4-Bromo-phenyl)-5-cyclopropyl-[1,2,4]oxadiazole



The title compound is prepared in analogy to 3-(4-bromo-phenyl)-5-methyl-[1,2,4]-oxadiazole (WO2006/40192 A1, 2006) starting from cyclopropane carbonyl chloride.

5 **Intermediate 52fca**

3-(4-Bromo-phenyl)-5-ethyl-[1,2,4]oxadiazole

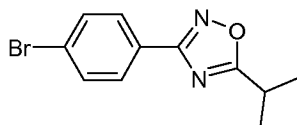


The title compound is prepared in analogy to 3-(4-bromo-phenyl)-5-methyl-[1,2,4]-oxadiazole (WO2006/40192 A1, 2006) starting from propionyl chloride.

10 .

Intermediate 52fcb

3-(4-Bromo-phenyl)-5-isopropyl-[1,2,4]oxadiazole

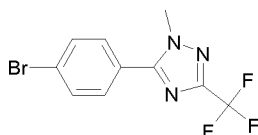


The title compound is prepared in analogy to 3-(4-bromo-phenyl)-5-methyl-[1,2,4]-oxadiazole (WO2006/40192 A1, 2006) starting from isobutyryl chloride.

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Intermediate 52fda

5-(4-Bromo-phenyl)-1-methyl-3-trifluoromethyl-1H-[1,2,4]triazole

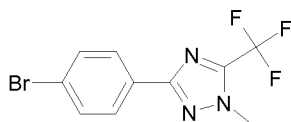


20 Intermediate 52fb (2.8 g) and potassium hydroxide (132 mg) are stirred in 30 mL of acetone, iodomethane (0.211 mL) is added and the reaction mixture is stirred at room temperature overnight. Solvent is concentrated under vacuum. The residue is purified by flash chromatography (cyclohexane/ethyl acetate 100:0→50:50) to give the title compound. Yield: 220 mg.

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Intermediate 52fdb

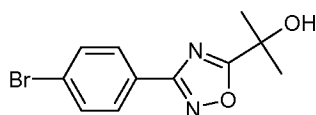
3-(4-Bromo-phenyl)-1-methyl-5-trifluoromethyl-1H-[1,2,4]triazole



The title compound is obtained by further elution from the flash chromatography performed in the preparation of Intermediate 52fda.

5 Intermediate 52fe

2-[3-(4-Bromo-phenyl)-[1,2,4]oxadiazol-5-yl]-propan-2-ol

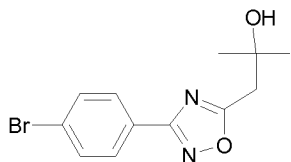


2-Hydroxyisobutyric acid (970 mg), N,N,N',N'-tetramethyl-O-(benzotriazol-1-yl)uronium tetrafluoroborate (1.79 g) and triethylamine (1.8 g) are stirred in 20 mL of acetonitrile at room temperature for 5 minutes, 4-bromo-N-hydroxybenzenecarboximidamide (WO2004/101546 A1, 2004) (1 g) is added and the reaction mixture is stirred at room temperature for 24 h. The mixture is concentrated under vacuum. The residue is purified by flash chromatography (cyclohexane/ethyl acetate 100:0→50:50) to give the title compound. Yield: 530 mg.

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Intermediate 52fea

1-[3-(4-Bromo-phenyl)-[1,2,4]oxadiazol-5-yl]-2-methyl-propan-2-ol

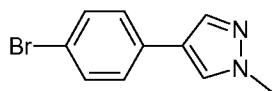


The title compound is prepared in analogy to Intermediate 52fe, starting from beta-hydroxy-isovaleric acid.

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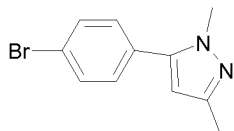
Intermediate 52ff

4-(4-Bromo-phenyl)-1-methyl-1H-pyrazole

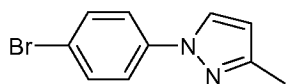


The title compound is prepared in analogy to Intermediate 52fa, starting from 1-methyl-4-(4,4,5,5-tetraethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole.

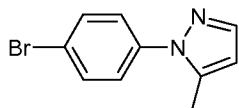
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Intermediate 52fg5-(4-Bromo-phenyl)-1,3-dimethyl-1H-pyrazole

The title compound is prepared in analogy to Intermediate 52fa, starting from 1,3-dimethyl-5-(4,4,5,5-tetranethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole

Intermediate 52fha1-(4-Bromo-phenyl)-3-methyl-1H-pyrazole

- 10 1-Bromo-4-iodo-bromobenzene (4 g), 3-methyl-pyrazole (2.85 g), N,N'-dimethylethylenediamine (0.38 mL), copper(I) iodide (673 mg) and cesium carbonate (3.45 g) are stirred in 20 mL of N,N-dimethylformamide at 100 °C for 24 h. Water is added and the reaction mixture is extracted with ethyl acetate. The organic phase is collected, dried over sodium sulfate and the solvent removed under vacuum. The residue is purified by flash chromatography (cyclohexane/ethyl acetate 100:0→80:20) to give the title compound. Yield: 650 mg.

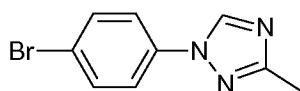
Intermediate 52fhb1-(4-Bromo-phenyl)-5-methyl-1H-pyrazole

20

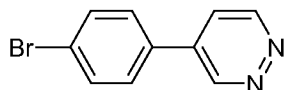
The title compounds is obtained by further elution from the column in the preparation of Intermediate 52fha.

Intermediate 52fi

- 25 1-(4-Bromo-phenyl)-3-methyl-1H-[1,2,4]triazole



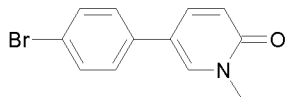
The title compound is prepared in analogy to Intermediate 52fha starting from 3-methyl-1H-1,2,4-triazole.

Intermediate 52fj4-(4-Bromo-phenyl)-pyridazine

- 5 4-(Tributylstannyl)pyridazine (1.1 g), tris(dibenzylideneacetone)dipalladium(0) (136 mg) tri-*o*-tolylphosphine (280 mg), triethylamine (1.24 g) and 1-bromo-4-iodo-benzene (927 mg) are stirred in 4 mL of N,N-dimethylformamide at 80 °C for 3 h. The solvent is removed and the residue is partitioned between ammonium chloride saturated water solution and dichloromethane. The organic phase is collected, dried
- 10 over sodium sulfate and the solvent removed under vacuum. The residue is purified by flash chromatography (cyclohexane/ethyl acetate 100:0→70:30) to give the title compound. Yield: 350 mg.

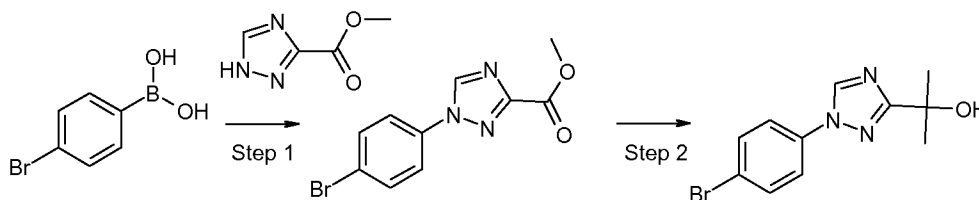
Intermediate 52fk

- 15 5-(4-Bromo-phenyl)-1-methyl-1H-pyridin-2-one



The title compound is prepared in analogy to Intermediate 52fa starting from 1-methyl-5-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)pyridin-2(1H)-one (WO2010/47982 A1, 2010).

20

Intermediate 52fl2-[1-(4-Bromo-phenyl)-1H-[1,2,4]triazol-3-yl]-propan-2-ol

- 25 Step 1: 1-(4-Bromo-phenyl)-1H-[1,2,4]triazole-3-carboxylic acid methyl ester
4-Bromophenylboronic acid (1.58 g), methyl-1,2,4-triazole-3-carboxylate (1 g), copper (I) acetate and pyridine (1.94 mL) are stirred in 20 mL of dichloromethane in oxygen atmosphere for 72 h. Ammonium hydroxide saturated aqueous solution is added and

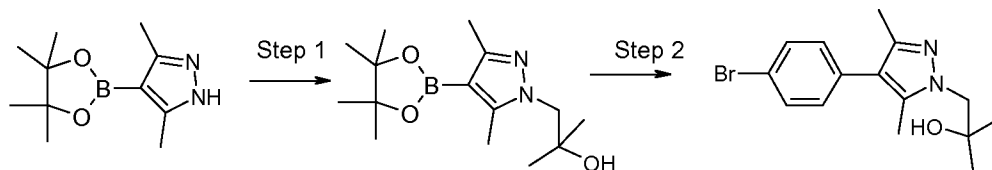
the reaction mixture is extracted with dichloromethane. The organic phase is collected, dried over sodium sulfate and the solvent removed under vacuum. The residue is purified by flash chromatography (cyclohexane/ethyl acetate 100:0→60:40) to give the title compound. Yield: 1.6 mg.

5 Step 2: 2-[1-(4-Bromo-phenyl)-1H-[1,2,4]triazol-3-yl]-propan-2-ol

1-(4-Bromo-phenyl)-1H-[1,2,4]triazole-3-carboxylic acid methyl ester (400 mg) is dissolved in 10 mL of dry tetrahydrofuran, methylmagnesium bromide (1 mL of a 3 M solution in tetrahydrofuran) is added and the reaction mixture is stirred at room temperature for 3 h. Water is added and the reaction mixture is extracted with ethyl acetate. The organic phase is collected, dried over sodium sulfate and the solvent removed under vacuum. The residue is purified by flash chromatography (cyclohexane/ethyl acetate 100:0→50:50) to give the title compound. Yield: 390 mg.

Intermediate 52fm

15 1-[4-(4-Bromo-phenyl)-3,5-dimethyl-pyrazol-1-yl]-2-methyl-propan-2-ol



Step 1: 1-[3,5-Dimethyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-pyrazol-1-yl]-2-methyl-propan-2-ol

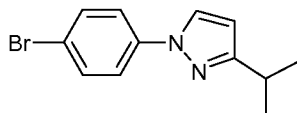
In a microwave vial, 3,5-dimethylpyrazole-4-boronic acid pinacol ester (500 mg) is dissolved in isobutylene oxide (1 mL), cesium carbonate (147 mg) is added and the reaction mixture is stirred at 120 °C for 30 min under microwave irradiation (100 W). Ethyl acetate is added and the reaction mixture filtered. The organic phase is concentrated under vacuum to give the title compound, used in the next step without further purification. Yield: 630 mg.

25 Step 2: 1-[4-(4-Bromo-phenyl)-3,5-dimethyl-pyrazol-1-yl]-2-methyl-propan-2-ol

The title compound is prepared in analogy to Intermediate 52fa, starting from 1-[3,5-dimethyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-pyrazol-1-yl]-2-methyl-propan-2-ol

30 **Intermediate 52fn**

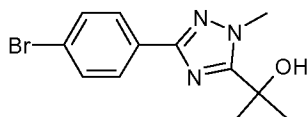
1-(4-Bromo-phenyl)-3-isopropyl-1H-pyrazole



The title compound is prepared in analogy to intermediate 52fha starting from 3-isopropylpyrazole

5 Intermediate 52fo

2-[5-(4-Bromo-phenyl)-2-methyl-2H-[1,2,4]triazol-3-yl]-propan-2-ol

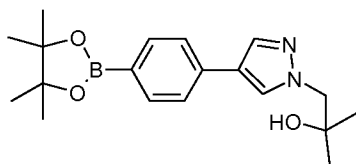


2-Hydroxyisobutyric acid (1.1 g), N,N,N',N'-tetramethyl-O-(benzotriazol-1-yl)uronium tetrafluoroborate (2.04g) and triethylamine (2 g) are stirred in 20 mL of acetonitrile at room temperature for 5 minutes, 4-bromo-N-(methylamino)benzenecarboximidamide (WO2009/105500 A1, 2009) (2 g) is added and the reaction mixture is stirred at room temperature for 24 h, then at 80 °C for 2 h. Solvent is concentrated under vacuum. The residue is purified by flash chromatography (cyclohexane/ethyl acetate 100:0→50:50) to give the title compound. Yield: 280 mg.

15

Intermediate 52ga

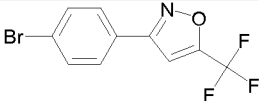
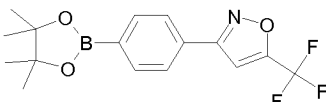
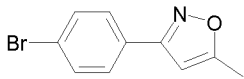
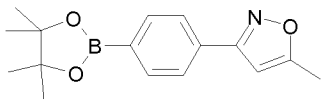
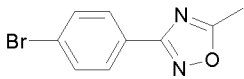
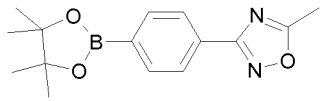
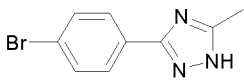
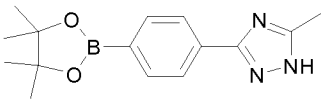
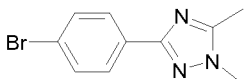
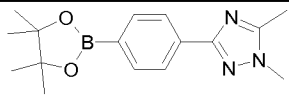
2-Methyl-1-{4-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-pyrazol-1-yl}-propan-2-ol

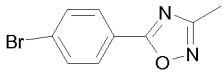
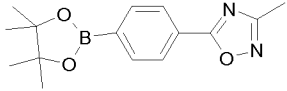
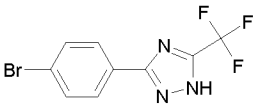
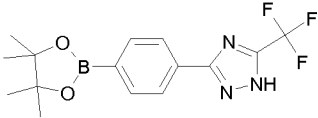
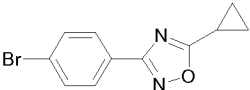
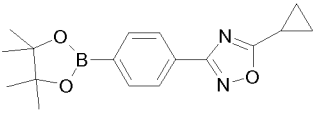
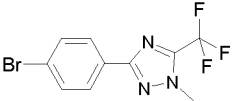
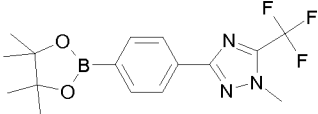
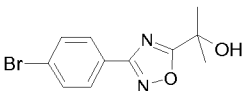
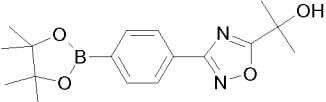
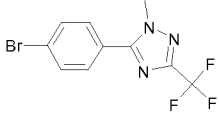
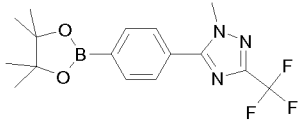


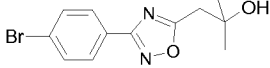
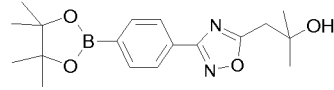
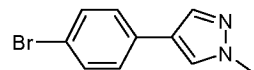
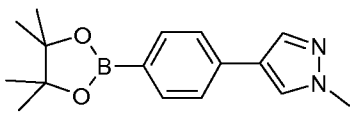
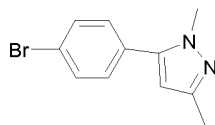
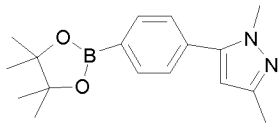
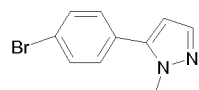
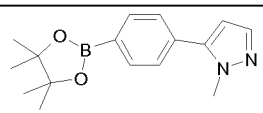
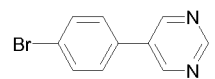
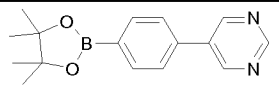
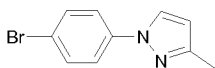
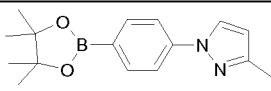
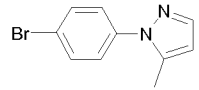
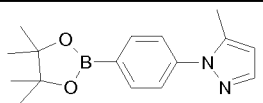
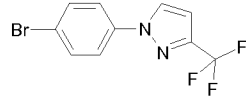
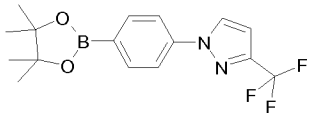
Intermediate 52fa (452 mg) is stirred in 25 mL of 1,4-dioxane, Bis(pinacolate)diboron (405 mg), 1,1'-bis(diphenylphosphino)ferrocenedichloropalladium(II) (100 mg) and potassium acetate (324 mg) are added and the reaction mixture is stirred under nitrogen atmosphere at 100 °C for 6 h. Solvent is removed. Water is added and the reaction mixture is extracted with ethyl acetate. The organic phase is collected, dried over sodium sulfate and the solvent removed under vacuum. The residue is purified by flash chromatography (cyclohexane/ethyl acetate 100:0→50:50) to give the title compound. Yield: 310 mg.

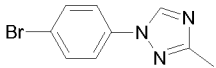
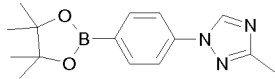
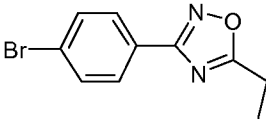
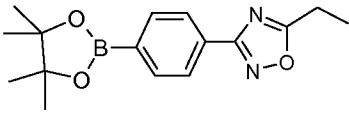
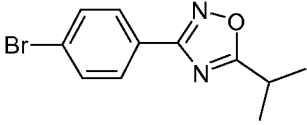
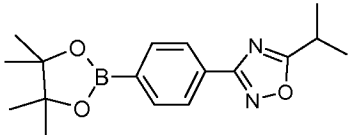
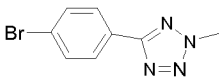
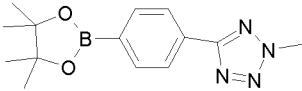
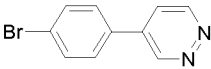
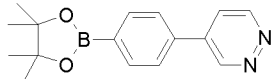
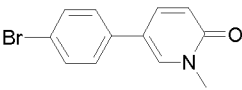
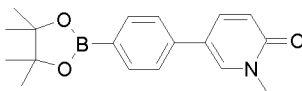
The intermediates in the following table are prepared from the corresponding starting bromo-aryl intermediates following a procedure analogous to that described for Intermediate 52ga.

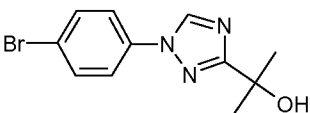
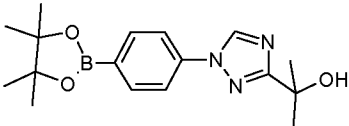
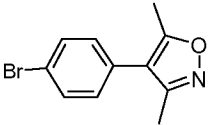
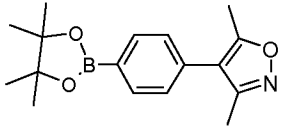
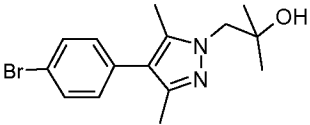
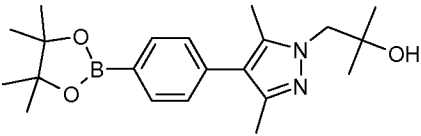
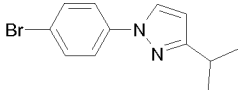
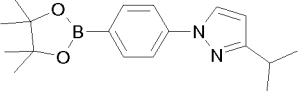
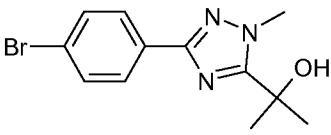
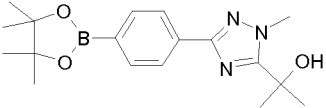
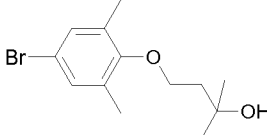
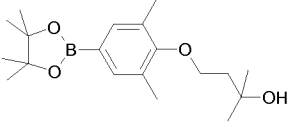
5

Starting bromoaryl Intermediate	Intermediate	Molecular structure and name
 Martins, Marcos A. P et al. Journal of Heterocyclic Chemistry, 1996, vol. 33, # 6 p. 1619 - 1622	52gb	 3-[4-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-5-trifluoromethyl-isoxazole
 Tang, Shibing et al. Organic Letters, 2009, vol. 11, # 17 p. 3982 - 3985	52gc	 5-Methyl-3-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-isoxazole
 WO2006/40192 A1, 2006 ;	52gd	 5-Methyl-3-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-[1,2,4]oxadiazole
 Ueda, Satoshi et al. Journal of the American Chemical Society, 2009, vol. 131, # 42 p. 15080 - 15081	52ge	 5-Methyl-3-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1H-[1,2,4]triazole
 WO2009/105500 A1, 2009 ;	52gf	 1,5-Dimethyl-3-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1H-[1,2,4]triazole

 WO2004/101546 A1, 2004	52gg	 3-Methyl-5-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-[1,2,4]oxadiazole
 52fb	52gh	 3-[4-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-5-trifluoromethyl-1H-[1,2,4]triazole
 52fc	52gi	 5-Cyclopropyl-3-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-[1,2,4]oxadiazole
 52fdb	52gj	 1-Methyl-3-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-5-trifluoromethyl-1H-[1,2,4]triazole
 52fe	52gk	 2-{3-[4-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-[1,2,4]oxadiazol-5-yl}-propan-2-ol
 52fda	52gl	 1-Methyl-5-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-3-trifluoromethyl-1H-[1,2,4]triazole

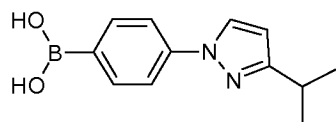
 52fea	52gka	 2-Methyl-1-{3-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-[1,2,4]oxadiazol-5-yl}-propan-2-ol
 52ff	52gm	 1-Methyl-4-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1H-pyrazole
 52fg	52gn	 1,3-Dimethyl-5-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1H-pyrazole
 WO2009/69044 A1, 2009	52go	 1-Methyl-5-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1H-pyrazole
 EP2166015 A1, 2010	52gp	 5-[4-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-pyrimidine
 52fha	52gra	 3-Methyl-1-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1H-pyrazole
 52fhb	52grb	 5-Methyl-1-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1H-pyrazole
 Suh, Jeehee et al.	52gs	 1-[4-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-

Bulletin of the Korean Chemical Society, 2012 , vol. 33, # 6 p. 2067 - 2070		yl)-phenyl]-3-trifluoromethyl-1H-pyrazole
 52fi	52gt	 3-Methyl-1-[4-(4,4,5,5-tetramethyl- [1,3,2]dioxaborolan-2-yl)-phenyl]-1H- [1,2,4]triazole
 52fca	52gu	 5-Ethyl-3-[4-(4,4,5,5-tetramethyl- [1,3,2]dioxaborolan-2-yl)-phenyl]- [1,2,4]oxadiazole
 52fcb	52gw	 5-Isopropyl-3-[4-(4,4,5,5-tetramethyl- [1,3,2]dioxaborolan-2-yl)-phenyl]- [1,2,4]oxadiazole
 WO2008/108602 A1, 2008	52gx	 2-Methyl-5-[4-(4,4,5,5-tetramethyl- [1,3,2]dioxaborolan-2-yl)-phenyl]-2 H-tetrazole
 52fj	52gy	 4-[4-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2- yl)-phenyl]-pyridazine
 52fk	52gz	

 52fl	52gza	 2-{1-[4-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1H-[1,2,4]triazol-3-yl}-propan-2-ol
 WO2004/74270 A2, 2004	52gzb	 3,5-Dimethyl-4-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-isoxazole
 52fm	52gzc	 1-{3,5-Dimethyl-4-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-pyrazol-1-yl}-2-methylpropan-2-ol
 52fn	52gzd	 3-Isopropyl-1-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1H-pyrazole
 52fo	52gze	 2-{2-Methyl-5-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-2H-[1,2,4]triazol-3-yl}-propan-2-ol
 50w	52gzf	 4-[2,6-Dimethyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenoxy]-2-methylbutan-2-ol

Intermediate 52gzda

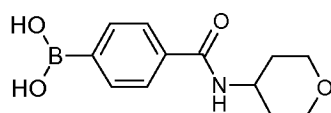
4-(3-Isopropyl-pyrazol-1-yl)-boronic acid



Intermediate 52gzd (3.6 g), sodium metaperiodate (24.7 g) and ammonium acetate (8.9 g) are stirred in 40 mL of acetone and 40 mL of water at room temperature overnight. The reaction mixture is filtered and the solvent concentrated. The residue is cooled to 0 °C and a 1 M sodium hydroxide water solution is added up to basic pH. The organic phase is extracted with dichloromethane, separated, dried over sodium sulfate and concentrated under vacuum to give the title compound. Yield: 390 mg.

10 **Intermediate 52gzg**

4-(Tetrahydro-pyran-4-ylcarbamoyl)-benzeneboronic acid

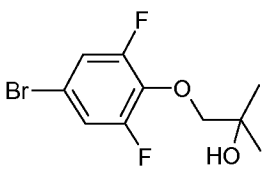
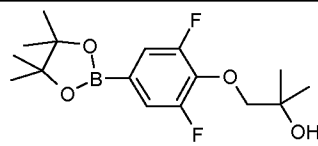
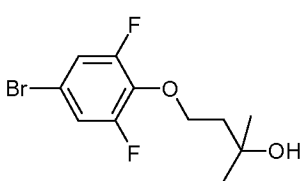
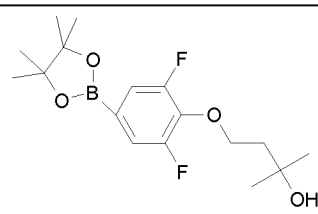
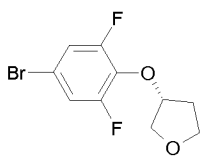
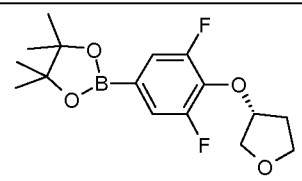
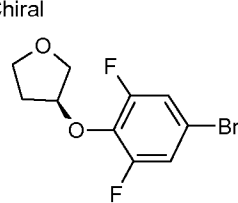
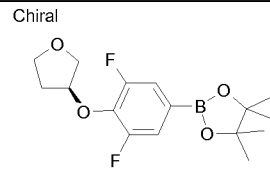
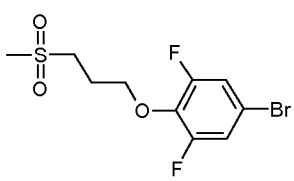
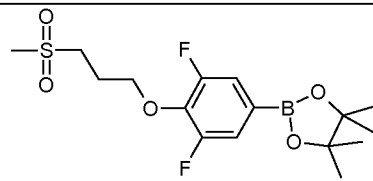


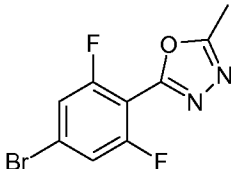
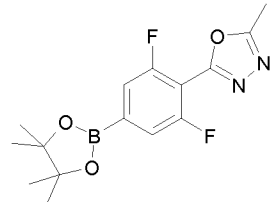
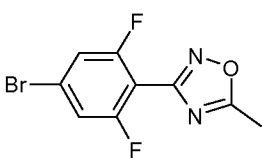
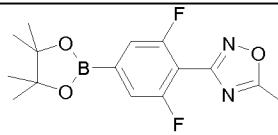
To a mixture of 4-carboxyphenylboronic acid (500 mg) and 4-aminoetrahydrofurane hydrochloride (413 mg) in 20 mL of tetrahydrofurane, N,N'-diisopropylethylamine (1,55 g) and N,N,N',N'-tetramethyl-O-(benzotriazol-1-yl)uronium tetrafluoroborate (953 mg) are added and the reaction mixture is stirred at room temperature overnight. The solvent is removed and the residue is partitioned between a 1 M hydrochloric acid aqueous solution and ethyl acetate. The solid precipitated is filtered and dried under vacuum to give the title compound. Yield: 537 mg.

20

The intermediates in the following table are prepared from the corresponding starting bromo-aryl intermediates following a procedure analogous to that described for Intermediate 52ga.

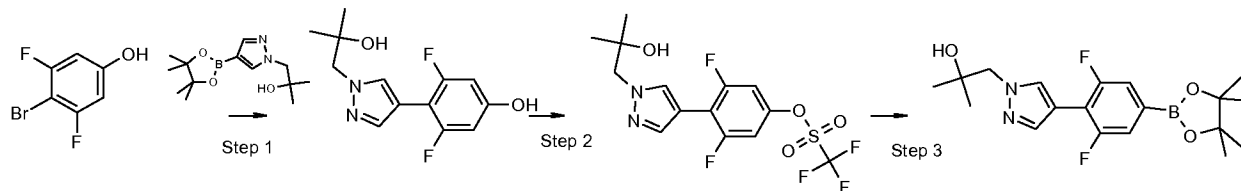
Starting bromo-aryl-intermediate	Intermediate	Molecular structure and name
50ua	52gzua	4-[2,6-Difluoro-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenoxy]methyl-4-(tetrahydro-2H-pyran-2-yl)methyl ether

		tetrahydro-pyran-4-ol
 50ub	52gzub	 1-[2,6-Difluoro-4-(4,4,5,5-tetramethyl- [1,3,2]dioxaborolan-2-yl)-phenoxy]-2-methyl- propan-2-ol
 50uc	52gzuc	 4-[2,6-Difluoro-4-(4,4,5,5-tetramethyl- [1,3,2]dioxaborolan-2-yl)-phenoxy]-2-methyl- butan-2-ol
 50ud Chiral	52gzud	 Chiral 2-{3,5-Difluoro-4-[(R)-(tetrahydro-furan-3-yl)oxy]- phenyl}-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane
 50ue Chiral	52gzue	 Chiral 2-{3,5-Difluoro-4-[(S)-(tetrahydro-furan-3-yl)oxy]- phenyl}-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane
 52uf	52gzuf	 2-[3,5-Difluoro-4-(3-methanesulfonyl-propoxy)- phenyl]-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane

 50ug	52gzug	 2-[2,6-Difluoro-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-5-methyl-[1,3,4]oxadiazole
 50uh	52gzuH	 3-[2,6-Difluoro-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-5-methyl-[1,2,4]oxadiazole

Intermediate 52gzui

1-{4-[2,6-Difluoro-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-pyrazol-1-yl}-2-methyl-propan-2-ol



5

Step1: 3,5-Difluoro-4-[1-(2-hydroxy-2-methyl-propyl)-1H-pyrazol-4-yl]-phenol

The title compound is prepared following what described in Step 1 in the preparation of Intermediate 52aa, starting from 1-[3,5-dimethyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-pyrazol-1-yl]-2-methyl-propan-2-ol and 4-bromo-3,5-difluorophenol.

Step2: Trifluoro-methanesulfonic acid 3,5-difluoro-4-[1-(2-hydroxy-2-methyl-propyl)-1H-pyrazol-4-yl]-phenyl ester

3,5-Difluoro-4-[1-(2-hydroxy-2-methyl-propyl)-1H-pyrazol-4-yl]-phenol (900 mg) is stirred at 0 °C in 10 mL of dichloromethane. Trifluoromethanesulfonic anhydride (0.41 mL) is added dropwise and the reaction mixture is stirred for 30 minutes. The reaction mixture is partitioned between a bicarbonate water saturated solution and

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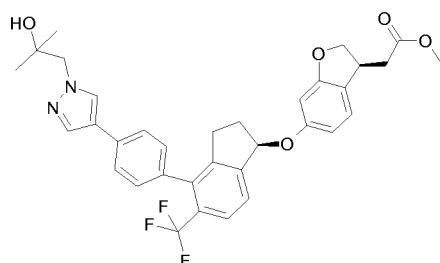
dichloromethane, the organic phase is separated, dried over sodium sulfate and concentrated under vacuum to give the title compound. Yield: 900 mg.

Step 3: 1-{4-[2,6-Difluoro-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-pyrazol-1-yl}-2-methyl-propan-2-ol

- 5 The title compound is prepared in analogy to Intermediate 52ga, starting from trifluoro-methanesulfonic acid 3,5-difluoro-4-[1-(2-hydroxy-2-methyl-propyl)-1H-pyrazol-4-yl]-phenyl ester

Intermediate 52ha

- 10 [(S)-6-((R)-4-{4-[1-(2-Hydroxy-2-methyl-propyl)-1H-pyrazol-4-yl]-phenyl}-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl]-acetic acid methyl ester

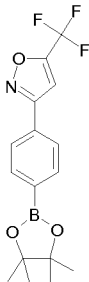
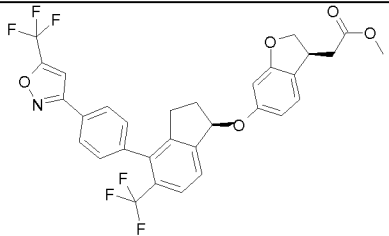
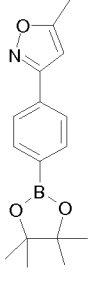
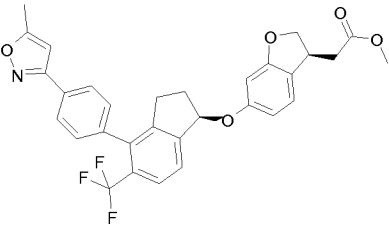
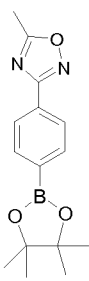
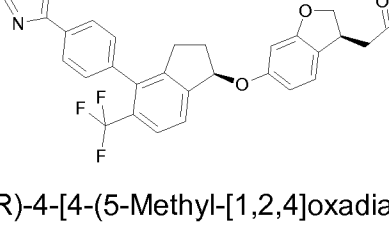
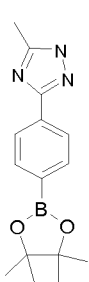
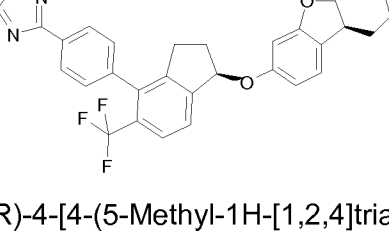


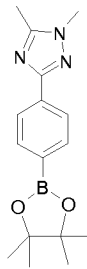
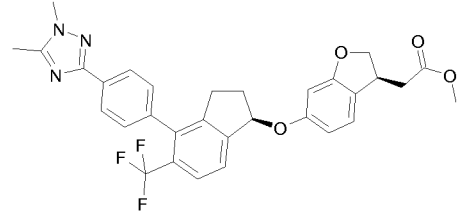
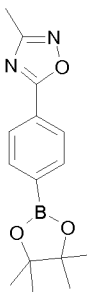
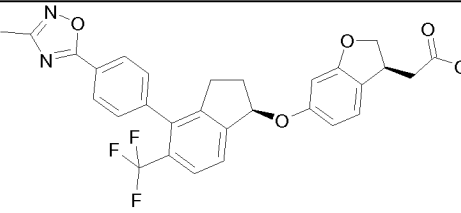
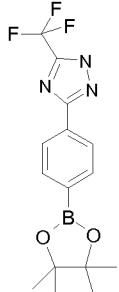
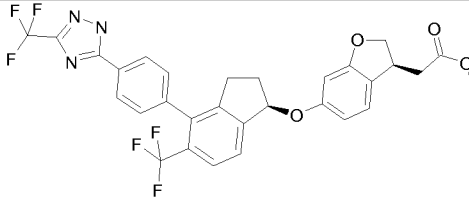
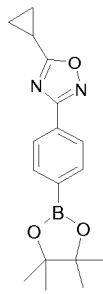
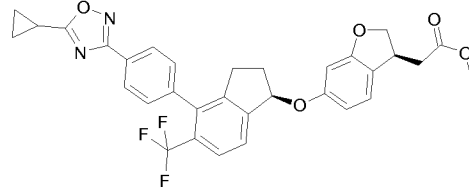
- Intermediate 52a (89 mg), Intermediate 52ga (86 mg), potassium carbonate (78 mg) 2,6-di-tert-butyl-4-methylphenol (21 mg) and tricyclohexyl-phosphine (4 mg) are stirred in 4 mL of 1,4-dioxane and 1 mL of water, tris(dibenzylideneacetone) dipalladium(0) (7 mg) is added and the reaction mixture is stirred at 110 °C for 1 h. Water is added and the reaction mixture is extracted with ethyl acetate. The organic phase is separated, dried over sodium sulfate and concentrated under vacuum. The residue is purified by chromatography on silica gel (cyclohexane/ethyl acetate 100:0→50:50) to give the title compound. Yield: 34 mg.

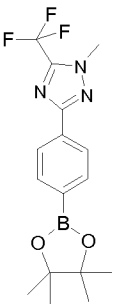
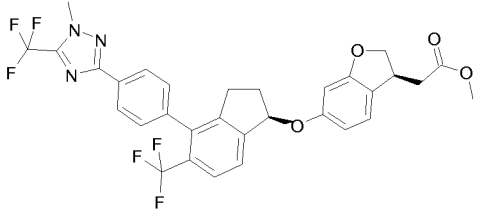
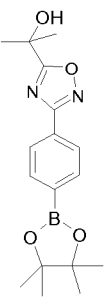
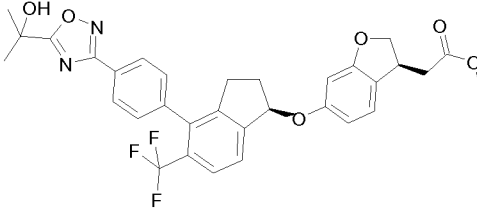
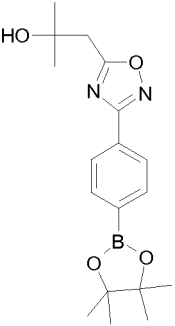
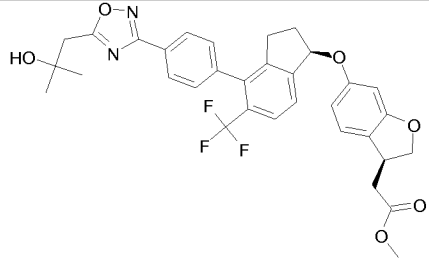
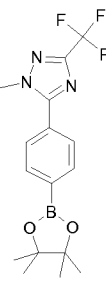
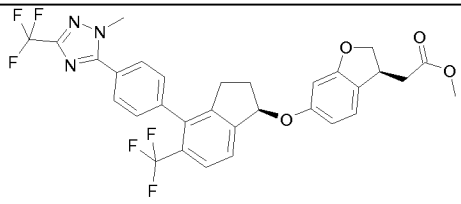
The intermediates in the following table are prepared from Intermediate 52a and the corresponding starting boronic ester intermediates following a analogous procedure analogous to that described for Intermediate 52ha.

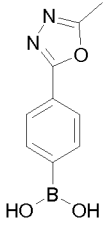
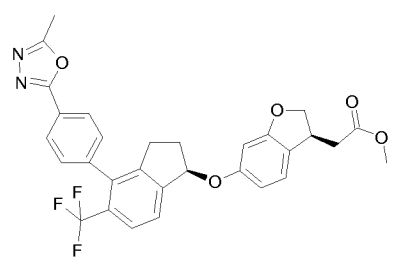
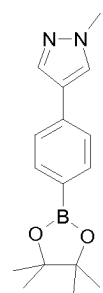
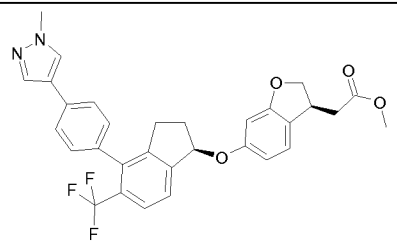
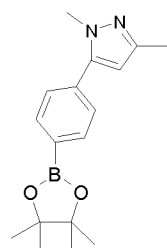
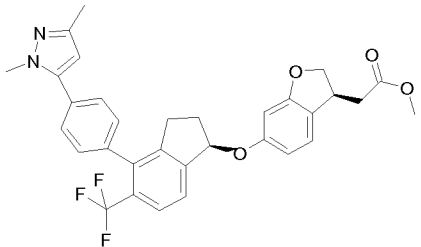
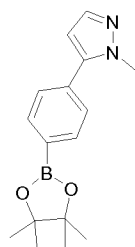
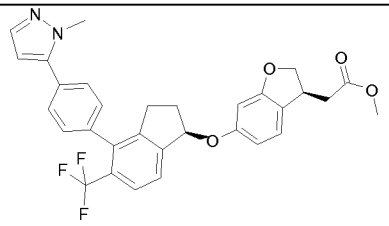
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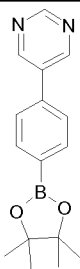
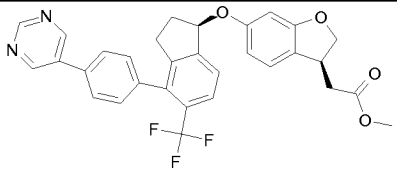
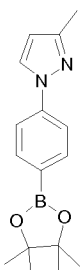
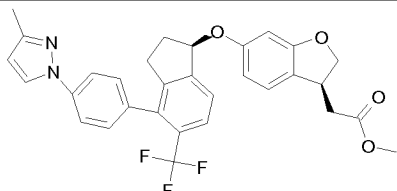
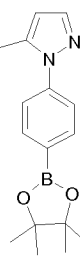
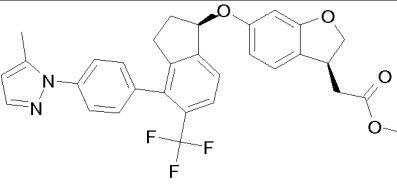
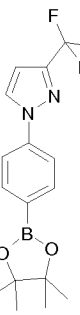
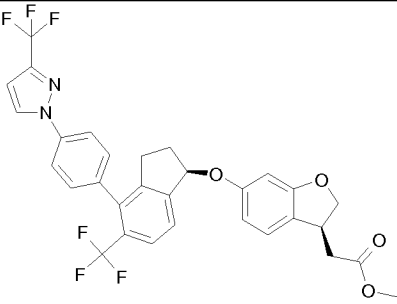
Starting boronic ester/acid Intermediate	Intermediate	Molecular structure and name

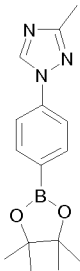
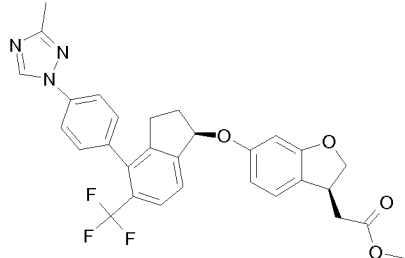
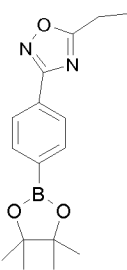
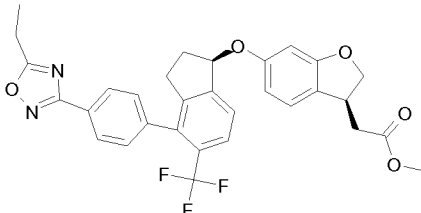
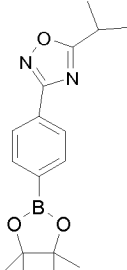
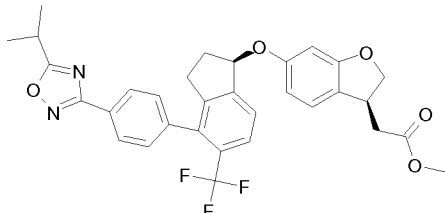
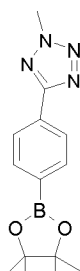
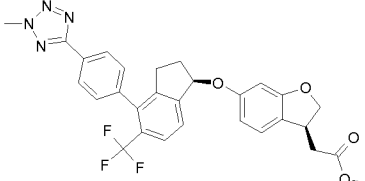
 52gb	52hb	 ((S)-6-((R)-5-Trifluoromethyl-4-[4-(5-trifluoromethyl-isoxazol-3-yl)-phenyl]-indan-1-yloxy}-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester
 52gc	52hc	 ((S)-6-((R)-4-[4-(5-Methyl-isoxazol-3-yl)-phenyl]-5-trifluoromethyl-indan-1-yloxy}-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester
 52gd	52hd	 ((S)-6-((R)-4-[4-(5-Methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-5-trifluoromethyl-indan-1-yloxy}-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester
 52ge	52he	 ((S)-6-((R)-4-[4-(5-Methyl-1H-[1,2,4]triazol-3-yl)-phenyl]-5-trifluoromethyl-indan-1-yloxy}-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester

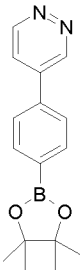
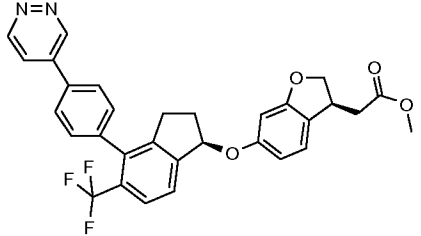
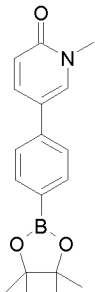
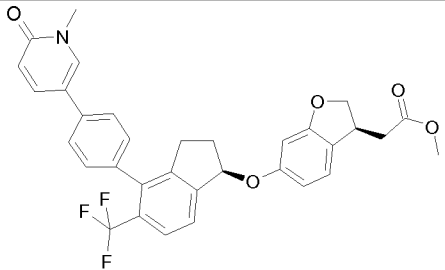
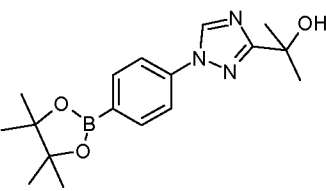
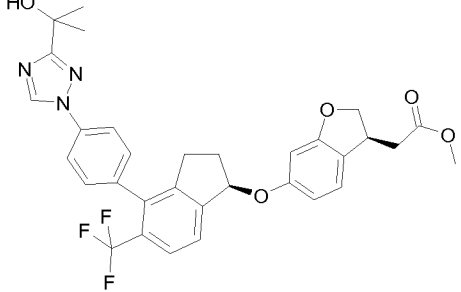
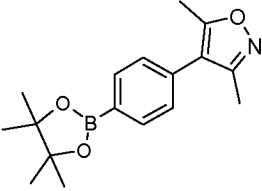
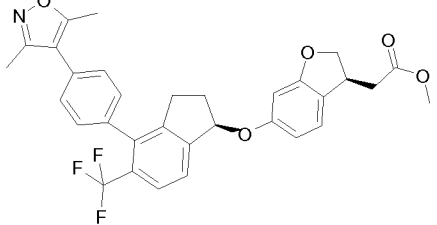
 52gf	52hf	 ((S)-6-{(R)-4-[4-(1,5-Dimethyl-1H-[1,2,4]triazol-3-yl)-phenyl]-5-trifluoromethyl-indan-1-yloxy}-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester
 52gg	52hg	 ((S)-6-{(R)-4-[4-(3-Methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-5-trifluoromethyl-indan-1-yloxy}-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester
 52gh	52hh	 ((S)-6-{(R)-5-Trifluoromethyl-4-[4-(5-trifluoromethyl-2H-[1,2,4]triazol-3-yl)-phenyl]-indan-1-yloxy}-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester
 52gi	52hi	 ((S)-6-{(R)-4-[4-(5-Cyclopropyl-[1,2,4]oxadiazol-3-yl)-phenyl]-5-trifluoromethyl-indan-1-yloxy}-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester

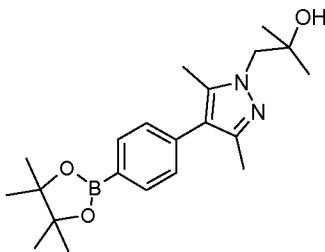
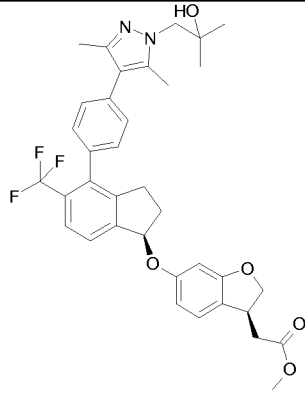
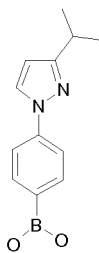
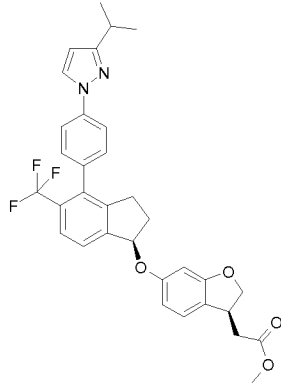
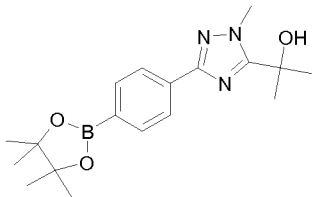
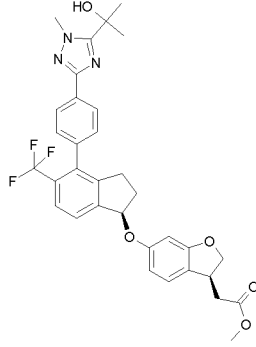
 52gj	52hj	 ((S)-6-((R)-4-[4-(1-Methyl-5-trifluoromethyl-1H-[1,2,4]triazol-3-yl)-phenyl]-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester
 52gk	52hk	 [(S)-6-((R)-4-{4-[5-(1-Hydroxy-1-methyl-ethyl)-[1,2,4]oxadiazol-3-yl]-phenyl}-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl]-acetic acid methyl ester
 52gka	52hka	 [(S)-6-((R)-4-{4-[5-(2-Hydroxy-2-methyl-propyl)-[1,2,4]oxadiazol-3-yl]-phenyl}-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl]-acetic acid methyl ester
 52gl	52hl	 ((S)-6-((R)-4-[4-(2-Methyl-5-trifluoromethyl-2H-[1,2,4]triazol-3-yl)-phenyl]-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester

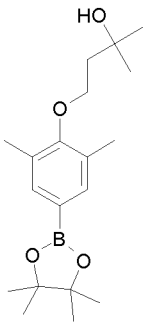
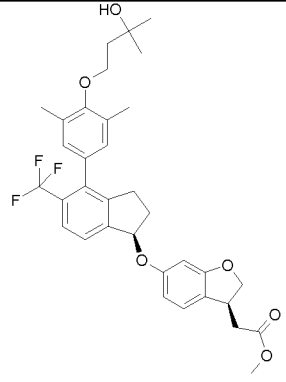
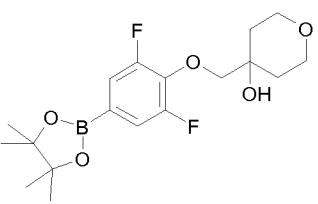
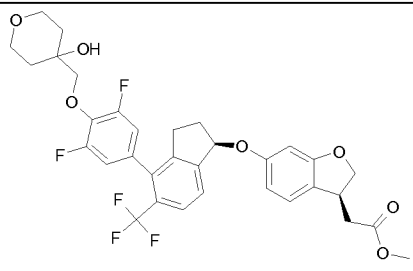
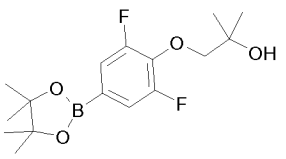
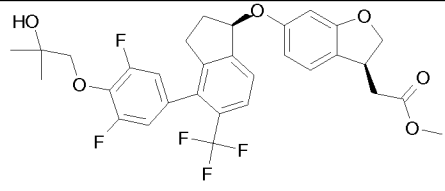
 4-(5-methyl-1,3,4-oxadiazol-2-yl)-benzeneboronic acid Commercially available	52hla	 ((S)-6-((R)-4-[4-(5-Methyl-[1,3,4]oxadiazol-2-yl)-phenyl]-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester
 52gm	52hm	 ((S)-6-((R)-4-[4-(1-Methyl-1H-pyrazol-4-yl)-phenyl]-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester
 52gn	52hn	 ((S)-6-((R)-4-[4-(2,5-Dimethyl-2H-pyrazol-3-yl)-phenyl]-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester
 52go	52ho	 ((S)-6-((R)-4-[4-(2-Methyl-2H-pyrazol-3-yl)-phenyl]-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester

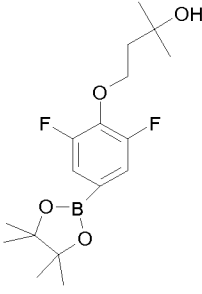
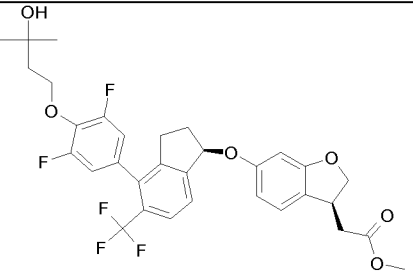
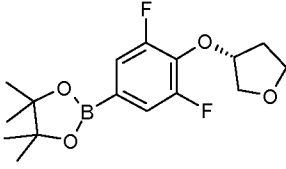
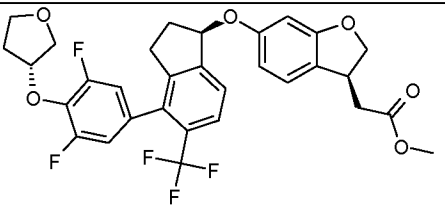
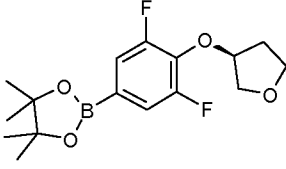
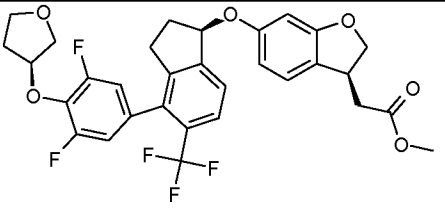
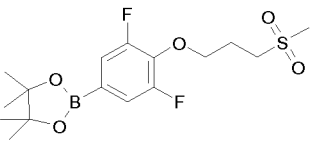
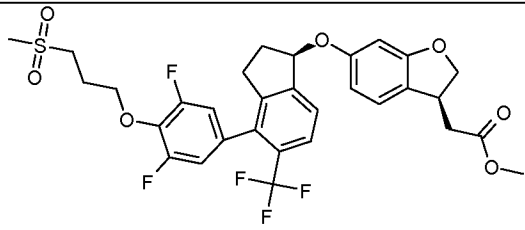
		ester
 52gp	52hp	 {(S)-6-[(R)-4-(4-Pyrimidin-5-yl-phenyl)-5-trifluoromethyl-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester
 52gra	52hra	 ((S)-6-[(R)-4-[4-(3-Methyl-pyrazol-1-yl)-phenyl]-5-trifluoromethyl-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester
 52grb	52hrb	 ((S)-6-[(R)-4-[4-(5-Methyl-pyrazol-1-yl)-phenyl]-5-trifluoromethyl-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester
 52gs	52hs	 ((S)-6-[(R)-5-Trifluoromethyl-4-[4-(3-trifluoromethyl-pyrazol-1-yl)-phenyl]-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester

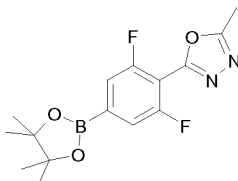
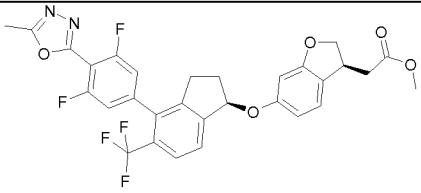
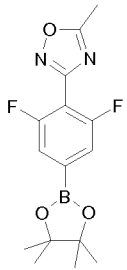
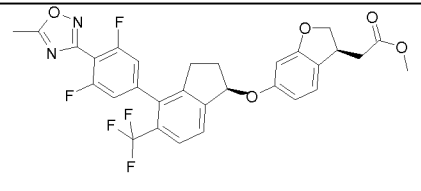
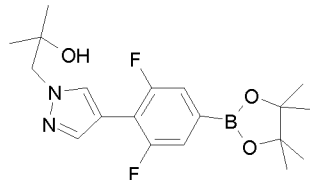
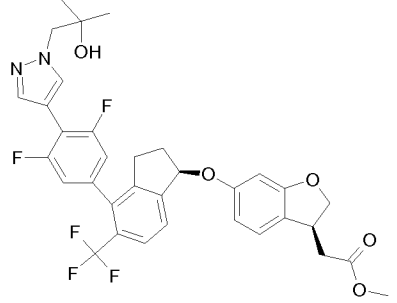
 52gt	52ht	 ((S)-6-((R)-4-[4-(3-Methyl-[1,2,4]triazol-1-yl)-phenyl]-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester
 52gu	52hu	 ((S)-6-((R)-4-[4-(5-Ethyl-[1,2,4]oxadiazol-3-yl)-phenyl]-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester
 52gw	52hw	 ((S)-6-((R)-4-[4-(5-Isopropyl-[1,2,4]oxadiazol-3-yl)-phenyl]-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester
 52gx	52hx	 ((S)-6-((R)-4-[4-(2-Methyl-2H-tetrazol-5-yl)-phenyl]-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester

 52gy	52hy	 {(S)-6-[(R)-4-(4-Pyridazin-4-yl-phenyl)-5-trifluoromethyl-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester
 52gz	52hz	 ((S)-6-[(R)-4-[4-(1-Methyl-6-oxo-1,6-dihydropyridin-3-yl)-phenyl]-5-trifluoromethyl-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester
 52gza	52hza	 [(S)-6-((R)-4-{3-[1-Hydroxy-1-methyl-ethyl]-[1,2,4]triazol-1-yl}-phenyl)-5-trifluoromethyl-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl]-acetic acid methyl ester
 52gzb	52hzb	 ((S)-6-[(R)-4-[4-(3,5-Dimethyl-isoxazol-4-yl)-phenyl]-5-trifluoromethyl-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester

 52gzc	52hzc	ester  [(S)-6-((R)-4-{4-[1-(2-Hydroxy-2-methyl-propyl)-3,5-dimethyl-1H-pyrazol-4-yl]-phenyl}-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl]-acetic acid methyl ester
 52gzda	52hzd	 ((S)-6-{(R)-4-[4-(3-Isopropyl-pyrazol-1-yl)-phenyl]-5-trifluoromethyl-indan-1-yloxy}-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester
 52gze	52hze	 [(S)-6-((R)-4-{4-[5-(1-Hydroxy-1-methyl-ethyl)-1-methyl-1H-[1,2,4]triazol-3-yl]-phenyl}-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl]-

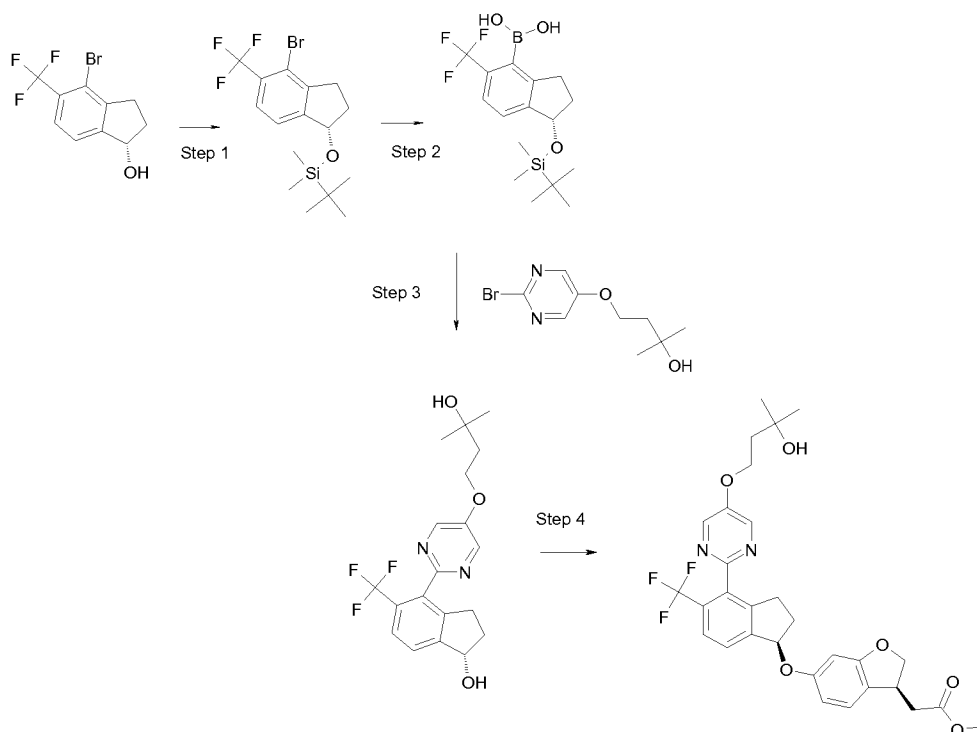
		acetic acid methyl ester
 52gzf	52hzf	 ((S)-6-((R)-4-[4-(3-Hydroxy-3-methylbutoxy)-3,5-dimethyl-phenyl]-5-trifluoromethyl-indan-1-yloxy}-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester
 52gzua	52hzg	 ((S)-6-((R)-4-[3,5-Difluoro-4-(4-hydroxy-tetrahydro-pyran-4-ylmethoxy)-phenyl]-5-trifluoromethyl-indan-1-yloxy}-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester
 52gzub	52hzh	 ((S)-6-((R)-4-[3,5-Difluoro-4-(2-hydroxy-2-methyl-propoxy)-phenyl]-5-trifluoromethyl-indan-1-yloxy}-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester

 52gzuc	52hzi	 ((S)-6-((R)-4-[3,5-Difluoro-4-(3-hydroxy-3-methyl-butoxy)-phenyl]-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester
 52gzud	52hzj	 [(S)-6-((R)-4-{3,5-Difluoro-4-[(R)-(tetrahydro-furan-3-yl)oxy]-phenyl}-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl]-acetic acid methyl ester
 52gzue	52hzk	 [(S)-6-((R)-4-{3,5-Difluoro-4-[(S)-(tetrahydro-furan-3-yl)oxy]-phenyl}-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl]-acetic acid methyl ester
 52gzuf	52hzi	 ((S)-6-((R)-4-[3,5-Difluoro-4-(3-methanesulfonyl-propoxy)-phenyl]-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester

		ifluoromethyl-indan-1-yloxy}-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester
 52gzug	52hzm	 ((S)-6-((R)-4-[3,5-Difluoro-4-(5-methyl-1,3,4)oxadiazol-2-yl)-phenyl]-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester
 52gzuh	52hzn	 ((S)-6-((R)-4-[3,5-Difluoro-4-(5-methyl-1,2,4)oxadiazol-3-yl)-phenyl]-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester
 52gzui	52hzo	 [(S)-6-((R)-4-{3,5-Difluoro-4-[1-(2-hydroxy-2-methyl-propyl)-1H-pyrazol-4-yl]-phenyl}-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester

Intermediate 52hzp

((S)-6-((R)-4-[5-(3-Hydroxy-3-methyl-butoxy)-pyrimidin-2-yl]-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester



Step 1: ((S)-4-Bromo-5-trifluoromethyl-indan-1-yloxy)-tert-butyl-dimethyl-silane

(S)-4-Bromo-5-trifluoromethyl-indan-1-ol (1 g), tert-butyl-dimethylchlorosilane (895 mg), imidazole (810 mg) and 4-dimethylamino pyridine (45 mg) are stirred in 20 mL of dichloromethane at room temperature for 1 h. The reaction mixture is washed with water, the organic phase is separated, dried over sodium sulfate and concentrated under vacuum. The residue is purified by flash chromatography (cyclohexane/ethyl acetate 100:0→90:10) to give the title compound. Yield: 1.32 g.

Step 2: (S)-1-(tert-Butyl-dimethyl-silanyloxy)-5-trifluoromethyl-indan-4-boronic acid

((S)-4-Bromo-5-trifluoromethyl-indan-1-yloxy)-tert-butyl-dimethyl-silane (1.2 g) is stirred in 20 mL of tetrahydrofuran at -78 °C, a 2 M solution of N-butyllithium in cyclohexane (1.82 mL) is added and the reaction mixture is stirred for 2 h. Triisopropyl borate (800 mg) is added and the reaction mixture is stirred at -78 °C for 30 minutes, then allowed to reach room temperature and stirred 1 h. Saturated ammonium chloride water solution is added and the reaction mixture is extracted with ethyl acetate. The organic phase is washed with brine, separated, dried over sodium sulfate and concentrated under vacuum to give the title compound. Yield: 1.14 g.

Step 3: (S)-4-[5-(3-Hydroxy-3-methyl-butoxy)-pyrimidin-2-yl]-5-trifluoromethyl-indan-

1-ol

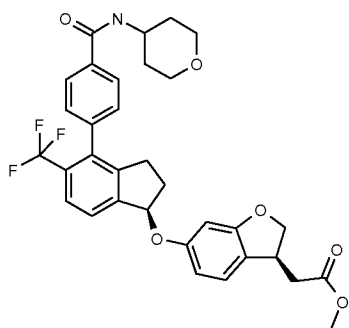
In a microwave vial, Intermediate 50z (99 mg), (S)-1-(tert-butyl-dimethyl-silanyloxy)-5-trifluoromethyl-indan-4-boronic acid (10 mg) tetrakis(triphenylphosphine) palladium(0) (46 mg) and bicarbonate saturated aqueous solution (450 mL) are suspended in 2 mL of 1,2-dimethoxyethane. The reaction mixture is irradiated in a MW oven at 120 °C for 1 h (50 W). Solvent is removed, saturated ammonium chloride water solution is added and the reaction mixture is extracted with dichloromethane. The organic phase is washed with brine, layers separated, the organic layer dried over sodium sulfate and concentrated under vacuum. The residue is purified by flash chromatography (cyclohexane/ethyl acetate 90:10→40:60) to give the title compound. Yield: 55 mg.

Step 4: ((S)-6-((R)-4-[5-(3-Hydroxy-3-methyl-butoxy)-pyrimidin-2-yl]-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester

The title compound is prepared in analogy to methyl 2-((S)-6-((R)-4-bromo-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate as in Step 6 for the preparation of Intermediate 1

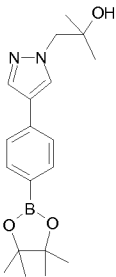
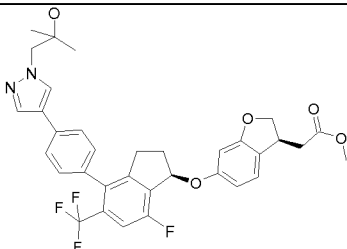
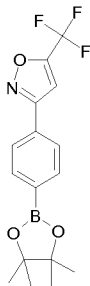
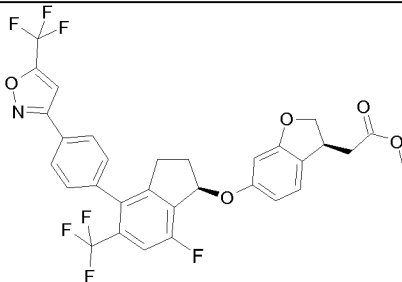
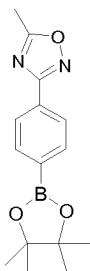
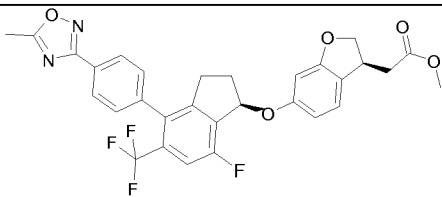
Intermediate 52hzq

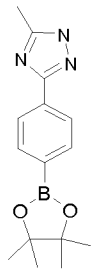
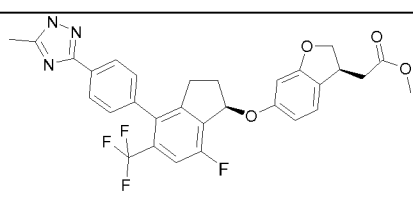
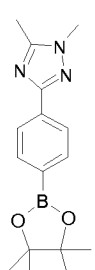
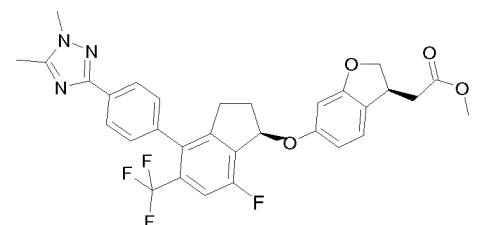
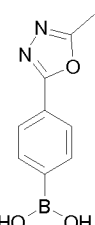
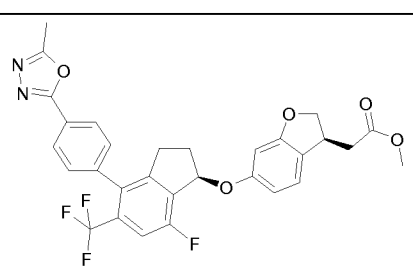
((S)-6-{(R)-4-[4-(Tetrahydro-pyran-4-yl)carbamoyl]-phenyl}-5-trifluoromethyl-indan-1-yl-oxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester

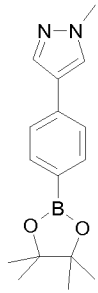
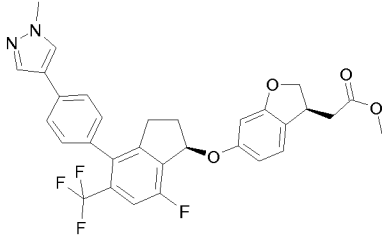
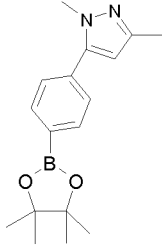
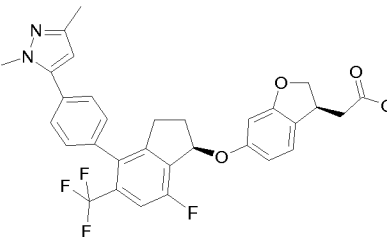
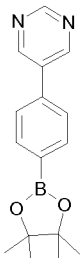
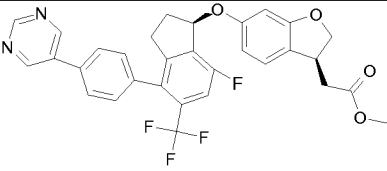
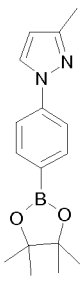
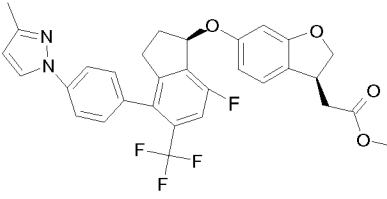


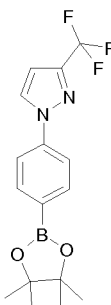
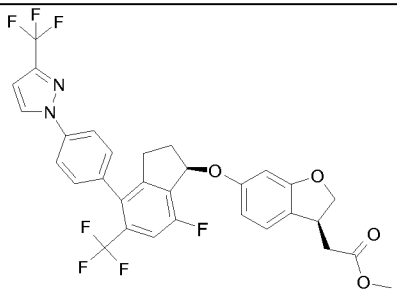
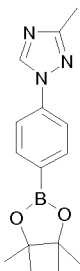
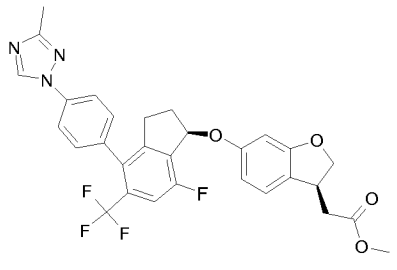
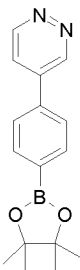
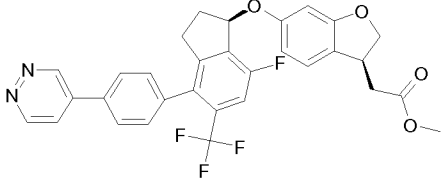
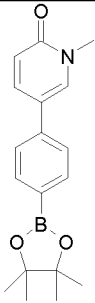
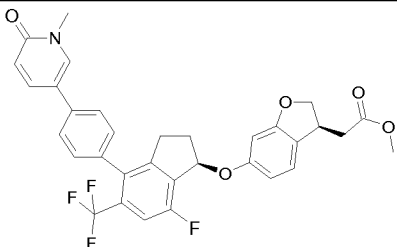
Intermediate 52a (70 mg), intermediate 52gzg (186 mg), 2-dicyclohexylphosphino-2'-(N,N'-dimethylamino)biphenyl (6 mg), tris(dibenzylideneacetone)dipalladium(0) (14 mg) and sodium carbonate (56 mg) are stirred in 10 mL of toluene and 5 mL of water at 90 °C for 4 h. then at room temperature overnight. The reaction mixture is washed with water, the organic phase is separated, dried over sodium sulfate and concentrated under vacuum. The residue is purified by flash chromatography (cyclohexane/ethyl acetate 70:30→50:50) to give the title compound. Yield: 31 mg.

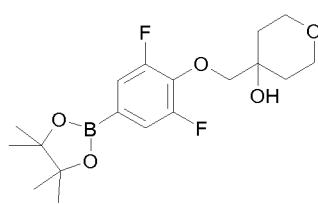
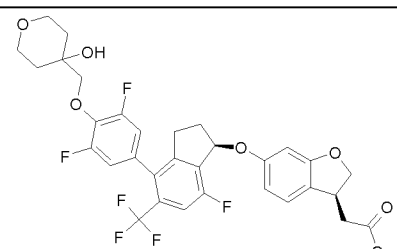
The intermediates in the following table are prepared from Intermediate 52b and the corresponding starting boronic ester intermediates following a procedure analogous to that described for Intermediate 52ha

Starting boronic ester/acid Intermediate	Intermediate	Molecular structure and name
 52ga	52ia	 [(S)-6-((R)-7-Fluoro-4-{4-[1-(2-hydroxy-2-methyl-propyl)-1H-pyrazol-4-yl]-phenyl}-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl]-acetic acid methyl ester
 52gb	52ib	 ((S)-6-((R)-7-Fluoro-5-trifluoromethyl-4-[4-(5-trifluoromethyl-isoxazol-3-yl)-phenyl]-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester
 52gd	52ic	 ((S)-6-((R)-7-Fluoro-4-[4-(5-methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid

		methyl ester
 52ge	52id	 ((S)-6-((R)-7-Fluoro-4-[4-(5-methyl-1H-[1,2,4]triazol-3-yl)-phenyl]-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester
 52gf	52ie	 ((S)-6-((R)-4-[4-(1,5-Dimethyl-1H-[1,2,4]triazol-3-yl)-phenyl]-7-fluoro-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester
 4-(5-methyl-1,3,4-oxadiazol-2-yl)-benzene boronic acid Commercially available	52if	 ((S)-6-((R)-7-Fluoro-4-[4-(5-methyl-[1,3,4]oxadiazol-2-yl)-phenyl]-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester

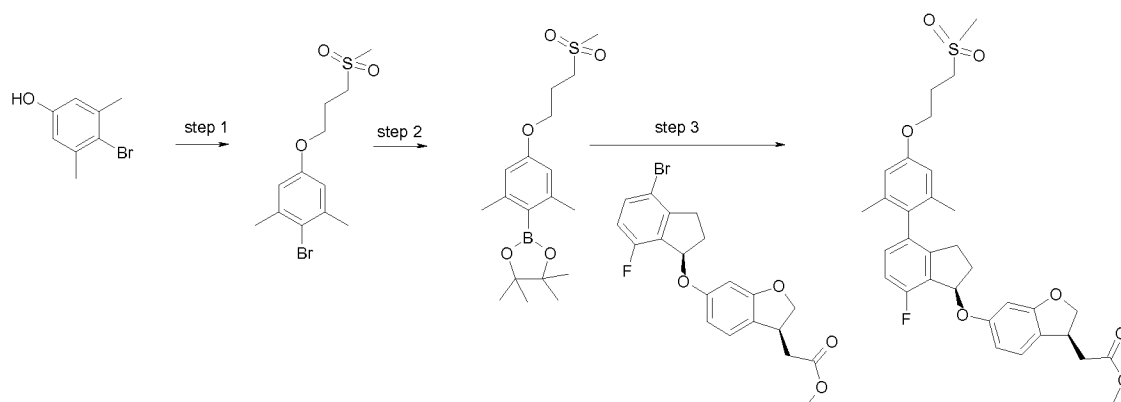
 52gm	52ig	 ((S)-6-((R)-7-Fluoro-4-[4-(1-methyl-1H-pyrazol-4-yl)-phenyl]-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester
 52gn	52ih	 ((S)-6-((R)-4-[4-(2,5-Dimethyl-2H-pyrazol-3-yl)-phenyl]-7-fluoro-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester
 52gp	52ii	 ((S)-6-((R)-7-Fluoro-4-(4-pyrimidin-5-yl-phenyl)-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester
 52gra	52ij	 ((S)-6-((R)-7-Fluoro-4-[4-(3-methyl-1H-pyrazol-1-yl)-phenyl]-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester

 52gs	52ik	 ((S)-6-((R)-7-Fluoro-5-trifluoromethyl-4-[4-(3-trifluoromethyl-pyrazol-1-yl)-phenyl]-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester
 52gt	52il	 ((S)-6-((R)-7-Fluoro-4-[4-(3-methyl-[1,2,4]triazol-1-yl)-phenyl]-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester
 52gy	52im	 ((S)-6-((R)-7-Fluoro-4-(4-pyridazin-4-yl-phenyl)-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester
 52in	52in	 ((S)-6-((R)-7-Fluoro-4-[4-(1-methyl

52gz		-6-oxo-1,6-dihydro-pyridin-3-yl)-phenyl]-5-trifluoromethyl-indan-1-yloxy}-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester
 52gzua	52io	 ((S)-6-((R)-4-[3,5-Difluoro-4-(4-hydroxy-tetrahydro-pyran-4-ylmethoxy)-phenyl]-7-fluoro-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester

Intermediate 53

Methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-(3-(methylsulfonyl)propoxy)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate



5

Step 1: 2-Bromo-1,3-dimethyl-5-(3-(methylsulfonyl)propoxy)benzene

4-Bromo-3,5-dimethylphenol (0.5 g), 3-methylthiopropyl bromide (0.25 mL), triphenyl phosphine (710 mg) and di-tert-butyl azodicarboxylate (624 mg) are dissolved in dichloromethane (10 mL) and stirred for 2 hours. 3-Chloroperbenzoic acid (1.3 g) is added and the mixture is stirred overnight. The mixture is washed with saturated sodium carbonate solution, the organic phase collected by passing through a phase separator cartridge and the solvent removed under vacuum. The residue is purified by chromatography on silica gel (cyclohexane/ethyl acetate 100:0→0:100) to give the title compound (480 mg).

10

Step 2: 2-(2,6-Dimethyl-4-(3-(methylsulfonyl)propoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

2-Bromo-1,3-dimethyl-5-(3-(methylsulfonyl)propoxy)benzene (100 mg), bis(pinacolato)diboron (158 mg), [1,1'-bis(diphenylphosphino)-ferrocene]-dichloropalladium-(II) (23 mg) and potassium acetate (92 mg) are suspended in dry 1,4-dioxane (3 mL) in a microwave vial and degassed for 5 minutes with a flow of nitrogen. The mixture is heated under microwave irradiation for 60 minutes at 110°C. The mixture is diluted with ethyl acetate, washed with water, the organic phase dried and the solvent removed under vacuum. The residue is purified by chromatography on silica gel (cyclohexane/ethyl acetate 100:0→0:100) to give the title compound (110 mg).

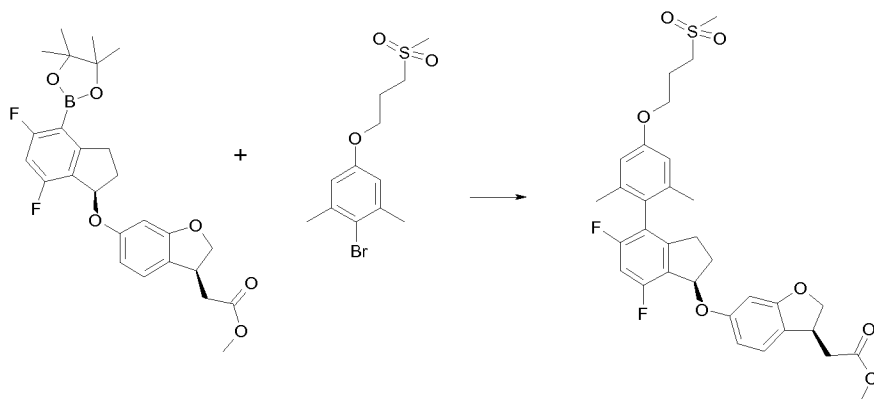
LC (method 19): $t_R = 1.24$ min; Mass spectrum: $m/z = 386$ $[M+NH_4]^+$.

Step 3: Methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-(3-(methylsulfonyl)propoxy)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

Methyl 2-((S)-6-((R)-4-bromo-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate [intermediate 13, step 3] (32 mg), 2-(2,6-dimethyl-4-(3-(methylsulfonyl)propoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (42 mg), [1,1'-bis(diphenylphosphino)-ferrocene]-dichloropalladium-(II) (6 mg), 1,1'-bis(diphenylphosphino)-ferrocene (4 mg) and caesium carbonate (50 mg) are suspended in toluene (2 mL) and degassed for 5 minutes with a flow of nitrogen. The mixture is heated under microwave irradiation for 90 minutes at 120°C. The mixture is diluted with ethyl acetate, washed with water, the organic phase dried and the solvent removed under vacuum. The residue is purified by chromatography on silica gel (cyclohexane/ethyl acetate 100:0→50:50) to give the title compound (9 mg). LC (method 19): $t_R = 1.38$ min; Mass spectrum: $m/z = 583$ $[M+H]^+$.

Intermediate 54

Methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-(3-(methylsulfonyl)propoxy)phenyl)-5,7-difluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

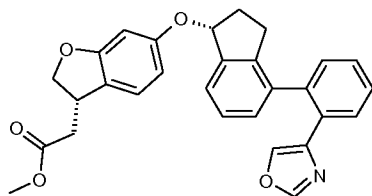


Methyl 2-((S)-6-((R)-5,7-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate (Intermediate 52, 220 mg), 2-bromo-1,3-dimethyl-5-(3-(methylsulfonyl)propoxy)benzene (Intermediate 53,

- 5 Step 1; 153 mg), palladium-(II)-acetate (7 mg), dicyclohexyl(2',6'-dimethoxybiphenyl-2-yl)phosphine (S-Phos) (13 mg) and K_3PO_4 (202 mg) are suspended in toluene (5 mL) and water (0.5 mL) and degassed for 5 minutes with a flow of argon. The mixture is heated under microwave irradiation for 2.5 hours at 120°C. The mixture is diluted with ethyl acetate, washed with water, the organic phase dried and the solvent
- 10 removed under vacuum. The residue is purified by chromatography on silica gel (cyclohexane/ethyl acetate 100:0→0:100) to give the title compound (29 mg).
LC (method 19): t_R = 1.38 min; Mass spectrum: m/z = 601 $[M+H]^+$.

Intermediate 55

- 15 Methyl 2-((S)-6-((1R)-4-(2-(oxazol-4-yl)phenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

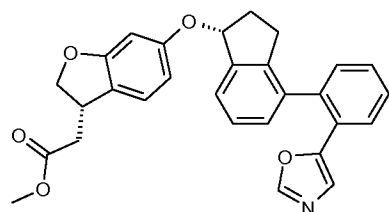


- Methyl 2-((S)-6-((R)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate (45 mg) and 5-(2-Bromophenyl)-1,3-oxazole (33.6 mg) are dissolved in dimethylformamide (1 mL) and purged with argon. [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane (1:1) (8.2 mg) and aqueous Cs_2CO_3 -solution (0.1 mL, 2 Mol/L) are added and the reaction mixture is shaken overnight in a sealed vial at 80°C. The reaction mixture is acidified with aqueous trifluoroacetic acid, filtrated and
- 20

chromatographed by HPLC on reversed phase. The product fractions are collected and lyophilized to give the title compound. Yield: 15.7 mg; LC (method 22): t_R = 1.67 min; Mass spectrum (ESI⁺): m/z = 490 [M+Na]⁺.

5 Intermediate 56

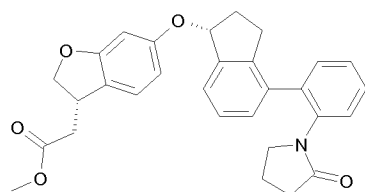
Methyl 2-((3S)-6-((1R)-4-(2-(oxazol-5-yl)phenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate



Methyl 2-((S)-6-((R)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate (45 mg) and 5-(2-Bromophenyl)-1,3-oxazole (33.6 mg) are dissolved in dimethylformamide (1 mL) and purged with argon. [1,1'-Bis(di-tert butylphosphino)-ferrocene]-dichloropalladium-(II) (6.5 mg) and aqueous Cs₂CO₃-solution (0.1 mL, 2 Mol/L) are added and the reaction mixture is shaken overnight in a sealed vial at 80°C. The reaction mixture is acidified with aqueous trifluoroacetic acid, filtrated and chromatographed by HPLC on reversed phase. The product fractions are collected and lyophilized to give the title compound. Yield: 25 mg; LC (method 22): t_R = 1.67 min; Mass spectrum (ESI⁺): m/z = 468 [M+H]⁺.

20 Intermediate 57

Methyl 2-((3S)-6-((1R)-4-(2-(2-oxopyrrolidin-1-yl)phenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

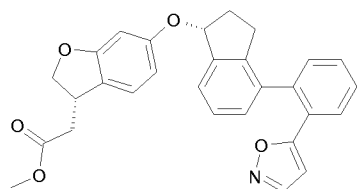


Methyl 2-((S)-6-((R)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate (45 mg) and 1-(2-bromophenyl)pyrrolidin-2-one (36.0 mg) are dissolved in dimethylformamide (1 mL) and purged with argon. [1,1'-Bis(di-tert butylphosphino)-ferrocene]-dichloropalladium-

(II) (6.5 mg) and aqueous Cs_2CO_3 -solution (0.1 mL, 2 Mol/L) are added and the reaction mixture is shaken overnight in a sealed vial at 80°C . The reaction mixture is acidified with aqueous trifluoroacetic acid, filtrated and chromatographed by HPLC on reversed phase. The product fractions are collected and lyophilized to give the title compound. Yield: 16.4 mg; LC (method 11): $t_R = 1.04$ min; Mass spectrum (ESI^+): $m/z = 484$ $[\text{M}+\text{H}]^+$.

Intermediate 58

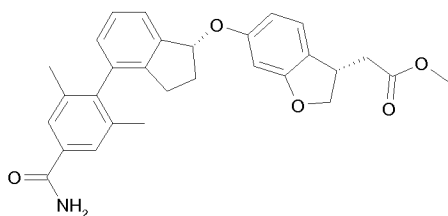
Methyl 2-((3S)-6-((1R)-4-(2-(isoxazol-5-yl)phenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate



Methyl 2-((S)-6-((R)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate (45 mg) and 5-(2-Bromophenyl)isoxazole (33.6 mg) are dissolved in dimethylformamide (1 mL) and purged with argon. $[1,1'$ -Bis(di-tert butylphosphino)-ferrocene]-dichloropalladium-(II) (6.5 mg) and aqueous Cs_2CO_3 -solution (0.1 mL, 2 Mol/L) are added and the reaction mixture is shaken 5 hours in a sealed vial at 80°C . The reaction mixture is acidified with aqueous trifluoroacetic acid, filtrated and chromatographed by HPLC on reversed phase. The product fractions are collected and lyophilized to give the title compound. Yield: 3 mg; LC (method 11): $t_R = 1.14$ min; Mass spectrum (ESI^+): $m/z = 490$ $[\text{M}+\text{Na}]^+$.

Intermediate 59

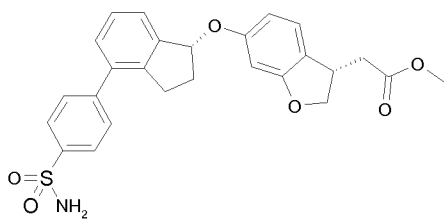
Methyl 2-((S)-6-((R)-4-(4-carbamoyl-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate



Methyl 2-((S)-6-((R)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate (45 mg) and 4-Bromo-3,5-dimethyl-benzamide (34.2 mg) are dissolved in dimethylformamide (1 mL) and purged with argon. [1,1'-Bis(di-tert butylphosphino)-ferrocene]-dichloropalladium-(II) (6.5 mg) and aqueous Cs₂CO₃-solution (0.1 mL, 2 Mol/L) are added and the reaction mixture is shaken 5 hours in a sealed vial at 80°C. The reaction mixture is acidified with aqueous trifluoroacetic acid, filtrated and chromatographed by HPLC on reversed phase. The product fractions are collected and lyophilized to give the title compound. Yield: 21.9 mg; LC (method 23): t_R = 1.88 min; Mass spectrum (ESI⁺): m/z = 472 [M+H]⁺.

Intermediate 60

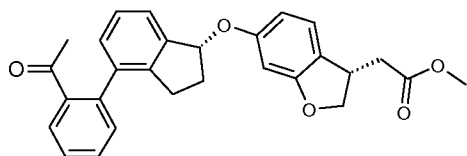
Methyl 2-((S)-6-((R)-4-(4-sulfamoylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate



Methyl 2-((S)-6-((R)-4-bromo-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate (40.3 mg) and 4-sulfamoylphenylboronic acid (40.2 mg) are dissolved in dimethylformamide (1 mL) and purged with argon. [1,1'-Bis(di-tert butylphosphino)-ferrocene]-dichloropalladium-(II) (6.5 mg) and aqueous Cs₂CO₃-solution (0.1 mL, 2 Mol/L) are added and the reaction mixture is shaken 12 hours in a sealed vial at 80°C. The reaction mixture is acidified with aqueous trifluoroacetic acid, filtrated and chromatographed by HPLC on reversed phase. The product fractions are collected and lyophilized to give the title compound. Yield: 4.8 mg.

Intermediate 61

Methyl 2-((3S)-6-((1R)-4-(2-acetylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

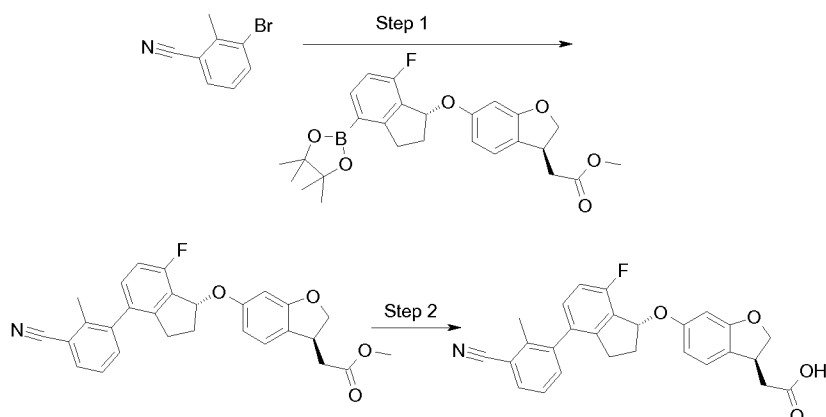


Methyl 2-((S)-6-((R)-4-bromo-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate (40.3 mg) and 2-acetylphenylboronic acid (32.8 mg) are dissolved in dimethylformamide (1 mL) and purged with argon. [1,1'-Bis(di-tert butylphosphino)-ferrocene]-dichloropalladium-(II) (6.5 mg) and aqueous Cs₂CO₃-solution (0.1 mL, 2
 5 Mol/L) are added and the reaction mixture is shaken 12 hours in a sealed vial at 80°C. The reaction mixture is acidified with aqueous trifluoroacetic acid, filtrated and chromatographed by HPLC on reversed phase. The product fractions are collected and lyophilized to give the title compound. Yield: 5.9 mg; LC (method 24): t_R = 1.38 min.

10

Intermediate 62

2-((3S)-6-((1R)-4-(3-Cyano-2-methylphenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



15 Step 1: Methyl 2-((3S)-6-((1R)-4-(3-cyano-2-methylphenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

In a microwave vial, methyl 2-((S)-6-((R)-7-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate (200 mg), 3-bromo-2-methylbenzonitrile (169 mg), K₃PO₄ (274 mg), Palladium-(II)-acetate (10 mg) and dicyclohexyl(2',6'-dimethoxybiphenyl-2-yl)phosphine (S-Phos) (18 mg) are suspended in toluene (10 mL) and water (2 mL) and purged for 10
 20 minutes with argon. The vial is sealed and the mixture is stirred at 100°C for 4 hours. After cooling to ambient temperature the mixture is partitioned between ethyl acetate and water. The organic phase is dried (MgSO₄) and concentrated. The residue is chromatographed on silica gel (cyclohexane/ethyl acetate 90:10) to give the title
 25 compound. Yield: 124 mg; LC (method 20): t_R = 8.09 min; Mass spectrum (ESI⁺): m/z = 558 [M+H]⁺.

Step 2: 2-((3S)-6-((1R)-4-(3-Cyano-2-methylphenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid

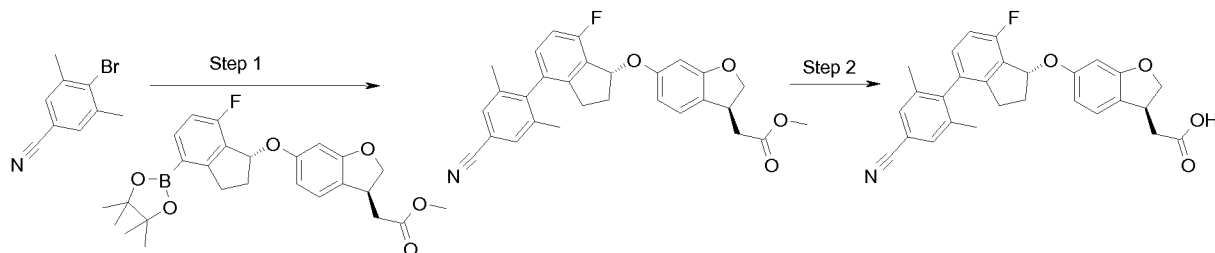
LiOHxH₂O (131 mg) is added to a solution of methyl 2-((3S)-6-((1R)-4-(3-cyano-2-methylphenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-

- 5 yl)acetate (119 mg) in tetrahydrofuran (1 mL), water (1 mL) and methanol (1 mL) at room temperature. The mixture is stirred at room temperature for 12 hours. The mixture is concentrated, cooled to 0°C, diluted with water and acidified with 4 M aqueous HCl solution. The resulting mixture is extracted with dichloromethane. The organic phase is dried (MgSO₄). The solvent is evaporated to give the title compound. Yield: 103 mg; LC (method 20): t_R = 6.30 min; Mass spectrum (ESI⁻): m/z = 442 [M-H]⁻.

Intermediate 63

2-((S)-6-((R)-4-(4-Cyano-2,6-dimethylphenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid

15



Step 1: Methyl 2-((S)-6-((R)-4-(4-cyano-2,6-dimethylphenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

- 20 In a microwave vial, methyl 2-((S)-6-((R)-7-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate (200 mg), 4-bromo-3,5-dimethylbenzonitrile (90 mg), K₃PO₄ (273 mg), Palladium-(II)-acetate (10 mg) and dicyclohexyl(2',6'-dimethoxybiphenyl-2-yl)phosphine (S-Phos) (17 mg) are suspended in toluene (10 mL) and water (2 mL) and purged for 10
- 25 minutes with argon. The vial is sealed and the mixture is stirred at 100°C for 4 hours. After cooling to ambient temperature the mixture is partitioned between ethyl acetate and water. The organic phase is dried (MgSO₄) and concentrated. The residue is chromatographed on silica gel (cyclohexane/ethyl acetate 90:10) to give the title compound. Yield: 85 mg; LC (method 19): t_R = 1.52 min; Mass spectrum (ESI⁺): m/z = 471 [M+H]⁺.
- 30

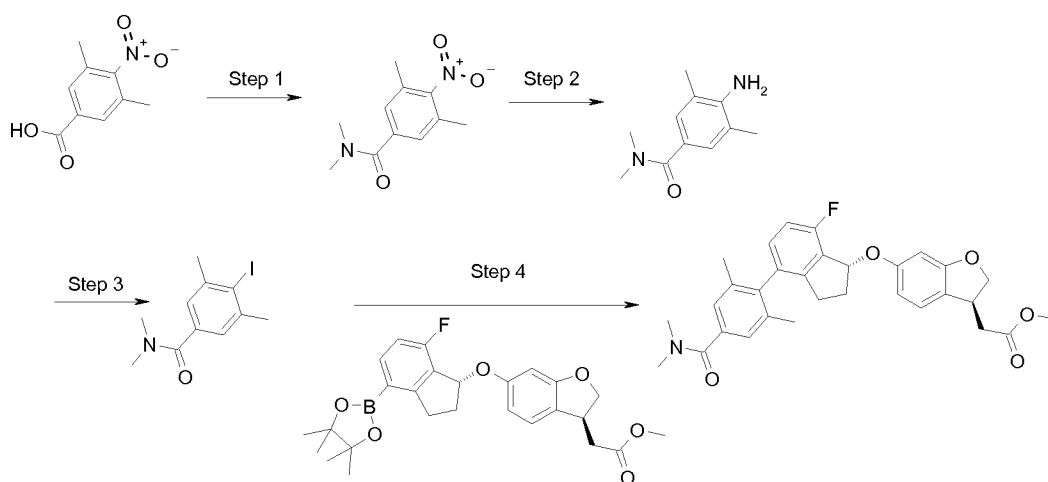
Step 2: 2-((S)-6-((R)-4-(4-Cyano-2,6-dimethylphenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid

LiOHxH₂O (38 mg) is added to a solution of methyl 2-((S)-6-((R)-4-(4-cyano-2,6-dimethylphenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-

- 5 yl)acetate (85 mg) in tetrahydrofuran (1 mL), water (1 mL) and methanol (1 mL) at room temperature. The mixture is stirred at room temperature for 12 hours. The mixture is concentrated, cooled to 0°C, diluted with water and acidified with 4 M aqueous HCl solution. The resulting mixture is extracted with dichloromethane. The organic phase is dried (MgSO₄). The solvent is evaporated and the residue is
- 10 chromatographed on silica gel (dichloroemthane/methanol/acetic acid 9:0.05:0.05) to give the title compound. Yield: 41 mg; LC (method 20): t_R = 6.91 min; Mass spectrum (ESI⁻): m/z = 456 [M-H]⁻.

Intermediate 64

- 15 Methyl 2-((S)-6-((R)-4-(4-(dimethylcarbamoyl)-2,6-dimethylphenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate



Step 1: N,N,3,5-Tetramethyl-4-nitrobenzamide

- 1,1'-Carbonyldiimidazole (914 mg) is added to a solution of 3,5-dimethyl-4-nitrobenzoic acid (1 g) in tetrahydrofuran (10 mL). The mixture is stirred for 3 hours at
- 20 room temperature, dimethylamine (7.7 mL, 2 M in tetrahydrofuran) is added and the mixture is stirred for further 30 minutes. After concentration the mixture is diluted with ethyl acetate and washed with hydrochloric acid (0.2 M), saturated aqueous NaHCO₃ solution and brine. The organic phase is dried (Na₂SO₄) and concentrated to give the
- 25 title compound. Yield: 1 g; LC (method 20): t_R = 5.11 min; Mass spectrum (ESI⁺): m/z = 223 [M+H]⁺.

Step 2: 4-Amino-N,N,3,5-tetramethylbenzamide

10% Palladium on carbon (100 mg) is added to a solution of N,N,3,5-tetramethyl-4-nitrobenzamide (1 g) in methanol (10 mL) and the mixture is hydrogenated for 3 hours under 2 bar hydrogen pressure. Then the catalyst is filtered off and washed with methanol. The combined mother liquors are concentrated to give the title compound. Yield: 1 g; LC (method 20): $t_R = 2.75$ min; Mass spectrum (ESI⁺): $m/z = 193$ [M+H]⁺.

Step 3: 4-Iodo-N,N,3,5-tetramethylbenzamide

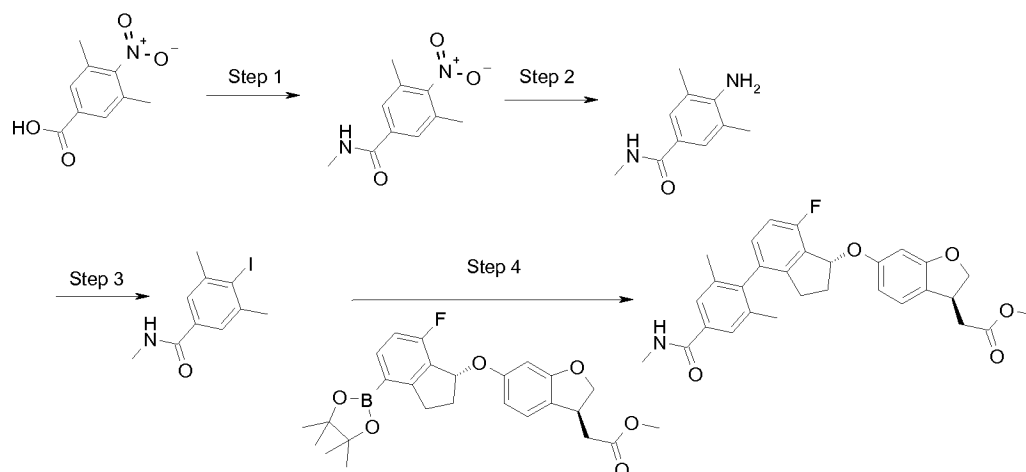
4-Amino-N,N,3,5-tetramethylbenzamide (500 mg) is dissolved in concentrated hydrochloric acid (2 mL), cooled to 0°C and treated dropwise with a solution of NaNO₂ (269 mg) in water (0.5 mL). The mixture is stirred for 1 hour and a solution of KI (1.3 g) in water (1.5 mL) is added dropwise. The mixture is stirred for 15 minutes, allowed to warm to room temperature and then partitioned between dichloromethane and water. The organic phase is washed with 10% aqueous solution of Na₂S₂O₃, dried (MgSO₄) and concentrated. The residue is chromatographed on silica gel (cyclohexane/ethyl acetate 100:0→50:50) to give the title compound. Yield: 300 mg; LC (method 20): $t_R = 6.32$ min; Mass spectrum (ESI⁺): $m/z = 304$ [M+H]⁺.

Step 4: Methyl 2-((S)-6-((R)-4-(4-(dimethylcarbamoyl)-2,6-dimethylphenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

In a microwave vial, methyl 2-((S)-6-((R)-7-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate (75 mg), 4-iodo-N,N,3,5-tetramethylbenzamide (97 mg), K₃PO₄ (102 mg) and dicyclohexyl(2',6'-dimethoxybiphenyl-2-yl)phosphine (S-Phos) (7 mg) are suspended in toluene (2 mL) and water (0.2 mL) and purged for 10 minutes with argon. Palladium-(II)-acetate (4 mg) are added, the vial is sealed and the mixture is stirred at 120°C for 5 hours. After cooling to ambient temperature the mixture is partitioned between ethyl acetate and water. The organic phase is dried (MgSO₄) and concentrated. The residue is chromatographed on silica gel (cyclohexane/ethyl acetate 100:0→80:20) to give the title compound. Yield: 70 mg; LC (method 25): $t_R = 1.41$ min; Mass spectrum (ESI⁺): $m/z = 518$ [M+H]⁺.

Intermediate 65

Methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-(methylcarbamoyl)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate



Step 1: N,3,5-Trimethyl-4-nitrobenzamide

1,1'-Carbonyldiimidazole (914 mg) is added to a suspension of 3,5-dimethyl-4-nitrobenzoic acid (1 g) in tetrahydrofuran (10 mL). The mixture is stirred for 3 hours at room temperature, methylamine (7.7 mL, 2 M in tetrahydrofuran) is added and the mixture is stirred for further 30 minutes. After concentration the mixture is diluted with ethyl acetate and washed with hydrochloric acid (0.2 M), saturated aqueous NaHCO₃ solution and brine. The organic phase is dried (Na₂SO₄) and concentrated to give the title compound. Yield: 1 g; LC (method 20): t_R = 4.82 min; Mass spectrum (ESI⁺): m/z = 209 [M+H]⁺.

Step 2: 4-Amino-N,3,5-trimethylbenzamide

10% Palladium on carbon (100 mg) is added to a solution of N,3,5-trimethyl-4-nitrobenzamide (1 g) in methanol (10 mL) and the mixture is hydrogenated for 3 hours under 3 bar hydrogen pressure. Then the catalyst is filtered off and washed with methanol. The combined mother liquours are concentrated to give the title compound. Yield: 850 mg; LC (method 21): t_R = 6.02; Mass spectrum (ESI⁺): m/z = 179 [M+H]⁺.

Step 3: 4-Iodo-N,3,5-trimethylbenzamide

4-Amino-N,3,5-trimethylbenzamide (850 mg) is dissolved in concentrated hydrochloric acid (2 mL), cooled to 0°C and treated dropwise with a solution of NaNO₂ (580 mg) in water (0.5 mL). The mixture is stirred for 1 hour and a solution of KI (2.8 g) in water (1.5 mL) is added dropwise. The mixture is stirred for 15 minutes, allowed to warm to room temperature and then partitioned between dichloromethane and water. The organic phase is washed with 10% aqueous solution of Na₂S₂O₃, dried (MgSO₄) and concentrated. The residue is chromatographed on silica gel

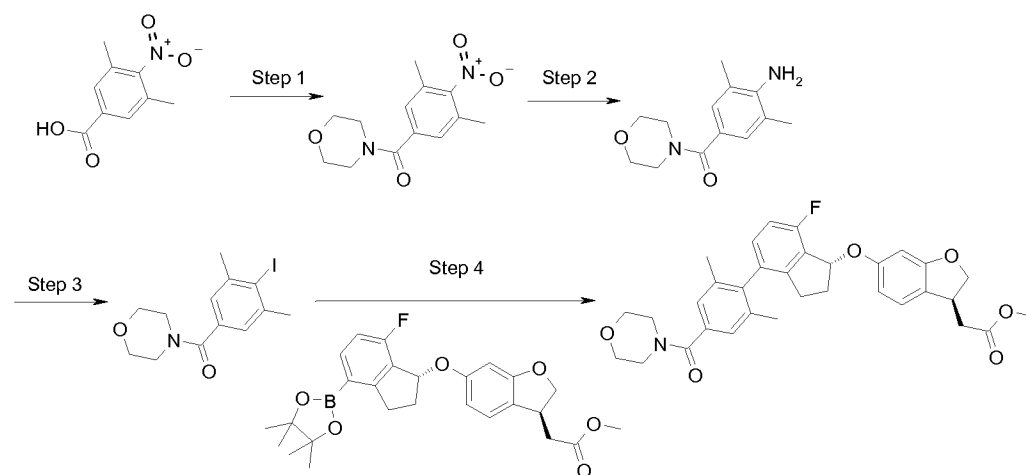
(cyclohexane/ethyl acetate 100:0→50:50) to give the title compound. Yield: 850 mg; LC (method 20): t_R = 5.88 min; Mass spectrum (ESI⁺): m/z = 290 [M+H]⁺.

Step 4: Methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-(methylcarbamoyl)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

- 5 In a microwave vial, methyl 2-((S)-6-((R)-7-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate (75 mg), 4-iodo-N,3,5-trimethylbenzamide (93 mg), K₃PO₄ (102 mg) and dicyclohexyl(2',6'-dimethoxybiphenyl-2-yl)phosphine (S-Phos) (7 mg) are suspended in toluene (1.8 mL) and water (0.2 mL) and purged for 10 minutes with argon.
- 10 Palladium-(II)-acetate (4 mg) is added, the vial is sealed and the mixture is stirred at 120°C for 5 hours. After cooling to ambient temperature the mixture is partitioned between ethyl acetate and water. The organic phase is dried (MgSO₄) and concentrated. The residue is chromatographed on silica gel (cyclohexane/ethyl acetate 100:0→80:20) to give the title compound. Yield: 16 mg; LC (method 25): t_R =
- 15 1.32 min; Mass spectrum (ESI⁺): m/z = 504 [M+H]⁺.

Intermediate 66

Methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-(morpholine-4-carbonyl)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate



Step 1: (3,5-Dimethyl-4-nitrophenyl)(morpholino)methanone

1,1'-Carbonyldiimidazole (1.66 g) is added to a solution of 3,5-dimethyl-4-nitrobenzoic acid (1 g) in tetrahydrofuran (10 mL). The mixture is stirred for 3 hours at room temperature, morpholine (0.9 mL) is added and the mixture is stirred for further

25 30 minutes. After concentration the mixture is diluted with ethyl acetate and washed with hydrochloric acid (0.2 M), saturated aqueous NaHCO₃ solution and brine. The

organic phase is dried (Na_2SO_4) and concentrated to give the title compound. Yield: 1.3 g; LC (method 20): $t_R = 5.10$ min; Mass spectrum (ESI^+): $m/z = 265$ $[\text{M}+\text{H}]^+$.

Step 2: (4-Amino-3,5-dimethylphenyl)(morpholino)methanone

10% Palladium on carbon (100 mg) is added to a solution of (3,5-dimethyl-4-nitrophenyl)(morpholino)methanone (1.3 g) in methanol (10 mL) and the mixture is hydrogenated for 3 hours under 2 bar hydrogen pressure. Then the catalyst is filtered off and washed with methanol. The combined mother liquors are concentrated to give the title compound. Yield: 1.1 g; LC (method 20): $t_R = 1.94$; Mass spectrum (ESI^+): $m/z = 235$ $[\text{M}+\text{H}]^+$.

Step 3: (4-Iodo-3,5-dimethylphenyl)(morpholino)methanone

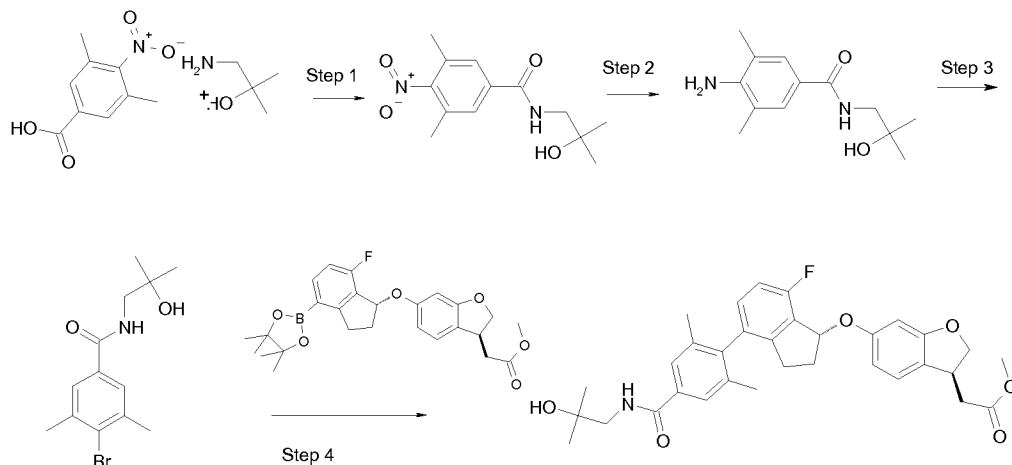
(4-Amino-3,5-dimethylphenyl)(morpholino)methanone (1.2 g) is dissolved in concentrated hydrochloric acid (2 mL), cooled to 0°C and treated dropwise with a solution of NaNO_2 (530 mg) in water (0.5 mL). The mixture is stirred for 1 hour and a solution of KI (2.6 g) in water (1.5 mL) is added dropwise. The mixture is stirred for 15 minutes at 0°C and for 12 hours at room temperature and is then partitioned between dichloromethane and water. The organic phase is washed with 10% aqueous solution of $\text{Na}_2\text{S}_2\text{O}_3$, dried (MgSO_4) and concentrated. The residue is chromatographed on silica gel (cyclohexane/ethyl acetate 100:0 $\rightarrow$ 50:50) to give the title compound. Yield: 1.1 g; LC (method 20): $t_R = 6.13$ min; Mass spectrum (ESI^+): $m/z = 346$ $[\text{M}+\text{H}]^+$.

Step 4: Methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-(morpholine-4-carbonyl)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

In a microwave vial, methyl 2-((S)-6-((R)-7-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate (75 mg), (4-iodo-3,5-dimethylphenyl)(morpholino)methanone (110 mg), K_3PO_4 (102 mg) and dicyclohexyl(2',6'-dimethoxybiphenyl-2-yl)phosphine (S-Phos) (7 mg) are suspended in toluene (2 mL) and water (0.2 mL) and purged for 10 minutes with argon. Palladium-(II)-acetate (4 mg) are added, the vial is sealed and the mixture is stirred at 120°C for 5 hours. After cooling to ambient temperature the mixture is partitioned between ethyl acetate and water. The organic phase is dried (MgSO_4) and concentrated. The residue is chromatographed on silica gel (cyclohexane/ethyl acetate 100:0 $\rightarrow$ 80:20) to give the title compound. Yield: 55 mg; LC (method 25): $t_R = 1.38$ min; Mass spectrum (ESI^+): $m/z = 560$ $[\text{M}+\text{H}]^+$.

Intermediate 66a

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



5 **Step 1:** N-(2-Hydroxy-2-methyl-propyl)-3,5-dimethyl-4-nitro-benzamide.

The title compound is prepared following a procedure analogous to that described in Step 1 in the preparation of Intermediate 66, starting from 1-amino-2-methyl-propan-2-ol (Kasai, Shizuo et al. Journal of Medicinal Chemistry, 2012 , vol. 55, # 9 p. 4336 – 4351).

10 **Step 2:** 4-Amino-N-(2-hydroxy-2-methyl-propyl)-3,5-dimethyl-benzamide.

The title compound is prepared following a procedure analogous to that described in Step 2 in the preparation of Intermediate 50x, starting from N-(2-hydroxy-2-methyl-propyl)-3,5-dimethyl-4-nitro-benzamide.

Step 3: 4-Bromo-N-(2-hydroxy-2-methyl-propyl)-3,5-dimethyl-benzamide.

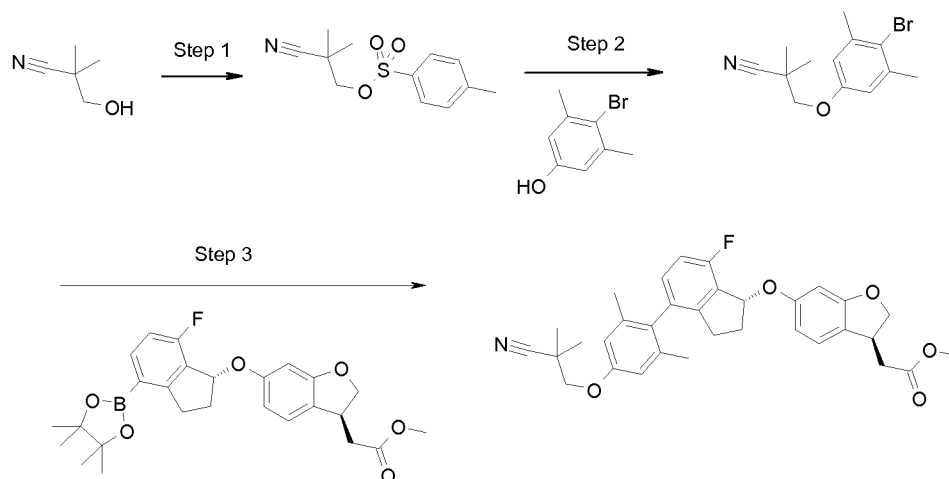
15 The title compound is prepared following a procedure analogous to that described in Step 3 in the preparation of Intermediate 50x, starting from 4-amino-N-(2-hydroxy-2-methyl-propyl)-3,5-dimethyl-benzamide.

Step 4: ((S)-6-((R)-7-Fluoro-4-[4-(2-hydroxy-2-methyl-propylcarbamoyl)-2,6-dimethyl-phenyl]-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester.

20 The title compound is prepared following a procedure analogous to that described in Step 6 in the preparation of Intermediate 1, starting from 4-bromo-N-(2-hydroxy-2-methyl-propyl)-3,5-dimethyl-benzamide.

Intermediate 67

25 Methyl 2-((S)-6-((R)-4-(4-(2-cyano-2-methylpropoxy)-2,6-dimethylphenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate



Step 1: 2-Cyano-2-methylpropyl 4-methylbenzenesulfonate

To a solution of 3-hydroxy-2,2-dimethylpropanenitrile (0.5 g) in dichloromethane (8 mL) and pyridine (1.5 mL) is added at 0°C p-toluene-sulfonylchloride (1.0 g) in portions. The mixture is stirred for 12 hours at room temperature, diluted with diethylether and washed with 1 M aqueous HCl solution and brine. After drying (MgSO₄) the solvent is evaporated and the residue is chromatographed on silica gel (petrole ether/ethyl acetate 90:10→50:50) to give the title compound. Yield: 770 mg; Mass spectrum (ESI⁺): m/z = 254 [M+H]⁺.

Step 2: 3-(4-Bromo-3,5-dimethylphenoxy)-2,2-dimethylpropanenitrile

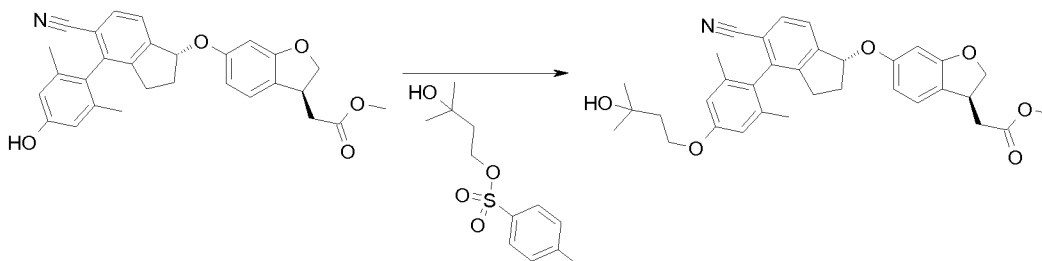
To a solution of 2-cyano-2-methylpropyl 4-methylbenzenesulfonate (760 mg) and 4-bromo-3,5-dimethylphenol (500 mg) in N,N-dimethylformamide (8 mL) is added Cs₂CO₃ (2.0 g). The mixture is stirred for 12 hours at 80°C, diluted with diethylether and washed with water and brine. After drying (MgSO₄) the solvent is evaporated and the residue is chromatographed on silica gel (petrole ether/ethyl acetate 90:10→60:40) to give the title compound. Yield: 572 mg; Mass spectrum (ESI⁺): m/z = 282 [M+H]⁺.

Step 3: Methyl 2-((S)-6-((R)-4-(4-(2-cyano-2-methylpropoxy)-2,6-dimethylphenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

The title compound is prepared from methyl 2-((S)-6-((R)-7-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate and 3-(4-bromo-3,5-dimethylphenoxy)-2,2-dimethylpropanenitrile following a procedure analogous to that described in Step 5 of Intermediate 12. LC (method 8): t_R = 0.89 min; Mass spectrum (ESI⁺): m/z = 544 [M+H]⁺.

Intermediate 68

Methyl 2-((S)-6-((R)-5-cyano-4-(4-(3-hydroxy-3-methylbutoxy)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate



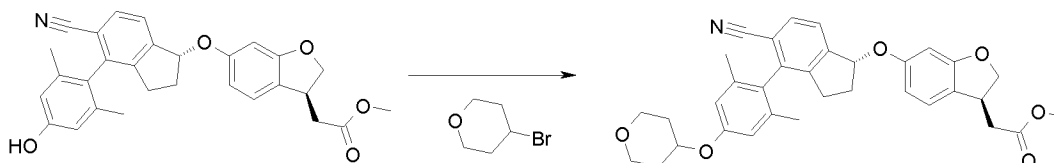
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The title compound is prepared from methyl 2-((S)-6-((R)-5-cyano-4-(4-hydroxy-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate and 3-hydroxy-3-methylbutyl 4-methylbenzenesulfonate following a procedure analogous to that described in Step 5 of Intermediate 39. LC (method 7): t_R = 1.17 min; Mass spectrum (ESI⁺): m/z = 578 [M+Na]⁺.

10

Intermediate 69

Methyl 2-((S)-6-((R)-5-cyano-4-(2,6-dimethyl-4-(tetrahydro-2H-pyran-4-yloxy)phenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate



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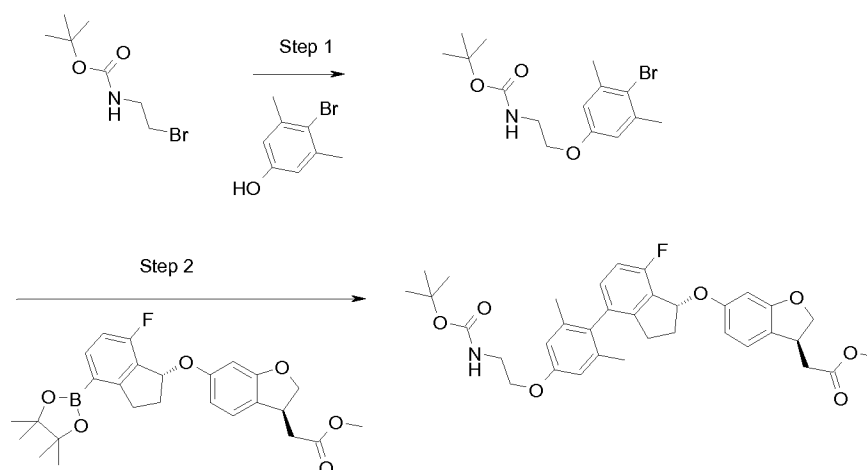
To a solution of methyl 2-((S)-6-((R)-5-cyano-4-(4-hydroxy-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate (136 mg) in N,N-dimethylformamide (2 mL) is added 4-bromotetrahydro-2H-pyran (72 mg) and Cs₂CO₃ (200 mg). The mixture is stirred for 12 hours at room temperature and 1 hour at 100°C. 4-Bromotetrahydro-2H-pyran (72 mg) is added and the mixture is heated to 100°C for further 3 hours. Then the mixture is diluted with ethyl acetate and washed successively with water and brine. The organic phase is dried (MgSO₄) and concentrated. The residue is chromatographed on silica gel (cyclohexane/ethyl acetate 99:1→40:60) to give the title compound. Yield: 37 mg; LC (method 7): t_R = 1.19 min; Mass spectrum (ESI⁺): m/z = 554 [M+H]⁺.

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Intermediate 70

Methyl 2-((S)-6-((R)-4-(4-(2-(tert-butoxycarbonylamino)ethoxy)-2,6-dimethylphenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate



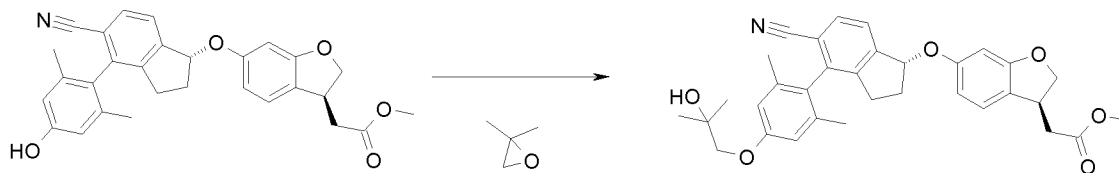
Step 1: tert-Butyl 2-(4-bromo-3,5-dimethylphenoxy)ethylcarbamate

- 5 To a solution of 4-bromo-3,5-dimethylphenol (200 mg) in N,N-dimethylformamide (5 mL) is added tert-butyl 2-bromoethylcarbamate (270 mg) and Cs₂CO₃ (810 mg). The mixture is stirred for 20 hours at room temperature. tert-Butyl 2-bromoethylcarbamate (110 mg) and Cs₂CO₃ (325 mg) are added and the mixture is stirred for 4 hours. Again tert-butyl 2-bromoethylcarbamate (110 mg) and Cs₂CO₃ (325 mg) are added and the mixture is stirred for 12 hours. The mixture is partitioned between water and diethylether. The organic phase is washed with brine and dried (MgSO₄). The solvent is evaporated and the residue is chromatographed on silica gel (cyclohexane/ethyl acetate 99:1→80:20) to give the title compound. Yield: 320 mg; LC (method 8): t_R = 0.66 min; Mass spectrum (ESI⁺): m/z = 344 [M+H]⁺.

- 15 Step 2: Methyl 2-((S)-6-((R)-4-(4-(2-(tert-butoxycarbonylamino)ethoxy)-2,6-dimethylphenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate
The title compound is prepared from methyl 2-((S)-6-((R)-7-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate and tert-butyl 2-(4-bromo-3,5-dimethylphenoxy)ethylcarbamate following a procedure analogous to that described in Step 5 of Intermediate 12. LC (method 8): t_R = 0.92 min; Mass spectrum (ESI⁺): m/z = 606 [M+H]⁺.

Intermediate 71

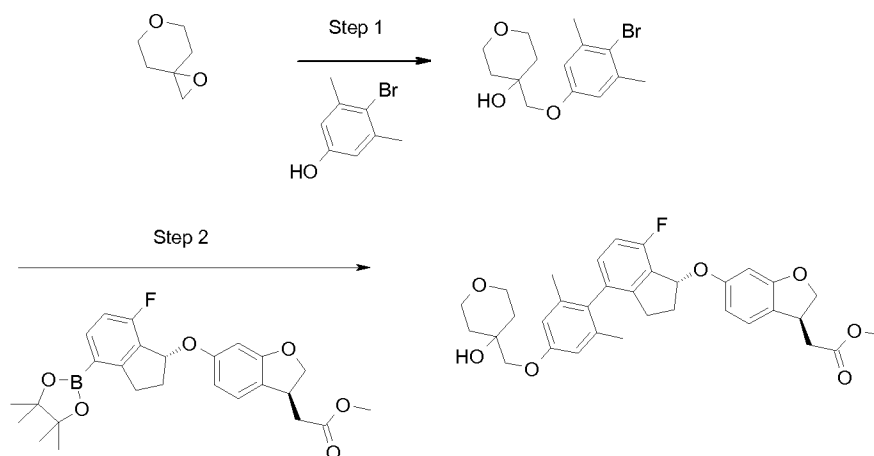
- 25 Methyl 2-((S)-6-((R)-5-cyano-4-(4-(2-hydroxy-2-methylpropoxy)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate



To a solution of methyl 2-((S)-6-((R)-5-cyano-4-(4-hydroxy-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate (120 mg) in N,N-dimethylformamide (2 mL) is added 2,2-dimethyloxirane (30 μ L) and Cs₂CO₃ (167 mg). The mixture is stirred for 12 hours at 100°C. 2,2-Dimethyloxirane (30 μ L) and Cs₂CO₃ (167 mg) are added and the mixture is stirred for 5 hours at 100°C. The mixture is then partitioned between saturated water and ethyl acetate. The organic phase is washed with brine, dried (MgSO₄) and concentrated. The residue is chromatographed on silica gel (cyclohexane/ethyl acetate 99:1→50:50) to give the title compound. Yield: 48 mg; LC (method 7): t_R = 1.16 min; Mass spectrum (ESI⁺): m/z = 542 [M+H]⁺.

Intermediate 72

Methyl 2-((S)-6-((R)-7-fluoro-4-(4-((4-hydroxytetrahydro-2H-pyran-4-yl)methoxy)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate



Step 1: 4-((4-Bromo-3,5-dimethoxyphenyl)methyl)tetrahydro-2H-pyran-4-ol

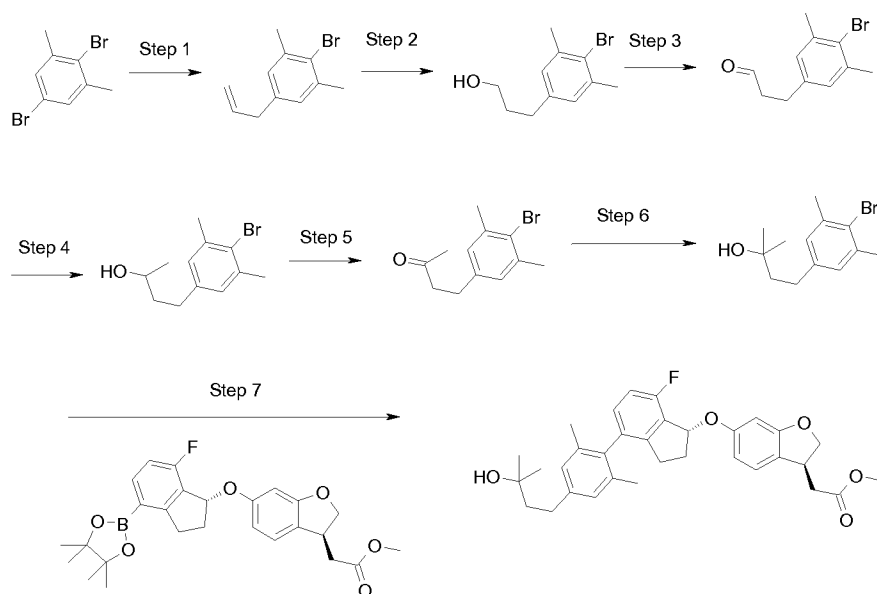
The title compound is prepared from 4-bromo-3,5-dimethylphenol and 1,6-dioxaspiro[2.5]octane following a procedure analogous to that described in Step 5 of Intermediate 1. LC (method 7): t_R = 1.04 min; Mass spectrum (ESI⁻): m/z = 313 [M-H]⁻.

Step 2: Methyl 2-((S)-6-((R)-7-fluoro-4-(4-((4-hydroxytetrahydro-2H-pyran-4-yl)methoxy)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

The title compound is prepared from methyl methyl 2-((S)-6-((R)-7-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate and 4-((4-bromo-3,5-dimethylphenoxy)methyl)tetrahydro-2H-pyran-4-ol following a procedure analogous to that described in Step 5 of Intermediate 12. The product is purified by HPLC on reversed phase. LC (method 7): $t_R = 1.17$ min; Mass spectrum (ESI⁺): $m/z = 577$ [M+H]⁺.

Intermediate 73

Methyl 2-((S)-6-((R)-7-fluoro-4-(4-(3-hydroxy-3-methylbutyl)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate



Step 1: 5-Allyl-2-bromo-1,3-dimethylbenzene

To a solution of isopropylmagnesium chloride (6.15 mL of a 2 M solution in tetrahydrofuran) in tetrahydrofuran (75 mL) is added dropwise at 0°C n-butyllithium (15.4 mL of a 1.6 M solution in n-hexane). The mixture is stirred for 10 minutes, a solution of 2,5-dibromo-1,3-dimethylbenzene (5 g) in tetrahydrofuran (75 mL) is added within 10 minutes. The mixture is stirred for 2 hours, cooled to -40°C and then CuCNxLiCl (5.5 mL of a 1 M solution in tetrahydrofuran) is added dropwise. After stirring for 5 minutes 3-bromopropene (6.6 mL) is added dropwise, the mixture is

stirred for 1 hour, warmed to room temperature and stirred for further 12 hours. Then the reaction is quenched by addition of saturated aqueous NH_4Cl solution. The mixture is extracted with diethylether, the organic phase is dried (MgSO_4) and concentrated. The residue is chromatographed on silica gel (dichloromethane) to give the title compound. Yield: 3.76 g; LC (method 8): $t_R = 0.83$ min; Mass spectrum (ESI^+): $m/z = 225$ $[\text{M}+\text{H}]^+$.

Step 2: 3-(4-Bromo-3,5-dimethylphenyl)propan-1-ol

A solution of 5-allyl-2-bromo-1,3-dimethylbenzene (1.0 g) is cooled to 0°C , 9-borabicyclo[3.3.1]nonane (9-BBN, 26 mL of a 0.5 M solution in tetrahydrofurane) is added dropwise and the mixture is stirred for 2 hours at room temperature. After cooling to 0°C NaOH (6.7 mL, 4 M) and H_2O_2 (6.7 mL, 35%) are added dropwise. The mixture is stirred for 12 hours while warming to room temperature. Then the mixture is partitioned between brine and diethylether. The organic phase is dried (MgSO_4) and concentrated. The residue is chromatographed on silica gel (cyclohexane/ethyl acetate 95:5 $\rightarrow$ 70:30) to give the title compound. Yield: 750 mg; LC (method 8): $t_R = 0.28$ min; Mass spectrum (ESI^+): $m/z = 260$ $[\text{M}+\text{NH}_4]^+$.

Step 3: 3-(4-Bromo-3,5-dimethylphenyl)propanal

To a solution of 3-(4-bromo-3,5-dimethylphenyl)propan-1-ol (250 mg) in dichloromethane (5 mL) is added at 0°C 1,1-dihydro-1,1,1-triacetoxy-1,2-benziodoxol-3(1H)-on (Dess-Martin periodinan, 2.7 mL of a 15% solution in dichloromethane). The mixture is stirred for 12 hours at room temperature, cooled to 0°C and 1,1-dihydro-1,1,1-triacetoxy-1,2-benziodoxol-3(1H)-on (Dess-Martin periodinan, 1.6 mL of a 15% solution in dichloromethane) is added. After stirring for 4 hours isopropanol (5 mL) is added, the mixture is stirred for 15 minutes and the solvents are evaporated in vacuo. The residue is chromatographed on silica gel (cyclohexane/ethyl acetate 99:1 $\rightarrow$ 70:30) to give the title compound. Yield: 120 mg; LC (method 8): $t_R = 0.38$ min; Mass spectrum (ESI^-): $m/z = 239$ $[\text{M}-\text{H}]^-$.

Step 4: 4-(4-Bromo-3,5-dimethylphenyl)butan-2-ol

To a solution of 3-(4-bromo-3,5-dimethylphenyl)propanal (120 mg) in tetrahydrofurane (2 mL) is added at 0°C methylmagnesium bromide (800 μL of a 1.4 M solution in tetrahydrofurane/toluene 1:3). After stirring for 30 minutes the mixture is partitioned between saturated aqueous NH_4Cl solution and diethylether. The organic phase is dried (MgSO_4) and concentrated. The residue is chromatographed on silica

gel (cyclohexane/ethyl acetate 99:1→70:30) to give the title compound. Yield: 130 mg; LC (method 8): $t_R = 0.37$ min; Mass spectrum (ESI⁺): $m/z = 274$ [M+NH₄]⁺.

Step 5: 4-(4-Bromo-3,5-dimethylphenyl)butan-2-one

To a solution of 4-(4-bromo-3,5-dimethylphenyl)butan-2-ol (130 mg) in dichloromethane (8 mL) is added at 0°C 1,1-dihydro-1,1,1-triacetoxy-1,2-benziodoxol-3(1H)-on (Dess-Martin periodinan, 1.4 mL of a 15% solution in dichloromethane). The mixture is stirred for 12 hours at room temperature. The solvents are evaporated in vacuo. The residue is chromatographed on silica gel (cyclohexane/ethyl acetate 99:1→70:30) to give the title compound. Yield: 100 mg; LC (method 8): $t_R = 0.44$ min; Mass spectrum (ESI⁺): $m/z = 255$ [M+H]⁺.

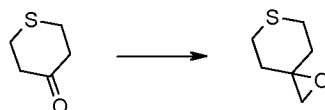
Step 6: 4-(4-Bromo-3,5-dimethylphenyl)-2-methylbutan-2-ol

To a solution of 4-(4-bromo-3,5-dimethylphenyl)butan-2-one (100 mg) in tetrahydrofurane (2 mL) is added at 0°C methylmagnesium bromide (840 µL of a 1.4 M solution in tetrahydrofurane/toluene 1:3). The mixture is stirred for 2 hours while warming to room temperature and then partitioned between saturated aqueous NH₄Cl solution and diethylether. The organic phase is dried (MgSO₄) and concentrated to give the title compound. Yield: 105 mg; LC (method 8): $t_R = 0.47$ min; Mass spectrum (ESI⁺): $m/z = 271$ [M+H]⁺.

Step 7: Methyl 2-((S)-6-((R)-7-fluoro-4-(4-(3-hydroxy-3-methylbutyl)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate
The title compound is prepared from methyl 2-((S)-6-((R)-7-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate and 4-(4-bromo-3,5-dimethylphenyl)-2-methylbutan-2-ol following a procedure analogous to that described in Step 5 of Intermediate 12. LC (method 8): $t_R = 0.83$ min; Mass spectrum (ESI⁺): $m/z = 533$ [M+H]⁺.

Intermediate 74

1-Oxa-6-thiaspiro[2.5]octane

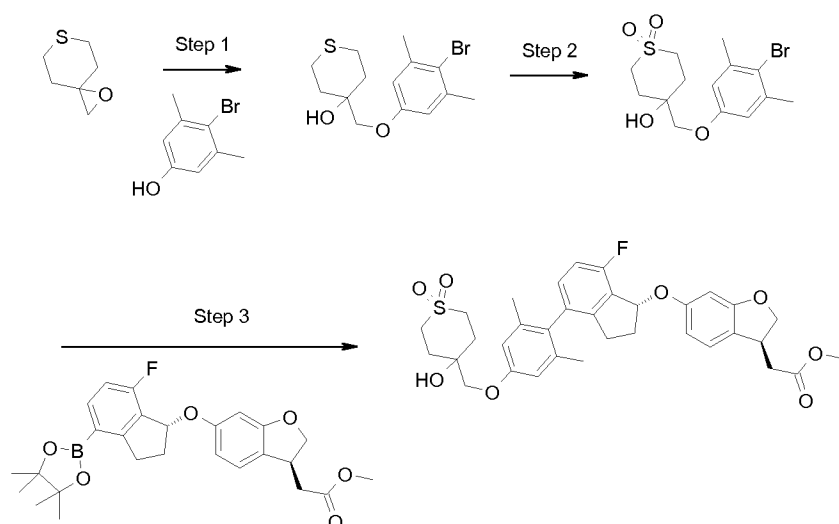


To a suspension of trimethylsulfoxonium iodide (2 g) in dimethylsulfoxide (15 mL) is added portionwise NaH (820 mg of a 60% dispersion in mineral oil). The mixture is stirred for 1 hour and a solution of dihydro-2H-thiopyran-4(3H)-one (2 g) in

dimethylsulfoxide (2 mL) is added dropwise. The mixture is stirred for 12 hours, diluted with ethylacetate and washed twice with water and brine. The organic phase is dried (MgSO_4) and concentrated. The residue is chromatographed on silica gel (cyclohexane/ethyl acetate 99:1 $\rightarrow$ 70:30) to give the title compound. Yield: 742 mg;
 5 LC (method 7): $t_R = 0.64$ min; Mass spectrum (ESI^+): $m/z = 131$ $[\text{M}+\text{H}]^+$.

Intermediate 75

Methyl 2-((S)-6-((R)-7-Fluoro-4-(4-((1,1-dioxo-4-hydroxytetrahydro-2H-thiopyran-4-yl)methoxy)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-
 10 dihydrobenzofuran-3-yl)acetate



Step 1: 4-((4-Bromo-3,5-dimethylphenoxy)methyl)tetrahydro-2H-thiopyran-4-ol

To a solution of 4-bromo-3,5-dimethylphenol (700 mg) in N,N-dimethylformamide (7 mL) is added Cs_2CO_3 (1.7 g) and 1-oxa-6-thiaspiro[2.5]octane (586 mg). The mixture is stirred for 12 hour at 100°C . The mixture is diluted with water and extracted twice with ethyl acetate. The combined organic phases are washed with water and brine, dried (MgSO_4) and concentrated. The residue is chromatographed on silica gel (cyclohexane/ethyl acetate 99:1 $\rightarrow$ 60:40) to give the title compound. Yield: 986 mg;
 15 LC (method 7): $t_R = 1.14$ min; Mass spectrum (ESI^+): $m/z = 348$ $[\text{M}+\text{NH}_4]^+$.

Step 2: 1,1-Dioxo-4-((4-bromo-3,5-dimethylphenoxy)methyl)tetrahydro-2H-thiopyran-4-ol

To a solution of 4-((4-bromo-3,5-dimethylphenoxy)methyl)tetrahydro-2H-thiopyran-4-ol (175 mg) in dichloromethane (3 mL) is added at -10°C meta-chloro-perbenzoic acid (MCPBA, 270 mg, 70%). The mixture is stirred for 12 hour while warming to
 25 room temperature. The mixture is diluted with dichloromethane and washed with 1 M

aqueous NaOH solution. The organic phase is dried (MgSO_4) and concentrated. The residue is chromatographed on silica gel (petrole ether/ethyl acetate 70:30→0:100) to give the title compound. Yield: 152 mg; Mass spectrum (ESI^+): $m/z = 380$ $[\text{M}+\text{NH}_4]^+$.

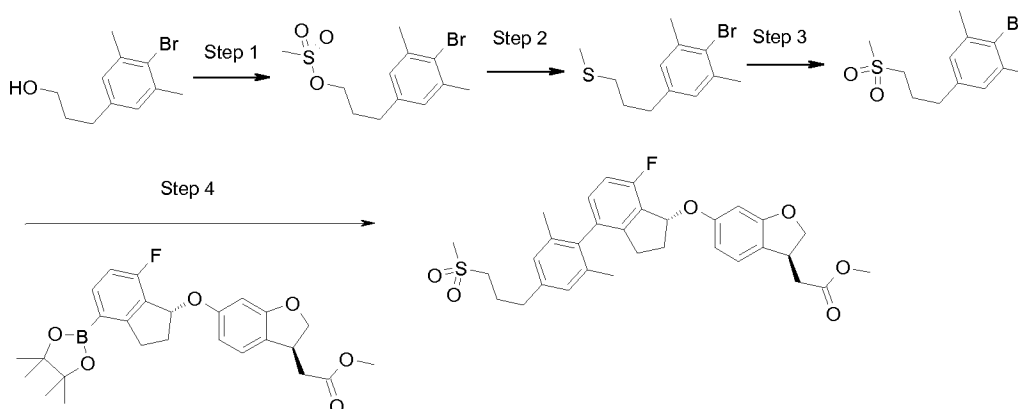
- 5 **Step 3:** Methyl 2-((S)-6-((R)-7-fluoro-4-(4-((1,1-dioxo-4-hydroxytetrahydro-2H-thiopyran-4-yl)methoxy)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

In a microwave vial methyl 2-((S)-6-((R)-7-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate (190 mg), 1,1-dioxo-4-((4-bromo-3,5-dimethylphenoxy)methyl)tetrahydro-2H-thiopyran-4-ol (150 mg), K_3PO_4 (250 mg) and dicyclohexyl(2',6'-dimethoxybiphenyl-2-yl)phosphine (S-Phos) (21 mg) are suspended in N,N-dimethylformamide (2 mL) and water (100 μL). The mixture is purged for 10 minutes with argon. Palladium-(II)-acetate (6 mg) is added, the vial is sealed and the mixture is stirred at 110°C for 3 hours. After cooling to room temperature the mixture is partitioned between diethylether and saturated aqueous NH_4Cl solution. The organic phase is dried (MgSO_4) and concentrated. The residue is chromatographed on silica gel (petrole ether/ethyl acetate 50:50→0:100) to give the title compound. Yield: 90 mg; LC (method 8): $t_R = 0.53$ min; Mass spectrum (ESI^+): $m/z = 625$ $[\text{M}+\text{H}]^+$.

20

Intermediate 76

Methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-(3-(methanesulfonyl)propyl)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate



- 25 **Step 1:** 3-(4-Bromo-3,5-dimethylphenyl)propyl methanesulfonate

To a cooled (0°C) solution of 3-(4-bromo-3,5-dimethylphenyl)propan-1-ol (250 mg) and triethylamine (160 μL) in dichloromethane (2 mL) is added methanesulfonyl

chloride (850 μ L). The mixture is stirred for 12 hours at room temperature. The mixture is partitioned between dichloromethane and saturated aqueous NaHCO_3 solution and stirred vigorously for 30 minutes. The organic phase is separated, washed with brine and dried (MgSO_4). The solvent is evaporated and the residue is chromatographed on silica gel (cyclohexane/ethyl acetate 80:20 $\rightarrow$ 50:50) to give the title compound. Yield: 235 mg; LC (method 8): t_R = 0.44 min; Mass spectrum (ESI^+): m/z = 343 $[\text{M}+\text{Na}]^+$.

Step 2: (3-(4-Bromo-3,5-dimethylphenyl)propyl)(methyl)sulfane

NaSMe (65 mg) is added to a solution of 3-(4-bromo-3,5-dimethylphenyl)propyl methanesulfonate (230 mg) in N,N -dimethylformamide (5 mL). The mixture is stirred for 12 hours. NaSMe (25 mg) is added and the mixture is stirred for 1 hour. Then the mixture is partitioned between water and diethylether. The organic phase is dried (MgSO_4) and concentrated. The residue is chromatographed on silica gel (cyclohexane/ethyl acetate 99:1 $\rightarrow$ 80:20) to give the title compound. Yield: 145 mg; LC (method 8): t_R = 0.88 min.

Step 3: 2-bromo-1,3-dimethyl-5-(3-(methylsulfonyl)propyl)benzene

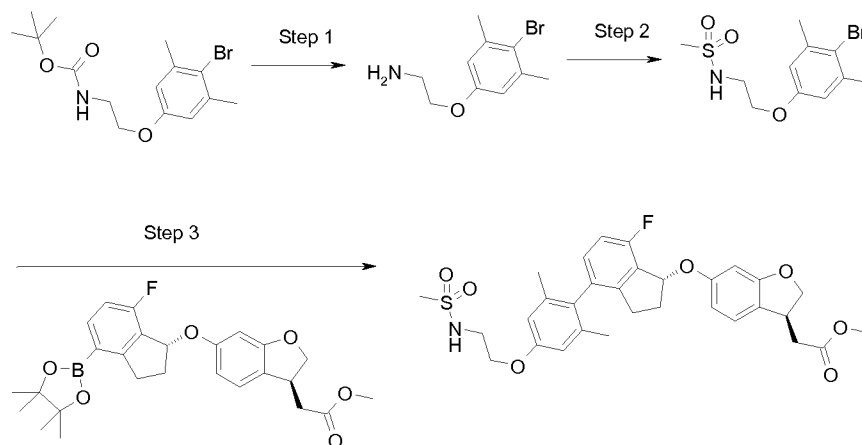
The title compound is prepared from (3-(4-bromo-3,5-dimethylphenyl)propyl)(methyl)sulfane following a procedure analogous to that described in Step 2 of Intermediate 75. LC (method 7): t_R = 1.04 min; Mass spectrum (ESI^+): m/z = 305 $[\text{M}+\text{H}]^+$.

Step 4: Methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-(3-(methylsulfonyl)propyl)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

The title compound is prepared from methyl 2-((S)-6-((R)-7-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate and 2-bromo-1,3-dimethyl-5-(3-(methylsulfonyl)propyl)benzene following a procedure analogous to that described in Step 5 of Intermediate 12. LC (method 8): t_R = 0.66 min; Mass spectrum (ESI^+): m/z = 567 $[\text{M}+\text{H}]^+$.

Intermediate 77

Methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-(2-(methylsulfonamido)ethoxy)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate



Step 1: 2-(4-Bromo-3,5-dimethylphenoxy)ethanamine

To a solution of tert-butyl 2-(4-bromo-3,5-dimethylphenoxy)ethylcarbamate (310 mg) in dichloromethane (8 mL) is added trifluoroacetic acid (700 μ L). The mixture is stirred for 12 hours at room temperature. Then saturated aqueous K_2CO_3 solution is added, the mixture is stirred for 30 minutes and the phases are separated. The organic phase is washed with saturated aqueous K_2CO_3 solution and dried ($MgSO_4$). The solvent is evaporated to give the title compound. Yield: 200 mg; LC (method 7): t_R = 0.83 min; Mass spectrum (ESI^+): m/z = 244 $[M+H]^+$.

Step 2: N-(2-(4-bromo-3,5-dimethylphenoxy)ethyl)methanesulfonamide

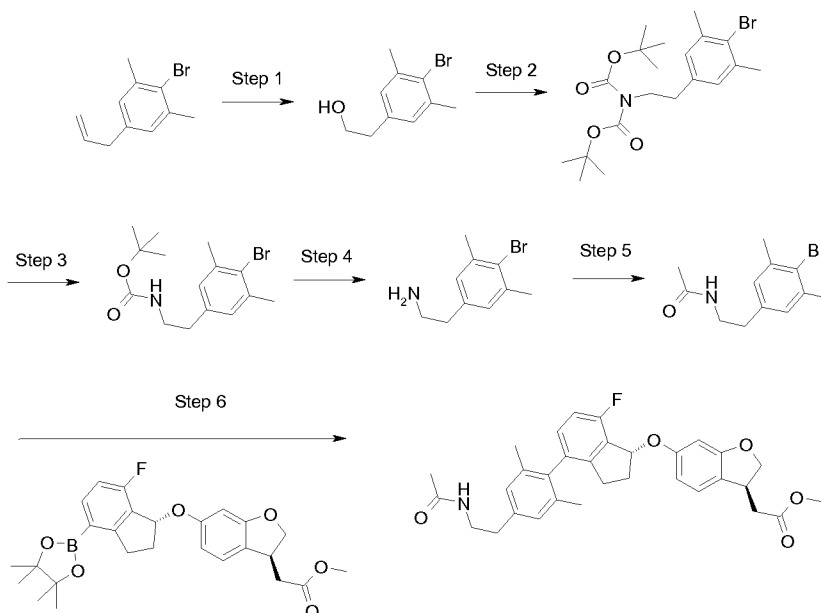
To a cooled ($0^\circ C$) solution of 2-(4-bromo-3,5-dimethylphenoxy)ethanamine (100 mg) and triethylamine (63 μ L) in dichloromethane (2 mL) is added methanesulfonyl chloride (32 μ L). The mixture is stirred for 2 hours at $0^\circ C$. Then the mixture is partitioned between dichloromethane and water. The organic phase is separated, washed with brine and dried ($MgSO_4$). The solvent is evaporated and the residue is purified by HPLC on reversed phase to give the title compound. Yield: 90 mg; LC (method 7): t_R = 1.01 min; Mass spectrum (ESI^+): m/z = 322 $[M+H]^+$.

Step 3: Methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-(2-(methanesulfonamido)ethoxy)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

The title compound is prepared from methyl 2-((S)-6-((R)-7-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate and N-(2-(4-bromo-3,5-dimethylphenoxy)ethyl)methanesulfonamide following a procedure analogous to that described in Step 5 of Intermediate 12. LC (method 8): t_R = 0.59 min; Mass spectrum (ESI^+): m/z = 584 $[M+H]^+$.

Intermediate 78

Methyl 2-((S)-6-((R)-4-(4-(2-acetamidoethyl)-2,6-dimethylphenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate



Step 1: 2-(4-Bromo-3,5-dimethylphenyl)ethanol

- 5 O_3 is bubbled through a cooled (-78°C) solution of 5-allyl-2-bromo-1,3-dimethylbenzene (2 g) in dichloromethane (70 mL) until a light blue color is observed. Then O_2 is bubbled through the solution until the color disappears. Afterwards methanol (70 mL) and NaBH_4 (1.45 g) are added and the mixture is stirred for 12 hours while warming to room temperature. The mixture is then partitioned between 1
- 10 M aqueous HCl solution and diethylether. The organic phase is dried (MgSO_4) and concentrated. The residue is chromatographed on silica gel (cyclohexane/ethyl acetate 95:5 $\rightarrow$ 70:30) to give the title compound. Yield: 390 mg; LC (method 8): t_R = 0.22 min; Mass spectrum (ESI^+): m/z = 211 $[\text{M}+\text{H}-\text{H}_2\text{O}]^+$.

Step 2: N,N-Di-tert.-butoxycarbonyl-2-(4-bromo-3,5-dimethylphenyl)ethanamine

- 15 A solution of di-tert.-butyl azodicarboxylate (2.85 g) in dichloromethane (10 mL) is added dropwise over 15 minutes to a solution of 2-(4-bromo-3,5-dimethylphenyl)ethanol (950 mg), di-tert.butyl-iminodicarboxylate (3.75 g) and tributylphosphine (4.4 mL) in dichloromethane (40 mL) at -10°C . The resulting solution is stirred for 2 hours while warming to room temperature and then partitioned
- 20 between saturated aqueous NaHCO_3 solution and dichloromethane. The aqueous phase is extracted with dichloromethane. The combined organic phases are dried (MgSO_4) and concentrated. The residue is chromatographed on silica gel

(cyclohexane/ethyl acetate 99:1→70:30) to give the title compound. Yield: 1.19 g; LC (method 8): t_R = 1.06 min; Mass spectrum (ESI⁺): m/z = 451 [M+Na]⁺.

Step 3: tert-Butyl 4-bromo-3,5-dimethylphenethylcarbamate

To a solution of N,N-di-tert.-butoxycarbonyl-2-(4-bromo-3,5-dimethylphenyl)ethanamine (1.19 g) in dichloromethane (25 mL) is added trifluoroacetic acid (320 μ L). The mixture is stirred for 12 hours at room temperature. Then the mixture is partitioned between saturated aqueous NaHCO₃ solution and dichloromethane. The organic phase is dried (MgSO₄), the solvent is evaporated and the residue is chromatographed on silica gel (cyclohexane/ethyl acetate 99:1→70:30) to give the title compound. Yield: 550 mg; LC (method 8): t_R = 0.68 min; Mass spectrum (ESI⁺): m/z = 328 [M+H]⁺.

Step 4: 2-(4-Bromo-3,5-dimethylphenyl)ethanamine

The title compound is prepared from tert-butyl 4-bromo-3,5-dimethylphenethylcarbamate following a procedure analogous to that described in Step 1 of Intermediate 77. LC (method 7): t_R = 0.83 min; Mass spectrum (ESI⁺): m/z = 228 [M+H]⁺.

Step 5: N-(4-Bromo-3,5-dimethylphenethyl)acetamide

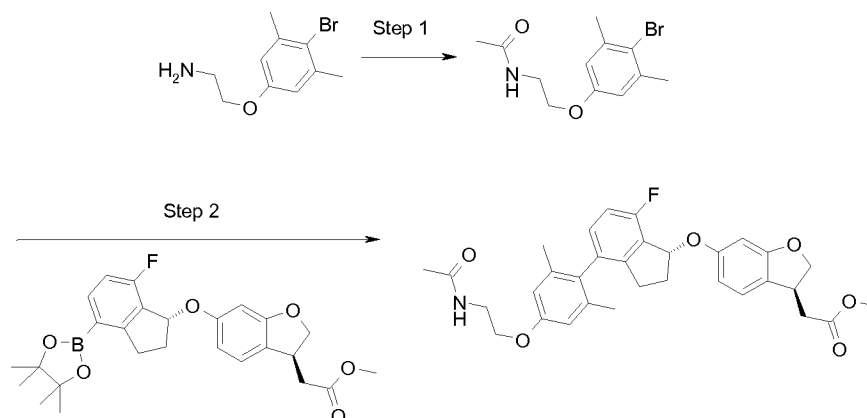
To a cooled (0°C) solution of 2-(4-bromo-3,5-dimethylphenyl)ethanamine (100 mg) and triethylamine (68 μ L) in dichloromethane (3 mL) is added acetyl chloride (31 μ L). The mixture is stirred for 2 hours at 0°C. Then the mixture is partitioned between dichloromethane and water. The organic phase is separated and dried (MgSO₄). The solvent is evaporated and the residue is purified by HPLC on reversed phase to give the title compound. Yield: 25 mg; LC (method 7): t_R = 0.98 min; Mass spectrum (ESI⁺): m/z = 270 [M+H]⁺.

Step 6: Methyl 2-((S)-6-((R)-4-(4-(2-acetamidoethyl)-2,6-dimethylphenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

The title compound is prepared from methyl 2-((S)-6-((R)-7-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate and N-(4-bromo-3,5-dimethylphenethyl)acetamide following a procedure analogous to that described in Step 5 of Intermediate 12. LC (method 8): t_R = 0.53 min; Mass spectrum (ESI⁺): m/z = 532 [M+H]⁺.

Intermediate 79

Methyl 2-((S)-6-((R)-4-(4-(2-acetamidoethoxy)-2,6-dimethylphenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate



Step 1: N-(2-(4-Bromo-3,5-dimethylphenoxy)ethyl)acetamide

- 5 The title compound is prepared from 2-(4-bromo-3,5-dimethylphenoxy)ethanamine following a procedure analogous to that described in Step 5 of Intermediate 78. LC (method 7): $t_R = 0.97$ min; Mass spectrum (ESI^+): $m/z = 286$ $[M+H]^+$.

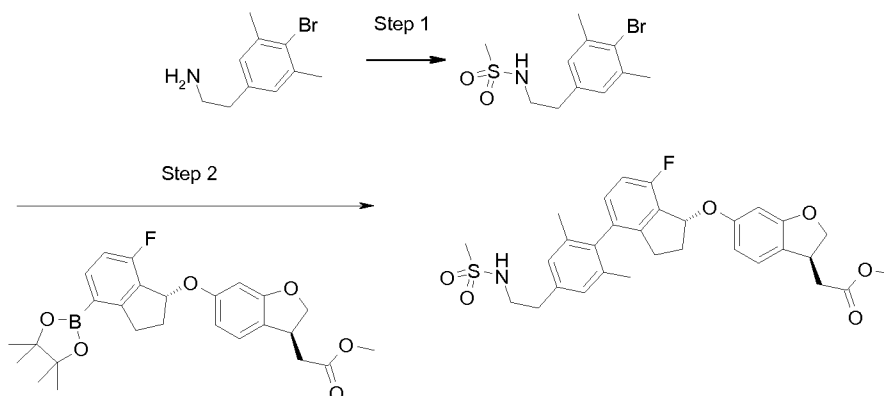
Step 2: Methyl 2-((S)-6-((R)-4-(4-(2-acetamidoethoxy)-2,6-dimethylphenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

- 10 The title compound is prepared from methyl 2-((S)-6-((R)-7-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate and N-(2-(4-bromo-3,5-dimethylphenoxy)ethyl)acetamide following a procedure analogous to that described in Step 5 of Intermediate 12. LC (method 8): $t_R = 0.50$ min; Mass spectrum (ESI^+): $m/z = 548$ $[M+H]^+$.

15

Intermediate 80

Methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-(2-(methanesulfonamido)ethyl)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate



- 20 Step 1: N-(2-(4-Bromo-3,5-dimethylphenethyl)methanesulfonamide

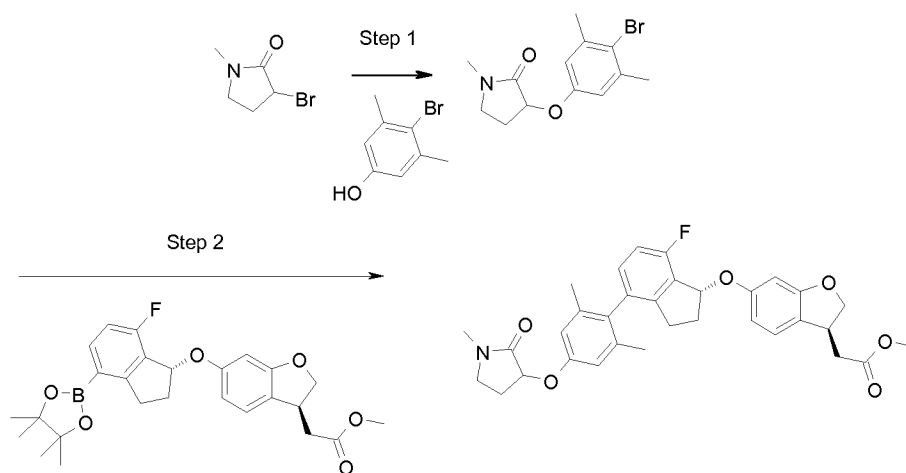
The title compound is prepared from 2-(4-bromo-3,5-dimethylphenyl)ethanamine following a procedure analogous to that described in Step 2 of Intermediate 77. LC (method 7): $t_R = 1.02$ min; Mass spectrum (ESI^+): $m/z = 306$ $[M+H]^+$.

Step 2: Methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-(2-(methylsulfonamido)ethyl)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

The title compound is prepared from methyl 2-((S)-6-((R)-7-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate and N-(4-bromo-3,5-dimethylphenethyl)methanesulfonamide following a procedure analogous to that described in Step 5 of Intermediate 12. LC (method 8): $t_R = 0.58$ min; Mass spectrum (ESI^+): $m/z = 568$ $[M+H]^+$.

Intermediate 81

Methyl 2-((3S)-6-((1R)-4-(2,6-dimethyl-4-(1-methyl-2-oxopyrrolidin-3-yloxy)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate



Step 1: 3-(4-Bromo-3,5-dimethylphenoxy)-1-methylpyrrolidin-2-one

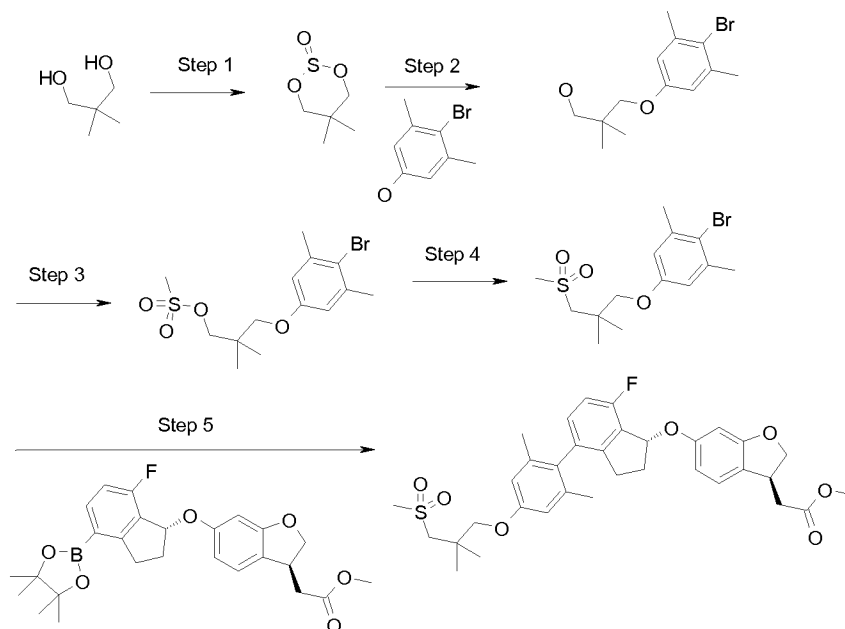
To a solution of 4-bromo-3,5-dimethylphenol (100 mg) in N,N-dimethylformamide (2 mL) is added 3-bromo-1-methylpyrrolidin-2-one (100 mg) and K_2CO_3 (105 mg). The mixture is stirred for 12 hours at room temperature. Then the mixture is partitioned between water and diethylether. The organic phase is dried ($MgSO_4$) and concentrated. The residue is chromatographed on silica gel (cyclohexane/ethyl acetate 80:20→50:50) to give the title compound. Yield: 65 mg; LC (method 7): $t_R = 1.0$ min; Mass spectrum (ESI^+): $m/z = 298$ $[M+H]^+$.

Step 2: Methyl 2-((3S)-6-((1R)-4-(2,6-dimethyl-4-(1-methyl-2-oxopyrrolidin-3-yloxy)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

The title compound is prepared from methyl 2-((S)-6-((R)-7-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate and 3-(4-bromo-3,5-dimethylphenoxy)-1-methylpyrrolidin-2-one following a procedure analogous to that described in Step 5 of Intermediate 12. LC (method 8): t_R = 0.60 min; Mass spectrum (ESI⁺): m/z = 560 [M+H]⁺.

Intermediate 82

Methyl 2-((S)-6-((R)-4-(4-(2,2-dimethyl-3-(methylsulfonyl)propoxy)-2,6-dimethylphenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate



Step 1: 5,5-Dimethyl-[1,3,2]dioxathiane-2-oxide

To a solution of 2,2-dimethyl-propane-1,3-diol (1 g) in dichloromethane (5 mL) is added dropwise at 0°C thionylchloride (735 μ L). The mixture is stirred for 3 hours at 40°C and then partitioned between saturated aqueous NaHCO₃ solution and dichloromethane. The organic phase is washed with brine and dried (MgSO₄). The solvent is evaporated to give the title compound. Yield: 1 g; TLC: r_f = 0.65 (silicagel, cyclohexane/ethyl acetate 3:1).

Step 2: 3-(4-Bromo-3,5-dimethylphenoxy)-2,2-dimethylpropan-1-ol

To a mixture of 4-bromo-3,5-dimethylphenol (625 mg) and Cs₂CO₃ (5 g) in N,N-dimethylformamide (10 mL) is added 5,5-dimethyl-[1,3,2]dioxathiane-2-oxide (467 mg). The mixture is stirred for 12 hours at 100°C and then partitioned between water and ethyl acetate. The organic phase is washed with brine and dried (MgSO₄). The

solvent is evaporated and the residue is purified by HPLC on reversed phase to give the title compound. Yield: 251 mg; LC (method 7): $t_R = 1.16$ min; Mass spectrum (ESI⁺): $m/z = 287$ [M+H]⁺.

Step 3: 3-(4-Bromo-3,5-dimethylphenoxy)-2,2-dimethylpropyl methanesulfonate

- 5 To a cooled (0°C) solution of 3-(4-bromo-3,5-dimethylphenoxy)-2,2-dimethylpropan-1-ol (251 mg) and triethylamine (160 µL) in dichloromethane (3 mL) is added methanesulfonyl chloride (75 µL). The mixture is stirred for 2 days while warming to room temperature. Then the mixture is diluted with dichloromethane, washed with saturated aqueous NaHCO₃ solution and dried (MgSO₄). The solvent is evaporated
- 10 and the residue is chromatographed on silica gel (cyclohexane/ethyl acetate 99:1→50:50) to give the title compound. Yield: 271 mg; LC (method 7): $t_R = 1.18$ min; Mass spectrum (ESI⁺): $m/z = 365$ [M+H]⁺.

Step 4: 2-Bromo-5-(2,2-dimethyl-3-(methylsulfonyl)propoxy)-1,3-dimethylbenzene

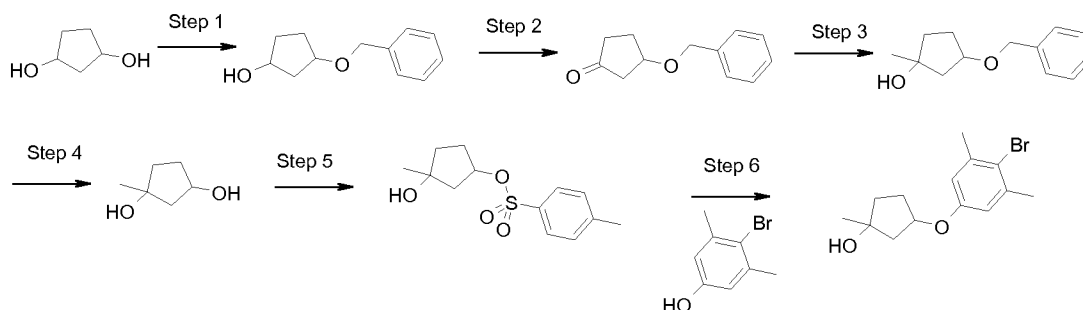
- 15 In a microwave vial sodium methanesulfinate (720 mg) is added to a solution of 3-(4-bromo-3,5-dimethylphenoxy)-2,2-dimethylpropyl methanesulfonate (271 mg) in N-methyl-2-pyrrolidinon (NMP) (8 mL). The mixture is heated to 180°C for 30 minutes. Then the mixture is diluted with diethylether, washed with water and brine and dried (MgSO₄). The solvent is evaporated and the residue is purified by HPLC on reversed
- 20 phase to give the title compound. Yield: 32 mg; LC (method 8): $t_R = 0.47$ min; Mass spectrum (ESI⁺): $m/z = 349$ [M+H]⁺.

Step 5: Methyl 2-((S)-6-((R)-4-(4-(2,2-dimethyl-3-(methylsulfonyl)propoxy)-2,6-dimethylphenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

- 25 The title compound is prepared from methyl 2-((S)-6-((R)-7-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate and 2-bromo-5-(2,2-dimethyl-3-(methylsulfonyl)propoxy)-1,3-dimethylbenzene following a procedure analogous to that described in Step 5 of Intermediate 12. LC (method 8): $t_R = 0.81$ min; Mass
- 30 spectrum (ESI⁺): $m/z = 611$ [M+H]⁺.

Intermediate 83

3-(4-Bromo-3,5-dimethylphenoxy)-1-methylcyclopentanol (enantiomer 1 and enantiomer 2)



Step 1: 3-(Benzyloxy)cyclopentanol

Under argon NaH (60% dispersion in mineral oil; 2.85 g) is added to a cold (0°C) solution of cyclopentane-1,3-diol (3.6 g) in N,N-dimethylformamide (40 mL). The mixture is stirred for 12 hours, followed by dropwise addition of (4.2 mL) and stirring for 12 hours at room temperature. Afterwards the mixture is partitioned between saturated aqueous NH₄Cl solution and diethylether. The organic phase is washed with water, dried (MgSO₄) and concentrated. The residue is chromatographed on silica gel (petrole ether/ethyl acetate 50:50→20:80) to give the title compound. Yield: 540 mg; LC (method 7): t_R = 0.85 min; Mass spectrum (ESI⁺): m/z = 193 [M+H]⁺.

Step 2: 3-(Benzyloxy)cyclopentanone

To a solution of 3-(benzyloxy)cyclopentanol (530 mg) in dichloromethane (8 mL) is added at 0°C 1,1-dihydro-1,1,1-triacetoxy-1,2-benziodoxol-3(1H)-one (Dess-Martin periodinan, 8 mL of a 15% solution in dichloromethane). The mixture is stirred for 3 hours, diluted with dichloromethane, washed with 1 M aqueous NaOH solution and dried (MgSO₄). The solvents are evaporated in vacuo and the residue is chromatographed on silica gel (petrole ether/ethyl acetate 90:10→40:60) to give the title compound. Yield: 430 mg; LC (method 7): t_R = 0.90 min; Mass spectrum (ESI⁺): m/z = 191 [M+H]⁺.

Step 3: 3-(Benzyloxy)-1-methylcyclopentanol

Methylmagnesium bromide (4.8 mL, 1.4 M solution in toluene/tetrahydrofuran 3:1) is added dropwise under argon to a solution of 3-(benzyloxy)cyclopentanone (420 mg) in tetrahydrofuran (10 mL) at -78°C. The mixture is stirred for 12 hours while warming to room temperature and partitioned between 1 M aqueous HCl solution and ethyl acetate. The aqueous phase is extracted with ethyl acetate. The combined organic phases are washed with brine and dried (MgSO₄). The solvents are evaporated in vacuo to give the title compound. Yield: 400 mg; LC (method 7): t_R = 0.93 min; Mass spectrum (ESI⁺): m/z = 229 [M+Na]⁺.

Step 4: 1-Methylcyclopentane-1,3-diol

The title compound is prepared from 3-(benzyloxy)-1-methylcyclopentanol following a procedure analogous to that described in Step 4 of Intermediate 39. The mixture is hydrogenated for 12 hours. TLC: $r_f = 0.18$ (silicagel, petrole ether/ethyl acetate 1:1).

Step 5: 3-Hydroxy-3-methylcyclopentyl 4-methylbenzenesulfonate

- 5 The title compound is prepared from 1-methylcyclopentane-1,3-diol following a procedure analogous to that described in Step 1 of Intermediate 46. TLC: $r_f = 0.48$ (silicagel, petrole ether/ethyl acetate 1:1).

Step 6: 3-(4-Bromo-3,5-dimethylphenoxy)-1-methylcyclopentanol (enantiomer 1 and enantiomer 2)

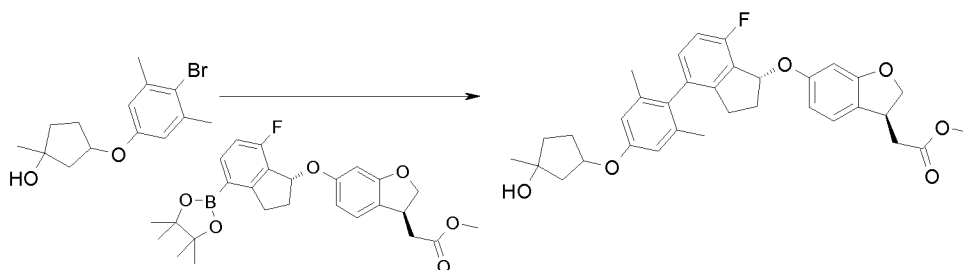
- 10 To a mixture of 4-bromo-3,5-dimethylphenol (300 mg) and Cs_2CO_3 (600 mg) in N,N-dimethylformamide (3 mL) is added 3-hydroxy-3-methylcyclopentyl 4-methylbenzenesulfonate (275 mg). The mixture is stirred for 12 hours at 50°C and then partitioned between water and diethylether. The organic phase is dried (MgSO_4) and concentrated. The residue is chromatographed on silica gel (petrole ether/ethyl acetate 90:10→30:70). The enantiomers are separated by SFC on chiral phase (column: Daicel IA, 5 μm , 250 mm x 10 mm; eluent: scCO_2 /(methanol+0.2% diethylamine) 85:15, 10 mL/min):

Enantiomer 1: $t_R = 4.7$ min; Yield: 31 mg; LC (method 8): $t_R = 0.47$ min; Mass spectrum (ESI^+): $m/z = 299$ $[\text{M}+\text{H}]^+$.

- 20 Enantiomer 2: $t_R = 5.7$ min; Yield: 42 mg; LC (method 8): $t_R = 0.47$ min; Mass spectrum (ESI^+): $m/z = 299$ $[\text{M}+\text{H}]^+$.

Intermediate 84

- 25 Methyl 2-((3S)-6-((1R)-7-fluoro-4-(4-(3-hydroxy-3-methylcyclopentyloxy)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate (diastereomer 1)

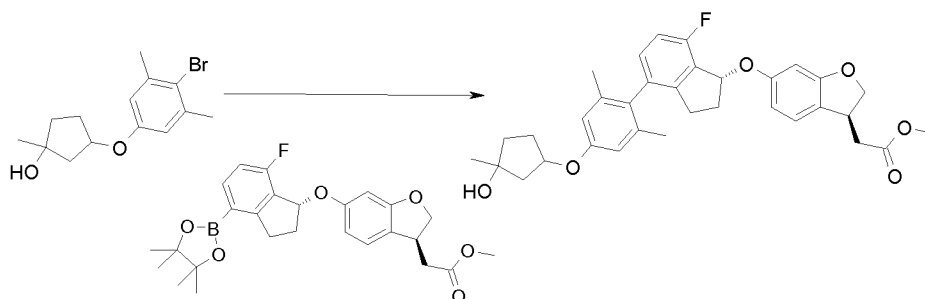


The title compound is prepared from methyl 2-((S)-6-((R)-7-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-

dihydrobenzofuran-3-yl)acetate and 3-(4-bromo-3,5-dimethylphenoxy)-1-methylcyclopentanol (enantiomer 1) following a procedure analogous to that described in Step 5 of Intermediate 12. LC (method 8): $t_R = 0.81$ min.

5 Intermediate 85

Methyl 2-((3S)-6-((1R)-7-fluoro-4-(4-(3-hydroxy-3-methylcyclopentyloxy)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate (diastereomer 2)

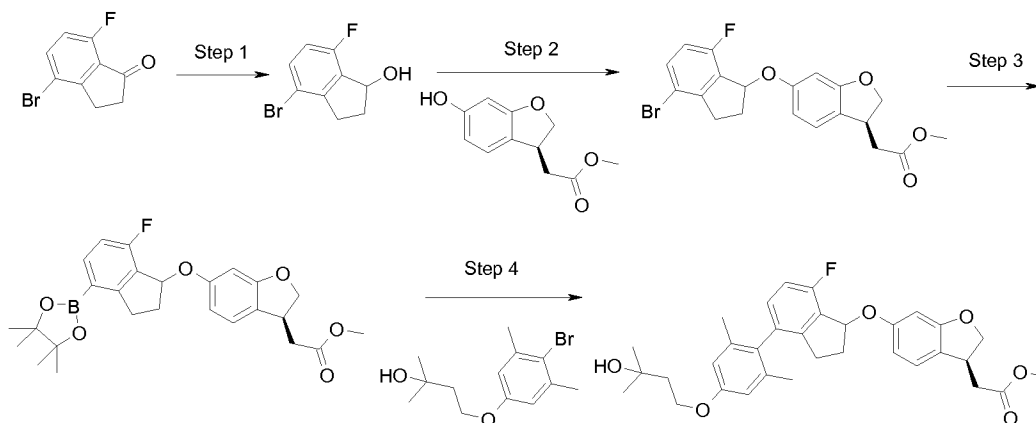


- 10 The title compound is prepared from methyl 2-((S)-6-((R)-7-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate and 3-(4-bromo-3,5-dimethylphenoxy)-1-methylcyclopentanol (enantiomer 2) following a procedure analogous to that described in Step 5 of Intermediate 12. LC (method 8): $t_R = 0.81$ min.

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Intermediate 86

Methyl 2-((3S)-6-(7-fluoro-4-(4-(3-hydroxy-3-methylbutoxy)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate



20 Step 1: 4-Bromo-7-fluoro-2,3-dihydro-1H-inden-1-ol

NaBH_4 (60 mg) is added portionwise under argon to a solution of 4-bromo-7-fluoro-2,3-dihydro-1H-inden-1-one (500 mg) in methanol (5 mL) at 0°C . The mixture is

stirred for 12 hours while warming to room temperature and partitioned between ice-water and ethyl acetate. 1 M aqueous HCl solution is added slowly under vigorous stirring. The phases are separated and the organic phase is washed with brine. After drying (MgSO₄) the solvents are evaporated in vacuo and the residue is chromatographed on silica gel (petrole ether/ethyl acetate 95:5→70:30) to give the title compound. Yield: 425 mg.

Step 2: Methyl 2-((3S)-6-(4-bromo-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

The title compound is prepared from 4-bromo-7-fluoro-2,3-dihydro-1H-inden-1-ol and (S)-methyl 2-(6-hydroxy-2,3-dihydrobenzofuran-3-yl)acetate following a procedure analogous to that described in Step 3 of Intermediate 12. Mass spectrum (ESI⁺): m/z = 421 [M+H]⁺.

Step 3: Methyl 2-((3S)-6-(7-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

The title compound is prepared from methyl 2-((3S)-6-(4-bromo-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate following a procedure analogous to that described in Step 4 of Intermediate 12. Mass spectrum (ESI⁺): m/z = 469 [M+H]⁺.

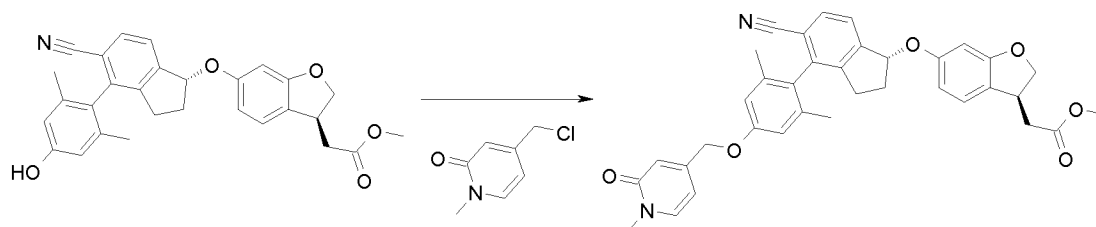
Step 4: Methyl 2-((3S)-6-(7-fluoro-4-(4-(3-hydroxy-3-methylbutoxy)-2,6-

dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

The title compound is prepared from methyl 2-((3S)-6-(7-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate and 4-(4-bromo-3,5-dimethylphenoxy)-2-methylbutan-2-ol following a procedure analogous to that described in Step 5 of Intermediate 12. LC (method 8): t_R = 0.74 min / 0.78 min (mixture of diastereomers); Mass spectrum (ESI⁺): m/z = 571 [M+Na]⁺.

Intermediate 87

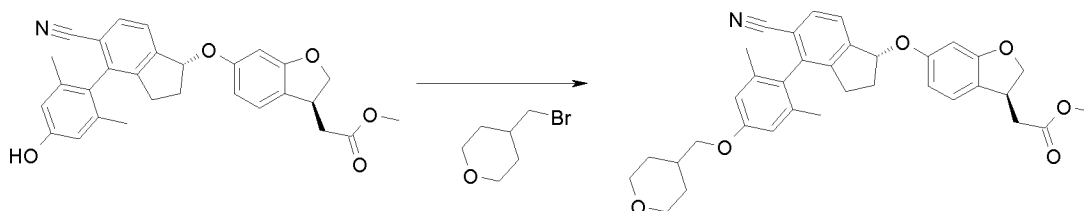
Methyl 2-((S)-6-((R)-5-cyano-4-(2,6-dimethyl-4-((1-methyl-2-oxo-1,2-dihydropyridin-4-yl)methoxy)phenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate



To a mixture of methyl 2-((S)-6-((R)-5-cyano-4-(4-hydroxy-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate (40 mg) and K_2CO_3 (15 mg) in N,N-dimethylformamide (2 mL) is added 4-(chloromethyl)-1-methylpyridin-2(1H)-one (15 mg). The mixture is stirred for 12 hours at 80°C and then partitioned between water and diethylether. The organic phase is dried ($MgSO_4$) and concentrated. The residue is purified by HPLC on reversed phase to give the title compound. Yield: 44 mg; LC (method 9): t_R = 1.11 min; Mass spectrum (ESI^+): m/z = 591 $[M+H]^+$.

Intermediate 88

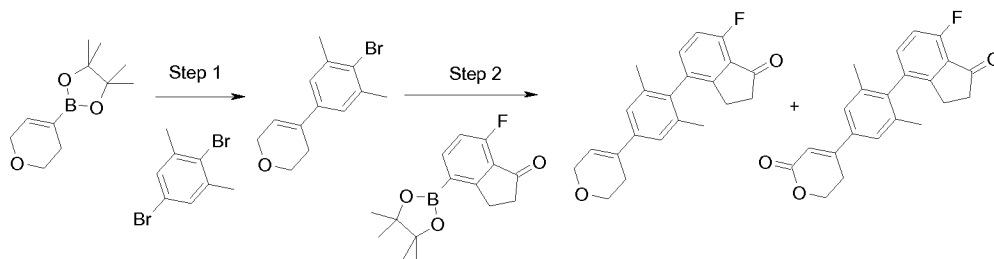
Methyl 2-((S)-6-((R)-5-cyano-4-(2,6-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methoxy)phenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate



To a mixture of methyl 2-((S)-6-((R)-5-cyano-4-(4-hydroxy-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate (40 mg) and K_2CO_3 (15 mg) in N,N-dimethylformamide (2 mL) is added 4-(bromomethyl)tetrahydro-2H-pyran (17 mg). The mixture is stirred for 12 hours at 80°C. K_2CO_3 (15 mg) and 4-(bromomethyl)tetrahydro-2H-pyran (17 mg) are added and the mixture is stirred for 6 hours at 80°C. Again K_2CO_3 (15 mg) and 4-(bromomethyl)tetrahydro-2H-pyran (17 mg) are added and the mixture is stirred for 12 hours at 80°C. Then the mixture is partitioned between water and diethylether. The organic phase is dried ($MgSO_4$) and concentrated. The residue is purified by HPLC on reversed phase to give the title compound. Yield: 35 mg; LC (method 9): t_R = 1.23 min; Mass spectrum (ESI^+): m/z = 568 $[M+H]^+$.

Intermediate 89

4-(4-(3,6-dihydro-2H-pyran-4-yl)-2,6-dimethylphenyl)-7-fluoro-2,3-dihydro-1H-inden-1-one and 4-(4-(7-fluoro-1-oxo-2,3-dihydro-1H-inden-4-yl)-3,5-dimethylphenyl)-5,6-dihydro-2H-pyran-2-one



5

Step 1: 4-(4-Bromo-3,5-dimethylphenyl)-3,6-dihydro-2H-pyran

In a microwave vial 2,5-dibromo-1,3-dimethylbenzene (800 mg), 2-(3,6-dihydro-2H-pyran-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (640 mg) and K_3PO_4 (1.3 g) are suspended in toluene (12 mL) and water (1.2 mL) and purged for 10 minutes with argon. [1,1'-Bis(diphenylphosphino)-ferrocene]-dichloropalladium-(II) (100 mg) is added, the vial is sealed and the mixture is stirred at 60°C for 12 hours. After cooling to room temperature the mixture is diluted with diethylether and washed with saturated aqueous NH_4Cl solution. The organic phase is dried ($MgSO_4$) and concentrated. The residue is chromatographed on silica gel (cyclohexane/ethyl acetate 99:1→60:40) to give the title compound. Yield: 404 mg.

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Step 2: 4-(4-(3,6-dihydro-2H-pyran-4-yl)-2,6-dimethylphenyl)-7-fluoro-2,3-dihydro-1H-inden-1-one and 4-(4-(7-fluoro-1-oxo-2,3-dihydro-1H-inden-4-yl)-3,5-dimethylphenyl)-5,6-dihydro-2H-pyran-2-one

In a microwave vial 7-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-one (200 mg), 4-(4-bromo-3,5-dimethylphenyl)-3,6-dihydro-2H-pyran (200 mg), K_3PO_4 (310 mg) and dicyclohexyl(2',6'-dimethoxybiphenyl-2-yl)phosphine (S-Phos) (25 mg) are suspended in toluene (2 mL), 1,4-dioxane (2 mL) and water (250 μL) and purged for 10 minutes with argon. Palladium-(II)-acetate (7 mg) is added, the vial is sealed and the mixture is stirred at 110°C for 3 hours. After cooling to room temperature the mixture is partitioned between diethylether and saturated aqueous NH_4Cl solution. The organic phase is dried ($MgSO_4$) and concentrated. The residue is chromatographed on silica gel (petrole ether/ethyl acetate 90:10→50:50) to give the title compounds.

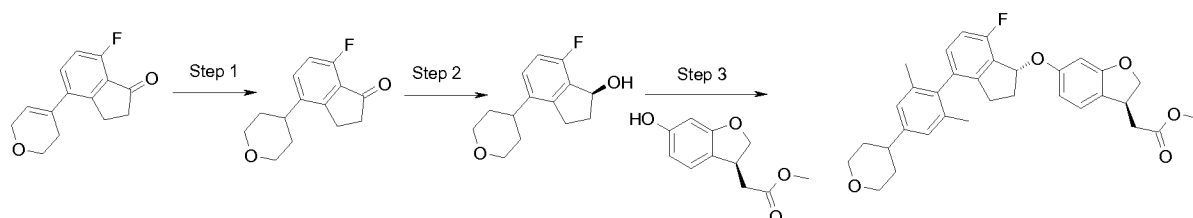
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4-(4-(3,6-dihydro-2H-pyran-4-yl)-2,6-dimethylphenyl)-7-fluoro-2,3-dihydro-1H-inden-1-one: Yield: 100 mg; LC (method 7): t_R = 1.10 min; Mass spectrum (ESI^+): m/z = 337 $[M+H]^+$.

4-(4-(7-fluoro-1-oxo-2,3-dihydro-1H-inden-4-yl)-3,5-dimethylphenyl)-5,6-dihydro-2H-pyran-2-one: Yield: 48 mg; LC (method 7): t_R = 0.99 min; Mass spectrum (ESI^+): m/z = 351 $[M+H]^+$.

Intermediate 90

Methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-(tetrahydro-2H-pyran-4-yl)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate



Step 1: 7-Fluoro-4-(tetrahydro-2H-pyran-4-yl)-2,3-dihydro-1H-inden-1-one

To a solution of 4-(3,6-dihydro-2H-pyran-4-yl)-7-fluoro-2,3-dihydro-1H-inden-1-one (100 mg) in tetrahydrofuran (10 mL) is added 10% palladium on activated carbon (30 mg) and the mixture is hydrogenated at a pressure of 2 bar for 12 hours. The catalyst is filtered off and washed with methanol. The combined mother liquors are concentrated and the residue is chromatographed on silica gel (petrole ether/ethyl acetate 80:20→50:50) to give the title compound. Yield: 55 mg; LC (method 8): t_R = 0.36 min; Mass spectrum (ESI^+): m/z = 339 $[M+H]^+$.

Step 2: (S)-7-Fluoro-4-(tetrahydro-2H-pyran-4-yl)-2,3-dihydro-1H-inden-1-ol

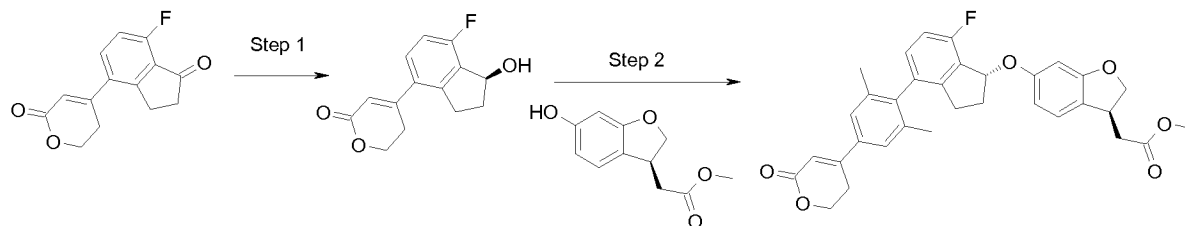
The title compound is prepared from 7-fluoro-4-(tetrahydro-2H-pyran-4-yl)-2,3-dihydro-1H-inden-1-one following a procedure analogous to that described in Step 1 of Intermediate 1. Mass spectrum (ESI^+): m/z = 363 $[M+Na]^+$.

Step 3: Methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-(tetrahydro-2H-pyran-4-yl)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

The title compound is prepared from (S)-7-fluoro-4-(tetrahydro-2H-pyran-4-yl)-2,3-dihydro-1H-inden-1-ol and (S)-methyl 2-(6-hydroxy-2,3-dihydrobenzofuran-3-yl)acetate following a procedure analogous to that described in Step 3 of Intermediate 12. LC (method 26): t_R = 0.95 min; Mass spectrum (ESI^+): m/z = 531 $[M+H]^+$.

Intermediate 91

Methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-(6-oxo-3,6-dihydro-2H-pyran-4-yl)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate



Step 1: (S)-4-(7-Fluoro-1-hydroxy-2,3-dihydro-1H-inden-4-yl)-5,6-dihydro-2H-pyran-2-one

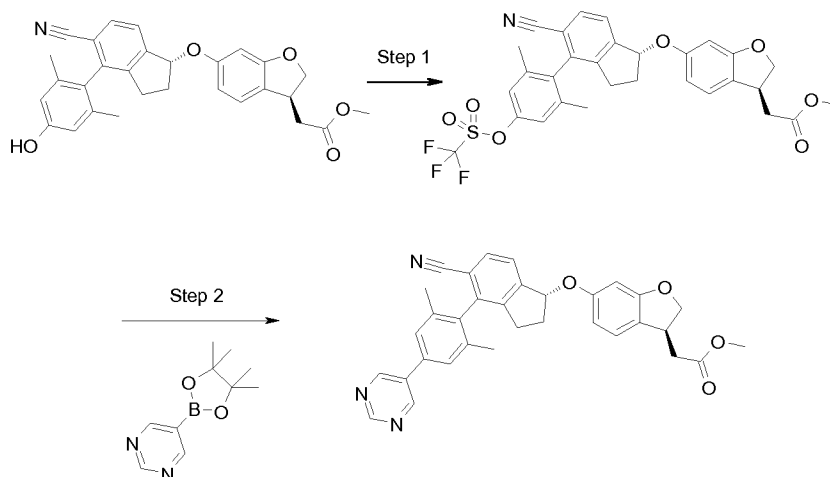
The title compound is prepared from 4-(7-fluoro-1-oxo-2,3-dihydro-1H-inden-4-yl)-5,6-dihydro-2H-pyran-2-one following a procedure analogous to that described in Step 1 of Intermediate 1. LC (method 7): $t_R = 0.97$ min; Mass spectrum (ESI^+): $m/z = 353 [M+H]^+$.

Step 2: Methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-(6-oxo-3,6-dihydro-2H-pyran-4-yl)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

The title compound is prepared from (S)-4-(7-fluoro-1-hydroxy-2,3-dihydro-1H-inden-4-yl)-5,6-dihydro-2H-pyran-2-one and (S)-methyl 2-(6-hydroxy-2,3-dihydrobenzofuran-3-yl)acetate following a procedure analogous to that described in Step 3 of Intermediate 12. LC (method 7): $t_R = 1.18$ min; Mass spectrum (ESI^+): $m/z = 543 [M+H]^+$.

Intermediate 92

Methyl 2-((S)-6-((R)-5-cyano-4-(2,6-dimethyl-4-(pyrimidin-5-yl)phenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate



Step 1: Methyl 2-((S)-6-((R)-5-cyano-4-(2,6-dimethyl-4-(trifluoromethylsulfonyloxy)phenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

- 5 Methyl 2-((S)-6-((R)-5-cyano-4-(4-hydroxy-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate (170 mg) and 2,6-dimethylpyridine (lutidine) (85 μ L) are dissolved in dichloromethane (2 mL) cooled to 0°C and treated dropwise with trifluoromethanesulfonic anhydride (80 μ L). The mixture is stirred for 4 hours at room temperature, cooled to 0°C, 2,6-dimethylpyridine (lutidine) (85 μ L) and trifluoromethanesulfonic anhydride (80 μ L) are added and the mixture is stirred for 12 hours while warming to room temperature. After cooling to 0°C 2,6-dimethylpyridine (lutidine) (85 μ L) and trifluoromethanesulfonic anhydride (80 μ L) are added and the mixture is stirred for 4 hours while warming to room temperature. The mixture is diluted with diethylether and washed with saturated aqueous NH_4Cl solution and brine. After drying (MgSO_4) the solvents are evaporated in vacuo and the residue is chromatographed on silica gel (cyclohexane/ethyl acetate 90:10→60:40) to give the title compound. Yield: 225 mg; LC (method 9): t_R = 1.25 min, Mass spectrum (ESI^+): m/z = 602 $[\text{M}+\text{H}]^+$.

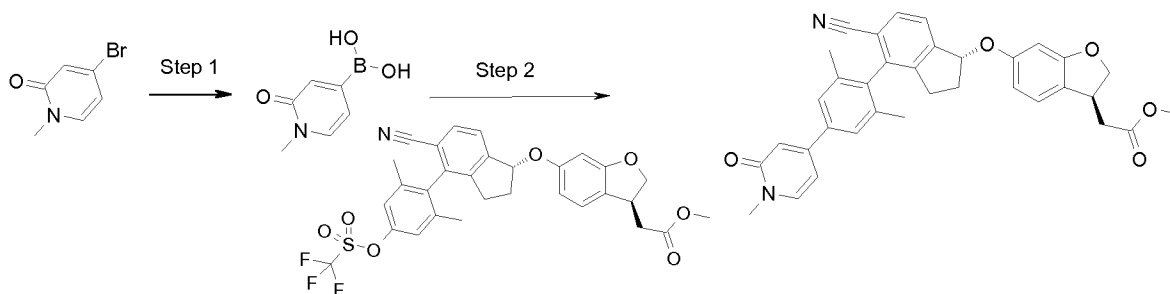
Step 2: Methyl 2-((S)-6-((R)-5-cyano-4-(2,6-dimethyl-4-(pyrimidin-5-yl)phenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

- 20 In a microwave vial methyl 2-((S)-6-((R)-5-cyano-4-(2,6-dimethyl-4-(trifluoromethylsulfonyloxy)phenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate (50 mg), 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidine (23 mg) and K_3PO_4 (40 mg) are suspended in tetrahydrofurane (2 mL). The mixture is purged for 10 minutes with argon. [1,1'-Bis(diphenylphosphino)-

ferrocene]-dichloropalladium dichloromethane complex (3 mg) is added, the vial is sealed and the mixture is stirred at 70°C for 12 hours. After cooling to room temperature the mixture is diluted with diethylether and washed with saturated aqueous NH₄Cl solution. The organic phase is dried (MgSO₄) and concentrated. The residue is purified by HPLC on reversed phase to give the title compound. Yield: 27 mg; LC (method 9): t_R = 1.13 min; Mass spectrum (ESI⁺): m/z = 532 [M+H]⁺.

Intermediate 93

Methyl 2-((S)-6-((R)-5-cyano-4-(2,6-dimethyl-4-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)phenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate



Step 1: 1-Methyl-2-oxo-1,2-dihydropyridin-4-ylboronic acid

A solution of 4-bromo-1-methylpyridin-2(1H)-one (8 g) in tetrahydrofuran (100 mL) is added dropwise to a cold (-18°C) solution of isopropylmagnesium chloride in tetrahydrofuran (32 mL of a 2 M solution). The mixture is stirred for 1 hour at -10°C and then trimethylborate (8.1 mL) is added dropwise. Afterwards the mixture is stirred for 12 hours while warming to room temperature. The mixture is cooled to 0°C, hydrochloric acid (19 mL, 4 N) is added and the mixture is diluted with ethyl acetate. After stirring for 12 hours the organic phase is decanted. Ethyl acetate (50 mL) and water (50 mL) is added to the residue followed by dichloromethane (250 mL). The mixture is stirred for 5 minutes and the precipitate formed is isolated by filtration. The solid material is triturated with diisopropylether, filtered and dried in vacuo. Yield: 4.6 g; Mass spectrum (ESI⁺): m/z = 154 [M+H]⁺.

Step 2: Methyl 2-((S)-6-((R)-5-cyano-4-(2,6-dimethyl-4-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)phenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

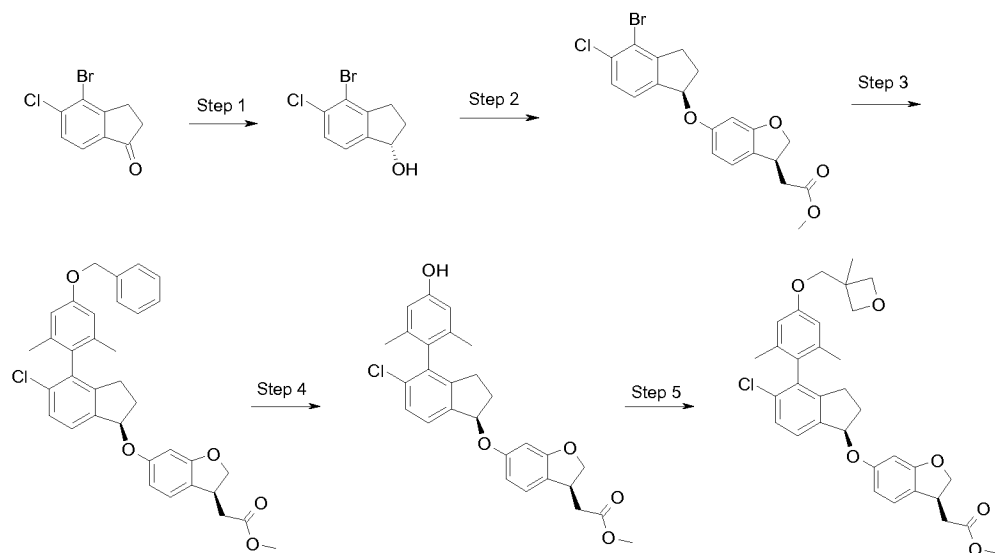
In a microwave vial methyl 2-((S)-6-((R)-5-cyano-4-(2,6-dimethyl-4-(trifluoromethylsulfonyloxy)phenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate (50 mg), 1-methyl-2-oxo-1,2-dihydropyridin-4-

ylboronic acid (17 mg) are mixed with aqueous Na₂CO₃ solution (125 µL, 2 M tetrahydrofuran (2 mL) and N,N-dimethylformamide (2mL). The mixture is purged for 5 minutes with argon. [1,1'-Bis(diphenylphosphino)-ferrocene]-dichloropalladium dichloromethane complex (3 mg) is added, the vial is sealed and the mixture is stirred at 70°C for 2 hours. After cooling to room temperature the mixture is diluted with diethylether and washed with saturated aqueous NH₄Cl solution. The organic phase is dried (MgSO₄) and concentrated. The residue is purified by HPLC on reversed phase to give the title compound. Yield: 32 mg; LC (method 9): t_R = 1.09 min; Mass spectrum (ESI⁺): m/z = 561 [M+H]⁺.

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Intermediate 94

Methyl 2-((S)-6-((R)-5-chloro-4-(2,6-dimethyl-4-((3-methyloxetan-3-yl)methoxy)phenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate



15 Step 1: (S)-4-Bromo-5-chloro-2,3-dihydro-1H-inden-1-ol

The title compound is prepared from 4-bromo-5-chloro-2,3-dihydro-1H-inden-1-one following a procedure analogous to that described in Step 1 of Intermediate 1. LC (method 7): t_R = 0.96 min; Mass spectrum (ESI⁻): m/z = 244, 246, 248 [M-H]⁻.

20 Step 2: Methyl 2-((S)-6-((R)-4-bromo-5-chloro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

The title compound is prepared from (S)-4-bromo-5-chloro-2,3-dihydro-1H-inden-1-ol and (S)-methyl 2-(6-hydroxy-2,3-dihydrobenzofuran-3-yl)acetate following a procedure analogous to that described in Step 3 of Intermediate 12. LC (method 8): t_R = 0.84 min; Mass spectrum (ESI⁺): m/z = 437, 439, 441 [M+H]⁺.

Step 3: Methyl 2-((S)-6-((R)-4-(4-(benzyloxy)-2,6-dimethylphenyl)-5-chloro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetateThe title compound is prepared from methyl 2-((S)-6-((R)-4-bromo-5-chloro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate and 4-(benzyloxy)-2,6-dimethyl phenylboronic acid following a procedure analogous to that described in Step 2 of Intermediate 39. LC (method 8): $t_R = 1.08$ min; Mass spectrum (ESI⁺): $m/z = 569$ [M+H]⁺.

Step 4: Methyl 2-((S)-6-((R)-5-chloro-4-(4-hydroxy-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

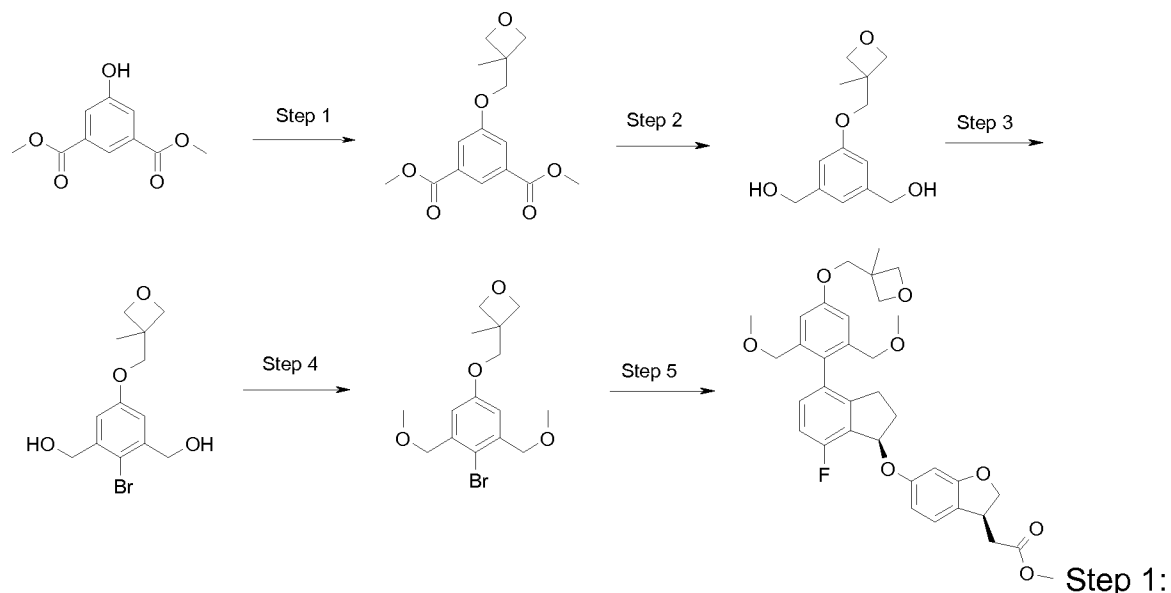
The title compound is prepared from methyl 2-((S)-6-((R)-4-(4-(benzyloxy)-2,6-dimethylphenyl)-5-chloro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate by hydrogenation in the presence of Raney nickel in tetrahydrofuran at room temperature. LC (method 8): $t_R = 0.63$ min; Mass spectrum (ESI⁻): $m/z = 477, 479$ [M-H]⁻.

Step 5: Methyl 2-((S)-6-((R)-5-chloro-4-(2,6-dimethyl-4-((3-methyloxetan-3-yl)methoxy)phenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

The title compound is prepared from methyl 2-((S)-6-((R)-5-chloro-4-(4-hydroxy-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate and 3-(bromomethyl)-3-methyloxetane following a procedure analogous to that described in Step 5 of Intermediate 39. LC (method 8): $t_R = 0.93$ min; Mass spectrum (ESI⁺): $m/z = 563, 565$ [M+H]⁺.

Intermediate 95

Methyl 2-((S)-6-((R)-4-(2,6-bis(methoxymethyl)-4-((3-methyloxetan-3-yl)methoxy)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate



Dimethyl 5-((3-methyloxetan-3-yl)methoxy)isophthalate

A mixture of dimethyl 5-hydroxyisophthalate (500 mg), (3-methyloxetan-3-yl)methyl 4-methylbenzenesulfonate (915 mg), and potassium carbonate (850 mg) in N,N-dimethylformamide (3 mL) is stirred at 50 °C for 5 h. The reaction mixture is diluted with water and the precipitate is filtered off, washed with water, and dried to give the title compound. LC (method 7): $t_R = 0.97$ min; Mass spectrum (ESI⁺): $m/z = 295$ [M+H]⁺.

Step 2: (5-((3-Methyloxetan-3-yl)methoxy)-1,3-phenylene)dimethanol

The title compound is prepared from dimethyl 5-((3-methyloxetan-3-yl)methoxy)isophthalate by reduction with lithium aluminum hydride in tetrahydrofuran. LC (method 7): $t_R = 0.69$ min; Mass spectrum (ESI⁺): $m/z = 239$ [M+H]⁺.

Step 3: (2-Bromo-5-((3-methyloxetan-3-yl)methoxy)-1,3-phenylene)dimethanol

NBS (212 mg) is added to ((5-((3-Methyloxetan-3-yl)methoxy)-1,3-phenylene)dimethanol (270 mg) in acetonitrile (5 mL) and the resulting mixture is stirred at room temperature for 3 h. The solvent is evaporated *in vacuo* and the residue is chromatographed on silica gel (cyclohexane/ethyl acetate 50:50→0:100) to give the title compound. LC (method 7): $t_R = 0.76$ min; Mass spectrum (ESI⁻): $m/z = 315$ [M-H]⁻.

Step 4: 3-((4-Bromo-3,5-bis(methoxymethyl)phenoxy)methyl)-3-methyloxetane

Sodium hydride (50 % in mineral oil; 150 mg) is added to (2-bromo-5-((3-methyloxetan-3-yl)methoxy)-1,3-phenylene)dimethanol (370 mg) in tetrahydrofuran (10 mL) under an argon atmosphere. The resulting mixture is stirred for 20 min at room temperature

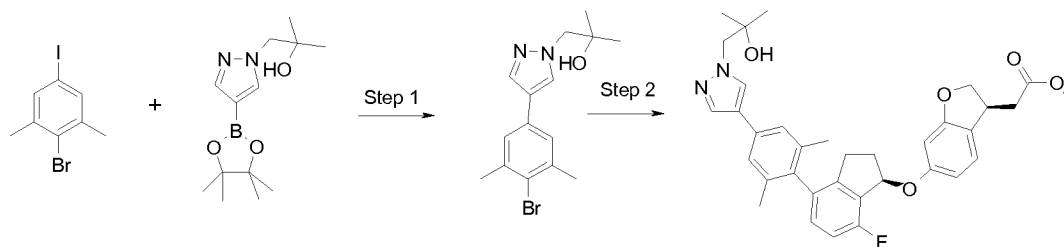
prior to the addition of methyl iodide (546 mg). The reaction mixture is stirred for 3 h at room temperature. More sodium hydride (50 % in mineral oil; 110 mg) and methyl iodide (200 μ L) are added and the mixture is stirred over night at room temperature. The reaction mixture is quenched with ice water and extracted with ethyl acetate. The combined extracts are washed with water, dried over MgSO_4 and concentrated *in vacuo*. The residue is chromatographed on silica gel (cyclohexane/ethyl acetate 90:10 $\rightarrow$ 60:40) to give the title compound. LC (method 7): t_R = 1.05 min; Mass spectrum (ESI^+): m/z = 362 $[\text{M}+\text{NH}_4]^+$.

Step 5: Methyl 2-((S)-6-((R)-4-(2,6-bis(methoxymethyl)-4-((3-methyloxetan-3-yl)methoxy)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

The title compound is prepared from methyl 2-((S)-6-((R)-7-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate and 3-((4-bromo-3,5-bis(methoxymethyl)phenoxy)methyl)-3-methyloxetane following a procedure analogous to that described in Step 5 of Intermediate 12. LC (method 8): t_R = 0.72 min; Mass spectrum (ESI^+): m/z = 607 $[\text{M}+\text{H}]^+$.

Intermediate 96

Methyl 2-((S)-6-((R)-7-fluoro-4-(4-(1-(2-hydroxy-2-methylpropyl)-1H-pyrazol-4-yl)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate



Step1: 1-(4-(4-Bromo-3,5-dimethylphenyl)-1H-pyrazol-1-yl)-2-methylpropan-2-ol

A mixture of 2-bromo-5-iodo-1,3-dimethylbenzene (1.00 g), 2-methyl-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl)propan-2-ol (1.11 g), and 2 M aqueous Na_2CO_3 solution (4.0 mL) in *N,N*-dimethylformamide is purged with argon for 3 min. $[1,1'$ -Bis(diphenylphosphino)-ferrocene]-dichloropalladium dichloromethane complex (85 mg) is added and the mixture is stirred at 60 $^\circ\text{C}$ for 3 h. After cooling to room temperature the mixture is diluted with water and ethyl acetate. The organic phase is washed with brine, dried over MgSO_4 and concentrated *in vacuo*. The

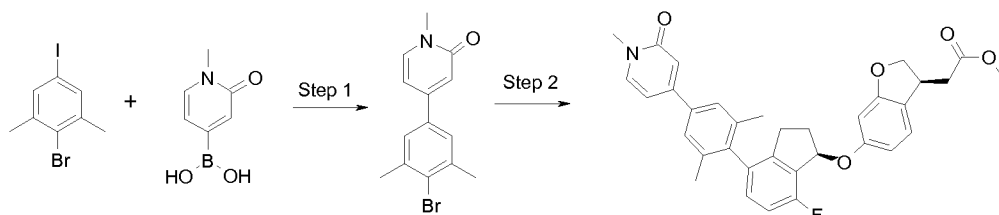
residue is purified by HPLC on reversed phase to give the title compound. LC (method 11): $t_R = 1.12$ min; Mass spectrum (ESI^+): $m/z = 323, 325 [M+H]^+$.

Step 2: Methyl 2-((S)-6-((R)-7-fluoro-4-(4-(1-(2-hydroxy-2-methylpropyl)-1H-pyrazol-4-yl)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

The title compound is prepared from methyl 2-((S)-6-((R)-7-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate and 1-(4-(4-bromo-3,5-dimethylphenyl)-1H-pyrazol-1-yl)-2-methylpropan-2-ol following a procedure analogous to that described in Step 5 of Intermediate 12. LC (method 11): $t_R = 1.23$ min; Mass spectrum (ESI^+): $m/z = 585 [M+H]^+$.

Intermediate 97

Methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate



Step 1: 4-(4-Bromo-3,5-dimethylphenyl)-1-methylpyridin-2(1H)-one

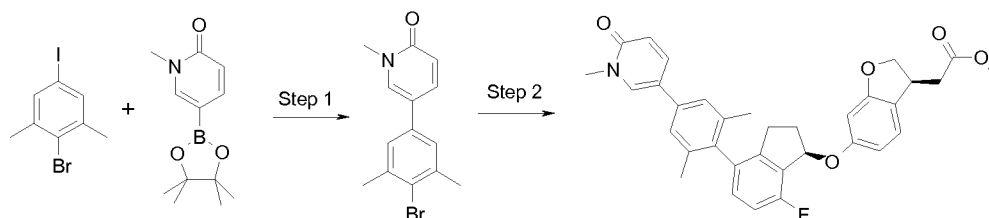
The title compound is prepared from 2-bromo-5-iodo-1,3-dimethylbenzene and 1-methyl-2-oxo-1,2-dihydropyridin-4-ylboronic acid following a procedure analogous to that described in Step 1 of Intermediate 96. LC (method 11): $t_R = 1.04$ min; Mass spectrum (ESI^+): $m/z = 292, 294 [M+H]^+$.

Step 2: Methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

The title compound is prepared from methyl 2-((S)-6-((R)-7-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate and 4-(4-bromo-3,5-dimethylphenyl)-1-methylpyridin-2(1H)-one following a procedure analogous to that described in Step 5 of Intermediate 12. LC (method 11): $t_R = 1.19$ min; Mass spectrum (ESI^+): $m/z = 554 [M+H]^+$.

Intermediate 98

Methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate



Step 1: 5-(4-Bromo-3,5-dimethylphenyl)-1-methylpyridin-2(1H)-one

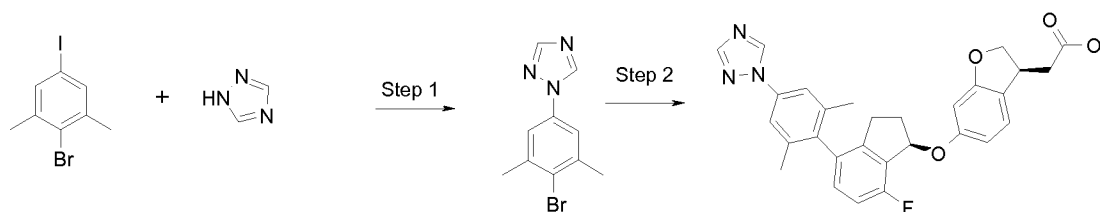
- 5 The title compound is prepared from 2-bromo-5-iodo-1,3-dimethylbenzene and 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2(1H)-one following a procedure analogous to that described in Step 1 of Intermediate 96. LC (method 11): $t_R = 1.05$ min; Mass spectrum (ESI⁺): $m/z = 292, 294$ [M+H]⁺.

Step 2: Methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

- 10 The title compound is prepared from methyl 2-((S)-6-((R)-7-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate and 5-(4-bromo-3,5-dimethylphenyl)-1-methylpyridin-2(1H)-one following a procedure analogous to that described in Step 5 of Intermediate 12.
- 15 LC (method 11): $t_R = 1.19$ min; Mass spectrum (ESI⁺): $m/z = 554$ [M+H]⁺.

Intermediate 99

Methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-(1H-1,2,4-triazol-1-yl)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate



Step 1: 1-(4-Bromo-3,5-dimethylphenyl)-1H-1,2,4-triazole

- 20 A mixture of 2-bromo-5-iodo-1,3-dimethylbenzene (500 mg), 1,2,4-triazole (340 mg), potassium carbonate (770 mg), and copper(I) iodide (232 mg) in N-methyl-2-pyrrolidinone is stirred at 130 °C over night. More potassium carbonate (770 mg) and copper(I) iodide (232 mg) are added and the mixture is heated to 150 °C for 4 h. After cooling to room temperature the mixture is diluted with tetrahydrofuran and filtered.
- 25 The filtrate is concentrated *in vacuo* and purified by HPLC on reversed phase to give

the title compound. LC (method 7): t_R = 0.99 min; Mass spectrum (ESI^+): m/z = 252, 254 $[M+H]^+$.

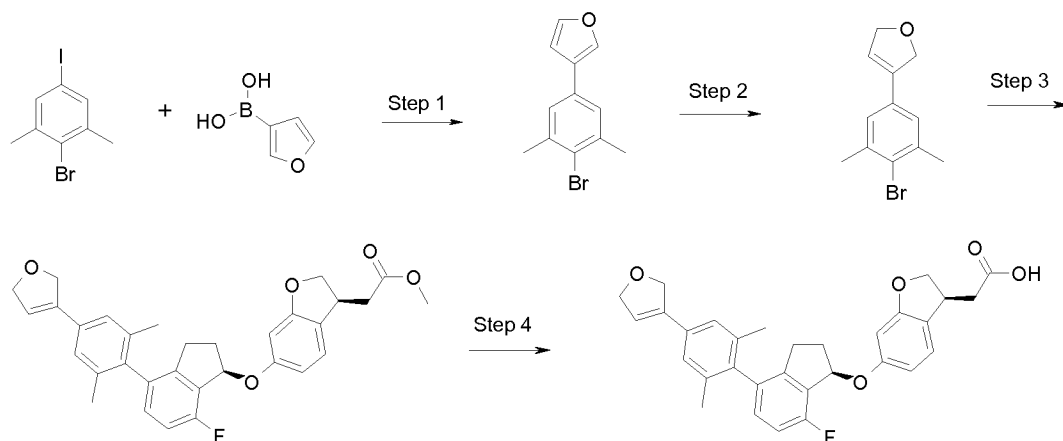
Step 2: Methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-(1H-1,2,4-triazol-1-yl)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

- 5 The title compound is prepared from methyl 2-((S)-6-((R)-7-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate and 1-(4-bromo-3,5-dimethylphenyl)-1H-1,2,4-triazole following a procedure analogous to that described in Step 5 of Intermediate 12. LC (method 7): t_R = 1.16 min; Mass spectrum (ESI^+): m/z = 514 $[M+H]^+$.

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Intermediate 100

2-((S)-6-((R)-4-(4-(2,5-Dihydrofuran-3-yl)-2,6-dimethylphenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



- 15 **Step 1:** 3-(4-Bromo-3,5-dimethylphenyl)furan

- A mixture of 2,5-dibromo-1,3-dimethylbenzene (2.00 g), 1-furan-3-ylboronic acid (856 mg), and 2 M aqueous Na_2CO_3 solution (11 mL) in 1,4-dioxane (40 mL) is purged with argon for 5 min. Tetrakis-triphenylphosphine-palladium-(0) (270 mg) is added and the mixture is stirred at 100 °C over night. More tetrakis-triphenylphosphine-palladium-(0) (50 mg) is added and the mixture is stirred for another 5 h at 100 °C. After cooling to room temperature the mixture is diluted with ethyl acetate and aqueous NH_4Cl solution. The aqueous phase is extracted with ethyl acetate and the combined extracts are washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue is chromatographed on silica gel (cyclohexane/ethyl acetate 100:0→90:10) to give the title compound. LC (method 7): t_R = 1.22 min; Mass spectrum (EI^+): m/z = 250 $[M]^+$.

Step 2: 3-(4-Bromo-3,5-dimethylphenyl)-2,5-dihydrofuran

Triethylsilane (3.67 mL) is added dropwise to a solution of 3-(4-bromo-3,5-dimethylphenyl)furan (580 mg) in trifluoroacetic acid and the resulting mixture is stirred at room temperature for 3 h. Saturated aqueous NaHCO₃ solution is added and the aqueous phase is separated and extracted with ethyl acetate. The combined extracts are washed with brine, dried over MgSO₄ and concentrated *in vacuo*. The residue is chromatographed on silica gel (cyclohexane/ethyl acetate 95:5) to give the title compound. LC (method 9): t_R = 1.16 min; Mass spectrum (ESI⁺): m/z = 251, 253 [M+H]⁺.

Step 3: Methyl 2-((S)-6-((R)-4-(4-(2,5-dihydrofuran-3-yl)-2,6-dimethylphenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

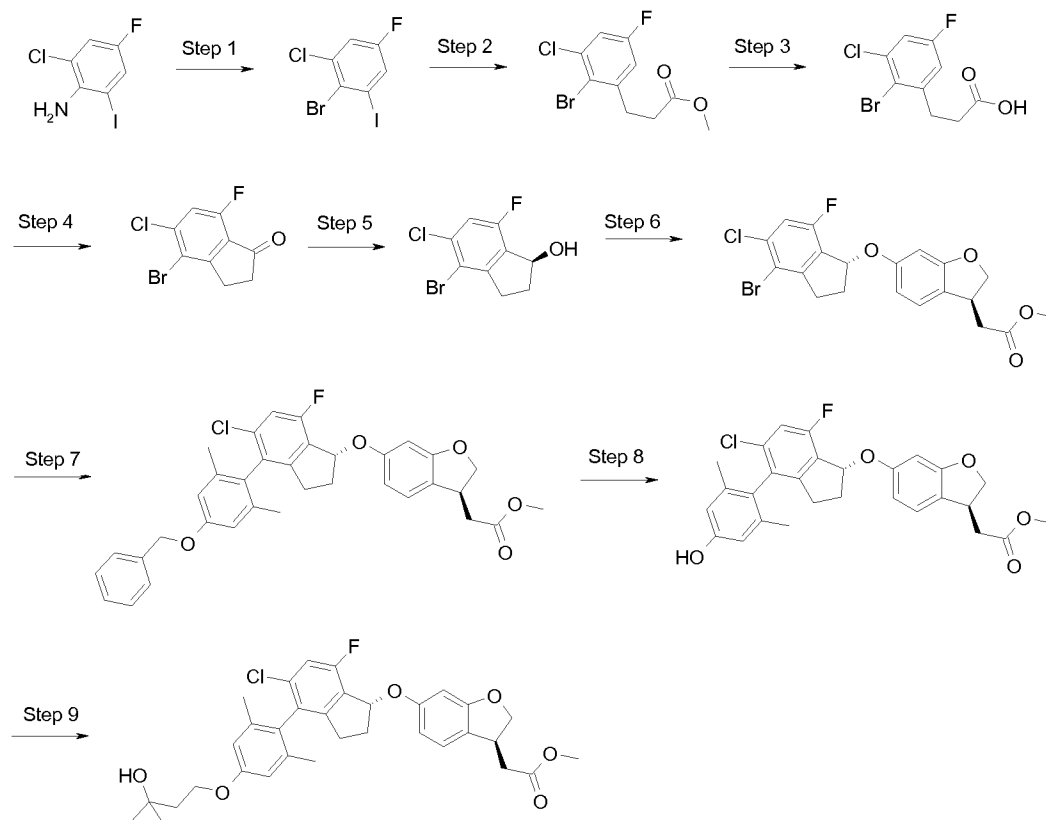
The title compound is prepared from methyl 2-((S)-6-((R)-7-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate and 3-(4-bromo-3,5-dimethylphenyl)-2,5-dihydrofuran following a procedure analogous to that described in Step 5 of Intermediate 12. LC (method 9): t_R = 1.26 min; Mass spectrum (ESI⁺): m/z = 515 [M+H]⁺.

Step 4: 2-((S)-6-((R)-4-(4-(2,5-Dihydrofuran-3-yl)-2,6-dimethylphenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid

The title compound is prepared from methyl 2-((S)-6-((R)-4-(4-(2,5-dihydrofuran-3-yl)-2,6-dimethylphenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate following a procedure analogous to that described in Step 2 of Intermediate 62 using NaOH instead of LiOHxH₂O. LC (method 9): t_R = 0.16 min; Mass spectrum (ESI⁺): m/z = 501 [M+H]⁺.

Intermediate 101

295

**Step 1: 2-Bromo-1-chloro-5-fluoro-3-iodobenzene**

Tert-butyl nitrite (4.00 ml) is added dropwise to a suspension of copper(II) bromide in acetonitrile (50 mL) at 0 °C. The mixture is heated to 65 °C and stirred for 30 min. A solution of 2-chloro-4-fluoro-6-iodo-phenylamine (6.30 g) in acetonitrile (15 mL) is added dropwise and the resulting mixture is stirred at 65 °C for 1 h. After cooling to room temperature the mixture is diluted with ethyl acetate and saturated NaHCO₃ solution. The aqueous phase is extracted with ethyl acetate and the combined extracts are washed with brine, dried over MgSO₄ and concentrated *in vacuo*. The residue is chromatographed on silica gel (cyclohexane/ethyl acetate 100:0→98:2) to give the title compound. LC (method 7): t_R = 1.18 min; Mass spectrum (EI⁺): m/z = 334 [M]⁺.

Step 2: Methyl 3-(2-bromo-3-chloro-5-fluorophenyl)propanoate

The title compound is prepared from 2-bromo-1-chloro-5-fluoro-3-iodobenzene following a procedure analogous to that described in Step 1 of Intermediate 17. LC (method 7): t_R = 1.11 min.

Step 3: 3-(2-Bromo-3-chloro-5-fluorophenyl)propanoic acid

The title compound is prepared from methyl 3-(2-bromo-3-chloro-5-fluorophenyl)propanoate following a procedure analogous to that described in Step 2

of Intermediate 17. LC (method 9): t_R = 0.99 min; Mass spectrum (ESI^-): m/z = 279 $[M-H]^-$.

Step 4: 4-Bromo-5-chloro-7-fluoro-2,3-dihydro-1H-inden-1-one

The title compound is prepared from 3-(2-bromo-3-chloro-5-fluorophenyl)propanoic acid following a procedure analogous to that described in Step 4 of Intermediate 25.

LC (method 9): t_R = 1.02 min; Mass spectrum (ESI^+): m/z = 263 $[M+H]^+$.

Step 5: (S)-4-Bromo-5-chloro-7-fluoro-2,3-dihydro-1H-inden-1-ol

The title compound is prepared from 4-bromo-5-chloro-7-fluoro-2,3-dihydro-1H-inden-1-one following a procedure analogous to that described in Step 1 of Intermediate 1.

LC (method 9): t_R = 0.99 min; Mass spectrum (ESI^-): m/z = 263 $[M-H]^-$.

Step 6: Methyl 2-((S)-6-((R)-4-bromo-5-chloro-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

The title compound is prepared from (S)-4-bromo-5-chloro-7-fluoro-2,3-dihydro-1H-inden-1-ol and (S)-methyl 2-(6-hydroxy-2,3-dihydrobenzofuran-3-yl)acetate following

a procedure analogous to that described in Step 3 of Intermediate 12. LC (method 9): t_R = 1.23 min; Mass spectrum (ESI^+): m/z = 455 $[M+H]^+$.

Step 7: Methyl 2-((S)-6-((R)-4-(4-(benzyloxy)-2,6-dimethylphenyl)-5-chloro-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

The title compound is prepared from methyl 2-((S)-6-((R)-4-bromo-5-chloro-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate and 4-(benzyloxy)-2,6-dimethylphenylboronic acid following a procedure analogous to that described in Step 3 of Intermediate 39. LC (method 9): t_R = 1.32 min.

Step 8: Methyl 2-((S)-6-((R)-5-chloro-7-fluoro-4-(4-hydroxy-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

The title compound is prepared from methyl 2-((S)-6-((R)-4-(4-(benzyloxy)-2,6-dimethylphenyl)-5-chloro-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-

dihydrobenzofuran-3-yl)acetate following a procedure analogous to that described in Step 4 of Intermediate 39. LC (method 9): t_R = 1.17 min; Mass spectrum (ESI^+): m/z = 497 $[M+H]^+$.

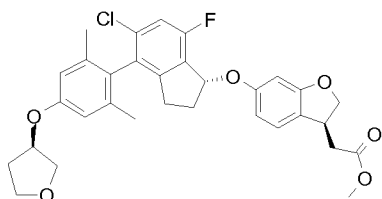
Step 9: Methyl 2-((S)-6-((R)-5-chloro-7-fluoro-4-(4-(3-hydroxy-3-methylbutoxy)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

The title compound is prepared from methyl 2-((S)-6-((R)-5-chloro-7-fluoro-4-(4-hydroxy-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate and 3-hydroxy-3-methylbutyl 4-methylbenzenesulfonate following a

procedure analogous to that described in Step 5 of Intermediate 39. LC (method 9): $t_R = 1.25$ min.

Intermediate 102

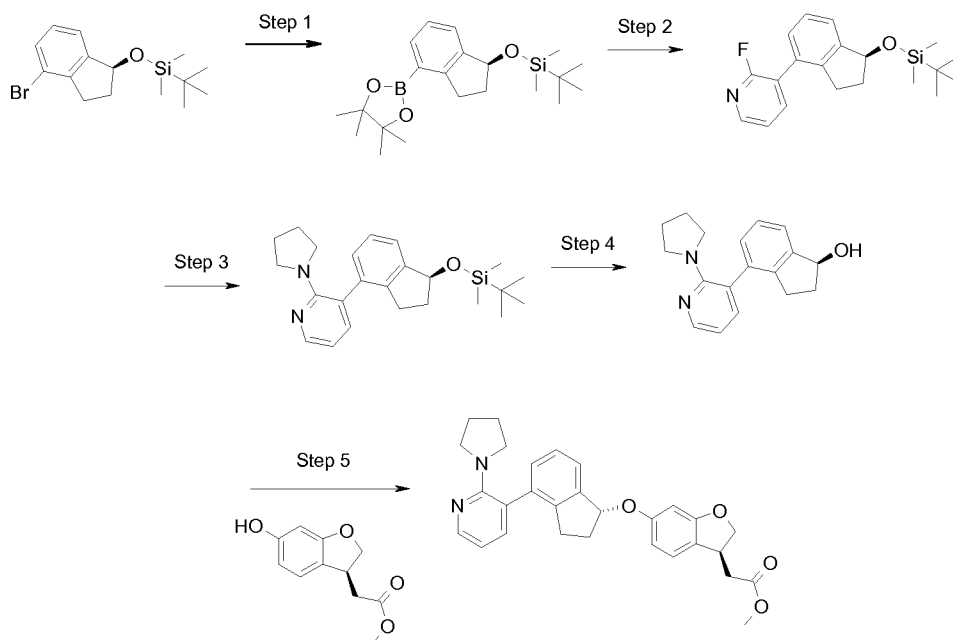
- 5 Methyl 2-((S)-6-((R)-5-chloro-4-(2,6-dimethyl-4-((R)-tetrahydrofuran-3-yloxy)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate



- The title compound is prepared from methyl 2-((S)-6-((R)-5-chloro-7-fluoro-4-(4-hydroxy-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate and (S)-tetrahydrofuran-3-yl 4-methylbenzenesulfonate following a procedure analogous to that described in Step 5 of Intermediate 39. LC (method 9): $t_R = 1.26$ min.

Intermediate 103

- 15 Methyl 2-((3S)-6-((1R)-4-(2-(pyrrolidin-1-yl)pyridin-3-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate



Step 1: (S)-tert-Butyldimethyl(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-yloxy)silane

The title compound is prepared from (S)-(4-bromo-2,3-dihydro-1H-inden-1-yloxy)(tert-butyl)dimethylsilane following a procedure analogous to that described in Step 4 of Intermediate 12. LC (method 8): $t_R = 1.26$ min.

Step 2: 3-((1S)-1-(tert-Butyldimethylsilyloxy)-2,3-dihydro-1H-inden-4-yl)-2-

5 fluoropyridine

The title compound is prepared from (S)-tert-butyldimethyl(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-yloxy)silane and 3-bromo-2-fluoropyridine following a procedure analogous to that described in Step 5 of Intermediate 12. LC (method 8): $t_R = 1.32$ min; Mass spectrum (ESI⁺): $m/z = 344$
10 [M+H]⁺.

Step 3: 3-((1S)-1-(tert-Butyldimethylsilyloxy)-2,3-dihydro-1H-inden-4-yl)-2-(pyrrolidin-1-yl)pyridine

To a solution of 3-((1S)-1-(tert-butyldimethylsilyloxy)-2,3-dihydro-1H-inden-4-yl)-2-fluoropyridine (230 mg) in N-methyl-pyrrolidon (NMP, 2 mL) is added pyrrolidine (166
15 μ L). The mixture is stirred for 12 hours at 100°C, partitioned between water and ethyl acetate and the aqueous phase is twice extracted with ethyl acetate. The combined organic phases are washed with brine, dried (MgSO₄) and concentrated to give the title compound. Yield: 260 mg; LC (method 7): $t_R = 1.15$ min.

Step 4: (1S)-4-(2-(Pyrrolidin-1-yl)pyridin-3-yl)-2,3-dihydro-1H-inden-1-ol

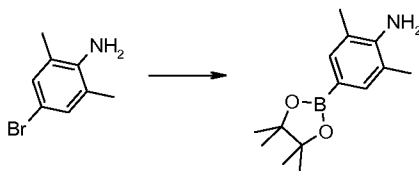
20 The title compound is prepared from 3-((1S)-1-(tert-butyldimethylsilyloxy)-2,3-dihydro-1H-inden-4-yl)-2-(pyrrolidin-1-yl)pyridine following a procedure analogous to that described in Step 4 of Intermediate 4. LC (method 7): $t_R = 0.70$ min.

Step 5: Methyl 2-((3S)-6-((1R)-4-(2-(pyrrolidin-1-yl)pyridin-3-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

25 The title compound is prepared from (1S)-4-(2-(pyrrolidin-1-yl)pyridin-3-yl)-2,3-dihydro-1H-inden-1-ol and (S)-methyl 2-(6-hydroxy-2,3-dihydrobenzofuran-3-yl)acetate following a procedure analogous to that described in Step 3 of Intermediate 12. LC (method 7): $t_R = 0.96$ min.

30 **Intermediate 104**

2,6-Dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline

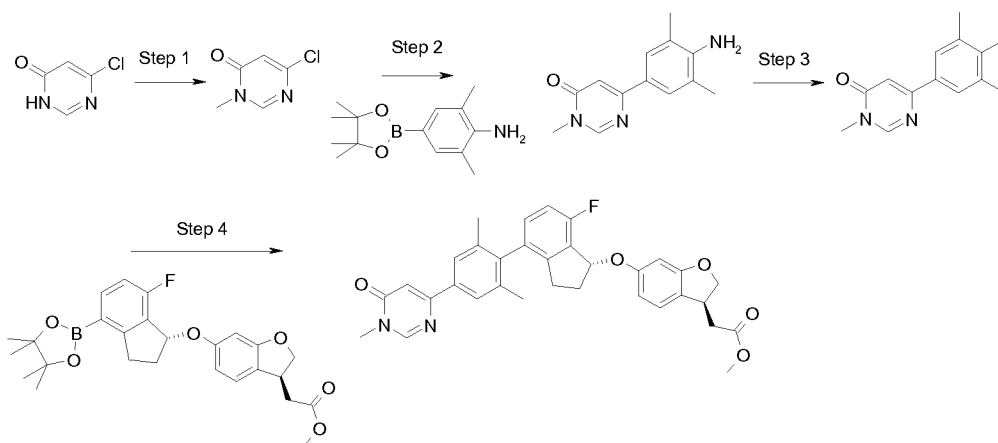


The title compound is prepared from 4-bromo-2,6-dimethylaniline following a procedure analogous to that described in Step 4 of Intermediate 12. LC (method 7): $t_R = 0.99$ min; Mass spectrum (ESI⁺): $m/z = 248$ [M+H]⁺.

5

Intermediate 105

Methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-(1-methyl-6-oxo-1,6-dihydropyrimidin-4-yl)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate



10 Step 1: 6-Chloro-3-methylpyrimidin-4(3H)-one

A mixture of 6-chloropyrimidin-4(3H)-one (5 g), methyl iodide (2.6 mL) and K₂CO₃ (10.6 g) in acetone (100 mL) is stirred at room temperature over night. The mixture is partitioned between water and ethyl acetate. The organic phase is washed with brine, dried (MgSO₄) and concentrated. The residue is triturated with diisopropylether to give the title compound. Yield: 5.1 g; LC (method 11): $t_R = 0.25$ min; Mass spectrum (ESI⁺): $m/z = 145$ [M+H]⁺.

15

Step 2: 6-(4-Amino-3,5-dimethylphenyl)-3-methylpyrimidin-4(3H)-one

The title compound is prepared from 6-chloro-3-methylpyrimidin-4(3H)-one and 2,6-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline following a procedure analogous to that described in Step 3 of Intermediate 5. The mixture is stirred for 12 hours at 65°C. LC (method 11): $t_R = 0.71$ min; Mass spectrum (ESI⁺): $m/z = 230$ [M+H]⁺.

20

Step 3: 6-(4-Iodo-3,5-dimethylphenyl)-3-methylpyrimidin-4(3H)-one

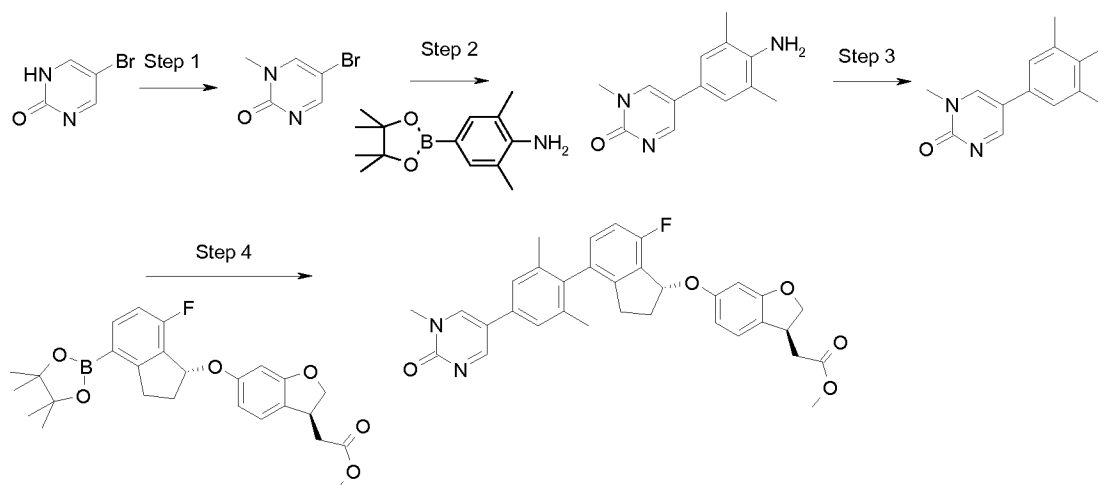
To a solution of 6-(4-amino-3,5-dimethylphenyl)-3-methylpyrimidin-4(3H)-one (2.6 g) and p-toluenesulfonic acid monohydrate (6.5 g) in tert.-butanol (30 mL) is added dropwise at 10-15°C a solution of NaNO₃ (1.6 g) and KI (4.7 g) in water (10 mL). The mixture is stirred for 20 minutes at 15°C and 3 hours at room temperature. Thereafter the mixture is treated with water (50 mL), saturated aqueous NaHCO₃ solution (20 mL) and 10% aqueous solution of Na₂S₂O₃ (20 mL). The mixture is extracted 4 times with ethyl acetate. The combined organic phases are washed with 10% aqueous solution of Na₂S₂O₃ and brine. After drying (MgSO₄) the solvents are evaporated. The crude product is used directly in the next step.

- 10 **Step 4:** Methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-(1-methyl-6-oxo-1,6-dihydropyrimidin-4-yl)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

The title compound is prepared from 6-(4-iodo-3,5-dimethylphenyl)-3-methylpyrimidin-4(3H)-one and methyl 2-((S)-6-((R)-7-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate following a procedure analogous to that described in Step 5 of Intermediate 12. LC (method 11): t_R = 1.19 min; Mass spectrum (ESI⁺): m/z = 555 [M+H]⁺.

20 Intermediate 106

Methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-(1-methyl-2-oxo-1,2-dihydropyrimidin-5-yl)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate



Step 1: 5-Bromo-1-methylpyrimidin-2(1H)-one

A mixture of 5-bromopyrimidin-2(1H)-one (3 g), methyl iodide (1.1 mL) and K_2CO_3 (2.4 g) in N,N-dimethylformamide (60 mL) is stirred for 5 hours at room temperature. The mixture is filtered and the mother liquor is concentrated. The residue is partitioned between water and dichloromethane. The organic phase is washed with
5 brine, dried ($MgSO_4$) and concentrated to give the title compound. Yield: 385 mg; LC (method 9): $t_R = 0.25$ min; Mass spectrum (ESI^+): $m/z = 189 [M+H]^+$.

Step 2: 5-(4-Amino-3,5-dimethylphenyl)-1-methylpyrimidin-2(1H)-one

The title compound is prepared from 5-bromo-1-methylpyrimidin-2(1H)-one and 2,6-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline following a procedure
10 analogous to that described in Step 3 of Intermediate 5. The mixture is stirred for 12 hours at 70°C. LC (method 9): $t_R = 0.63$ min; Mass spectrum (ESI^+): $m/z = 230 [M+H]^+$.

Step 3: 5-(4-Iodo-3,5-dimethylphenyl)-1-methylpyrimidin-2(1H)-one

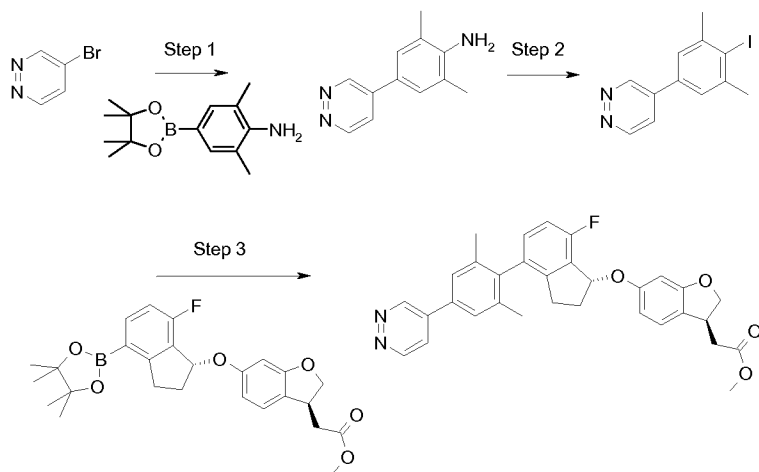
The title compound is prepared from 5-(4-amino-3,5-dimethylphenyl)-1-methylpyrimidin-2(1H)-one following a procedure analogous to that described in Step
15 3 of Intermediate 105. LC (method 9): $t_R = 0.96$ min; Mass spectrum (ESI^+): $m/z = 341 [M+H]^+$.

Step 4: Methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-(1-methyl-2-oxo-1,2-dihydropyrimidin-5-yl)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate
20

The title compound is prepared from 5-(4-iodo-3,5-dimethylphenyl)-1-methylpyrimidin-2(1H)-one and methyl 2-((S)-6-((R)-7-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate following a procedure analogous to that described in Step 5 of
25 Intermediate 12. LC (method 14): $t_R = 1.08$ min; Mass spectrum (ESI^+): $m/z = 555 [M+H]^+$.

Intermediate 107

Methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-(pyridazin-4-yl)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate
30



Step 1: 2,6-Dimethyl-4-(pyridazin-4-yl)aniline

The title compound is prepared from 4-bromopyridazine hydrobromide and 2,6-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline following a procedure analogous to that described in Step 3 of Intermediate 5. The mixture is stirred for 12 hours at 70°C. LC (method 9): $t_R = 0.66$ min; Mass spectrum (ESI^+): $m/z = 200$ $[M+H]^+$.

Step 2: 4-(4-Iodo-3,5-dimethylphenyl)pyridazine

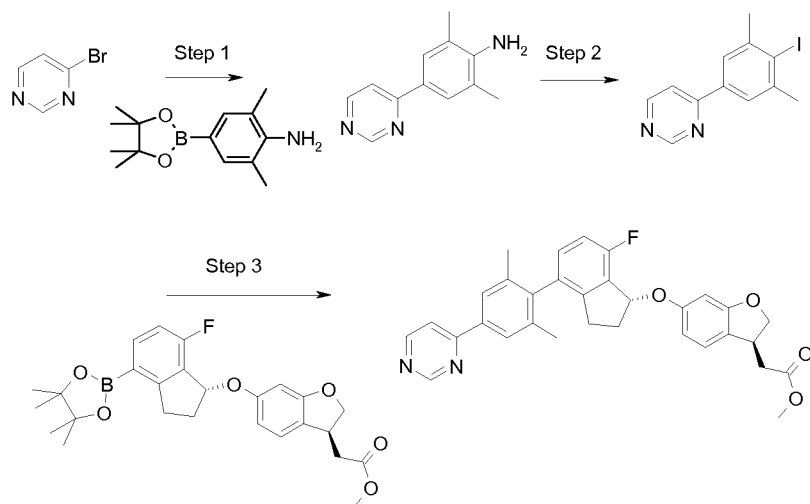
The title compound is prepared from 2,6-dimethyl-4-(pyridazin-4-yl)aniline following a procedure analogous to that described in Step 3 of Intermediate 105. LC (method 9): $t_R = 1.02$ min; Mass spectrum (ESI^+): $m/z = 311$ $[M+H]^+$.

Step 3: Methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-(pyridazin-4-yl)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

The title compound is prepared from 4-(4-iodo-3,5-dimethylphenyl)pyridazine and methyl 2-((S)-6-((R)-7-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate following a procedure analogous to that described in Step 5 of Intermediate 12. LC (method 15): $t_R = 1.20$ min; Mass spectrum (ESI^+): $m/z = 525$ $[M+H]^+$.

Intermediate 108

Methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-(pyrimidin-4-yl)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate



Step 1: 2,6-Dimethyl-4-(pyrimidin-4-yl)aniline

The title compound is prepared from 4-bromopyrimidine hydrochloride and 2,6-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline following a procedure analogous to that described in Step 3 of Intermediate 5. The mixture is stirred for 12 hours at 70°C. LC (method 9): $t_R = 0.74$ min; Mass spectrum (ESI⁺): $m/z = 200$ [M+H]⁺.

Step 2: 4-(4-Iodo-3,5-dimethylphenyl)pyrimidine

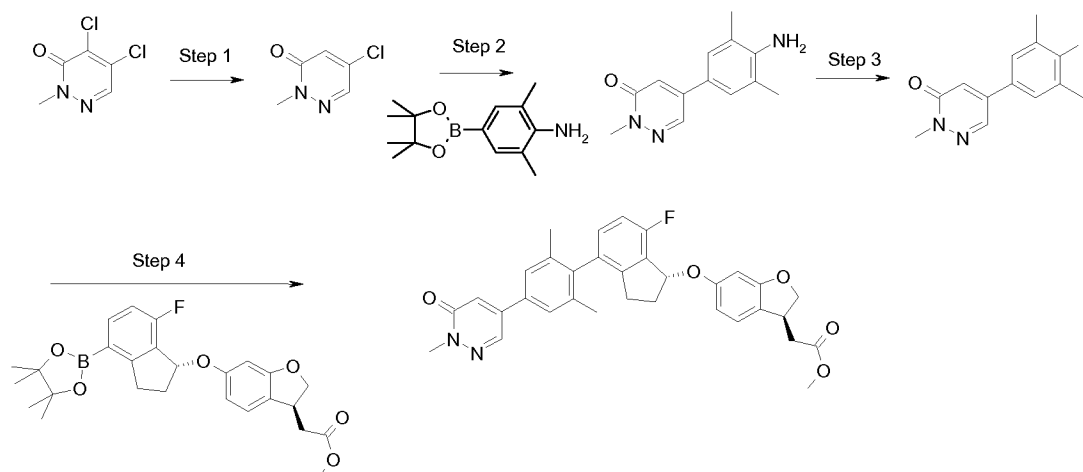
The title compound is prepared from 2,6-dimethyl-4-(pyrimidin-4-yl)aniline following a procedure analogous to that described in Step 3 of Intermediate 105. LC (method 9): $t_R = 1.10$ min; Mass spectrum (ESI⁺): $m/z = 311$ [M+H]⁺.

Step 3: Methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-(pyrimidin-4-yl)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

The title compound is prepared from 4-(4-iodo-3,5-dimethylphenyl)pyrimidine and methyl 2-((S)-6-((R)-7-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate following a procedure analogous to that described in Step 5 of Intermediate 12. LC (method 15): $t_R = 1.26$ min.

Intermediate 109

Methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-(1-methyl-6-oxo-1,6-dihydropyridazin-4-yl)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate



Step 1: 5-Chloro-2-methylpyridazin-3(2H)-one

4,5-Dichloro-2-methylpyridazin-3(2H)-one (1 g) is dissolved in aqueous HI solution (57 %, 8.5 mL) and the mixture is heated to reflux for 12 hours. After cooling to room temperature the mixture is treated with aqueous $\text{Na}_2\text{S}_2\text{O}_3$ solution (30 %, 100 mL) and stirred for 1 hour. The mixture is then extracted three times with dichloromethane. The combined organic phases are washed with brine, dried (MgSO_4) and concentrated. The residue is triturated with diisopropylether. Yield: 414 mg; Mass spectrum (ESI^+): $m/z = 145 [\text{M}+\text{H}]^+$.

Step 2: 5-(4-Amino-3,5-dimethylphenyl)-2-methylpyridazin-3(2H)-one

The title compound is prepared from 5-chloro-2-methylpyridazin-3(2H)-one and 2,6-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline following a procedure analogous to that described in Step 3 of Intermediate 5. The mixture is stirred for 12 hours at 60°C . LC (method 9): $t_R = 0.79$ min; Mass spectrum (ESI^+): $m/z = 230 [\text{M}+\text{H}]^+$.

Step 3: 5-(4-Iodo-3,5-dimethylphenyl)-2-methylpyridazin-3(2H)-one

The title compound is prepared from 5-(4-amino-3,5-dimethylphenyl)-2-methylpyridazin-3(2H)-one following a procedure analogous to that described in Step 3 of Intermediate 105. LC (method 9): $t_R = 1.06$ min; Mass spectrum (ESI^+): $m/z = 341 [\text{M}+\text{H}]^+$.

Step 4: Methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-(1-methyl-6-oxo-1,6-dihydropyridazin-4-yl)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

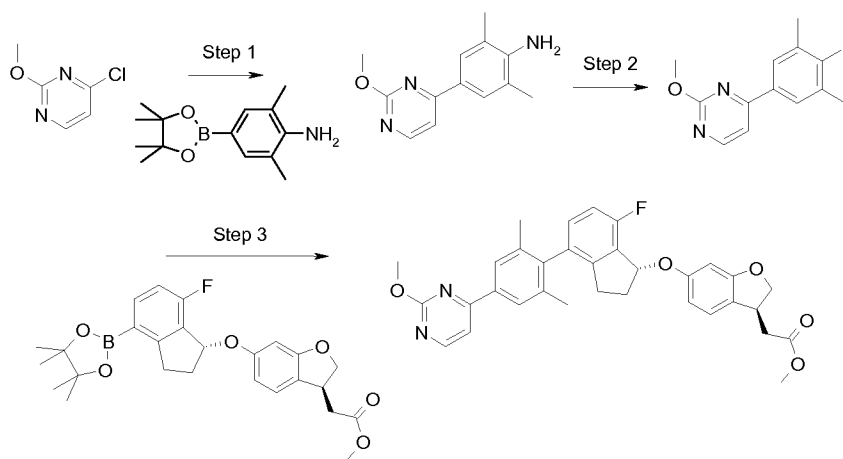
The title compound is prepared from 5-(4-iodo-3,5-dimethylphenyl)-2-methylpyridazin-3(2H)-one and methyl 2-((S)-6-((R)-7-fluoro-4-(4,4,5,5-tetramethyl-

1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate following a procedure analogous to that described in Step 5 of Intermediate 12. LC (method 14): $t_R = 1.18$ min; Mass spectrum (ESI⁺): $m/z = 555$ [M+H]⁺.

5

Intermediate 110

Methyl 2-((S)-6-((R)-7-fluoro-4-(4-(2-methoxypyrimidin-4-yl)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate



10 Step 1: 4-(2-Methoxypyrimidin-4-yl)-2,6-dimethylaniline

The title compound is prepared from 4-chloro-2-methoxypyrimidine and 2,6-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline following a procedure analogous to that described in Step 3 of Intermediate 5. The mixture is stirred for 12 hours at 60°C. LC (method 14): $t_R = 0.89$ min; Mass spectrum (ESI⁺): $m/z = 230$ [M+H]⁺.

15

Step 2: 4-(4-Iodo-3,5-dimethylphenyl)-2-methoxypyrimidine

The title compound is prepared from 5-(4-amino-3,5-dimethylphenyl)-2-methylpyridazin-3(2H)-one following a procedure analogous to that described in Step 3 of Intermediate 105. LC (method 14): $t_R = 1.18$ min; Mass spectrum (ESI⁺): $m/z = 341$ [M+H]⁺.

20

Step 3: Methyl 2-((S)-6-((R)-7-fluoro-4-(4-(2-methoxypyrimidin-4-yl)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

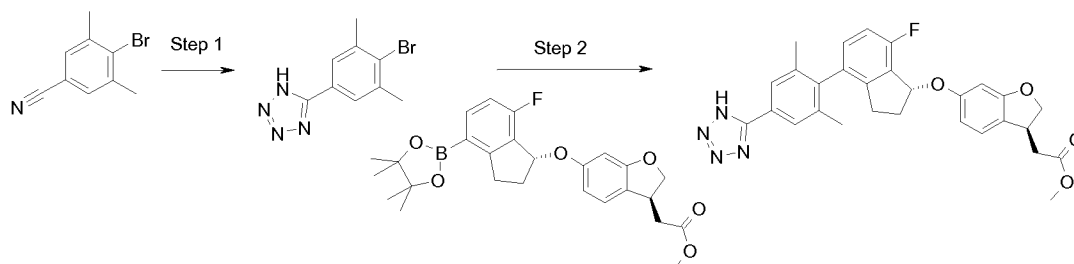
The title compound is prepared from 4-(4-iodo-3,5-dimethylphenyl)-2-methoxypyrimidine and methyl 2-((S)-6-((R)-7-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

25

following a procedure analogous to that described in Step 5 of Intermediate 12. LC (method 8): $t_R = 0.82$ min; Mass spectrum (ESI⁺): $m/z = 555$ [M+H]⁺.

Intermediate 111

5 Methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-(1H-tetrazol-5-yl)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate



Step 1: 5-(4-Bromo-3,5-dimethylphenyl)-1H-tetrazole

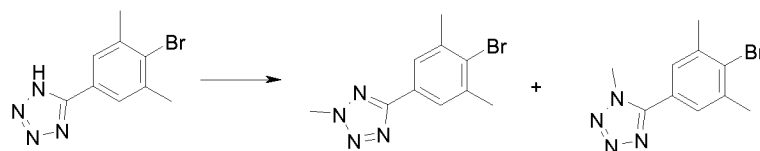
To a solution of 4-bromo-3,5-dimethylbenzonitrile (1 g) in N,N-dimethylformamide (10 mL) is added NH₄Cl (770 mg) and NaN₃ (800 mg) and the mixture is heated to 100°C for 12 hours. After cooling to room temperature the mixture is diluted with water. The formed precipitate is filtered off, washed with water and dried to give the title compound. Yield: 650 mg; Mass spectrum (ESI⁺): $m/z = 253$ [M+H]⁺.

Step 2: Methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-(1H-tetrazol-5-yl)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

The title compound is prepared from 5-(4-bromo-3,5-dimethylphenyl)-1H-tetrazole and methyl 2-((S)-6-((R)-7-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate following a procedure analogous to that described in Step 5 of Intermediate 12. LC (method 11): $t_R = 1.05$ min; Mass spectrum (ESI⁺): $m/z = 515$ [M+H]⁺.

Intermediate 112

5-(4-Bromo-3,5-dimethylphenyl)-2-methyl-2H-tetrazole and 5-(4-bromo-3,5-dimethylphenyl)-1-methyl-1H-tetrazole



To a solution of 5-(4-bromo-3,5-dimethylphenyl)-1H-tetrazole (780 mg) in N,N-dimethylformamide (12 mL) is added KOH (432 mg) and MeI (210 μ L) and the

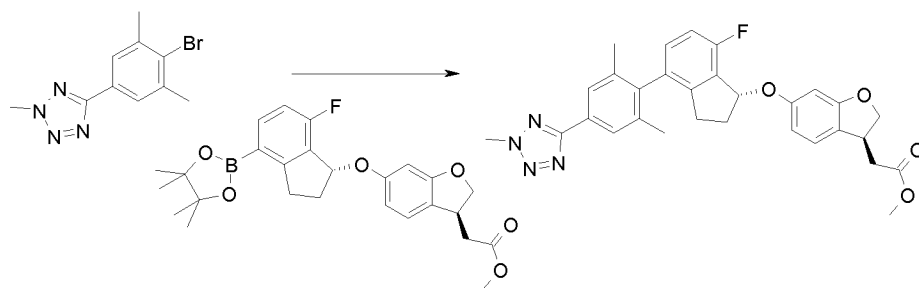
mixture is stirred for 4 hours at room temperature. Then the mixture is diluted with water and extracted 3 times with dichloromethane. The combined organic phases are washed with water, dried (MgSO_4) and concentrated. The residue is chromatographed on silica gel (cyclohexane/ethyl acetate 95:5→70:30) to give the title compounds.

5-(4-bromo-3,5-dimethylphenyl)-1-methyl-1H-tetrazole: Yield: 135 mg; LC (method 11): $t_R = 1.03$ min; Mass spectrum (ESI^+): $m/z = 267$ $[\text{M}+\text{H}]^+$.

5-(4-bromo-3,5-dimethylphenyl)-2-methyl-2H-tetrazole: Yield: 660 mg; LC (method 11): $t_R = 1.16$ min; Mass spectrum (ESI^+): $m/z = 267$ $[\text{M}+\text{H}]^+$.

Intermediate 113

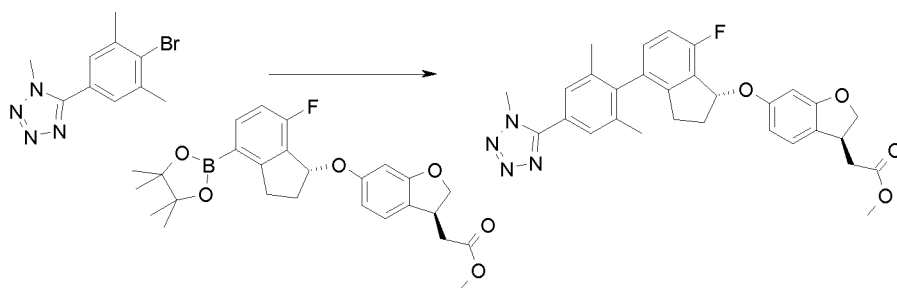
Methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-(2-methyl-2H-tetrazol-5-yl)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate



The title compound is prepared from 5-(4-bromo-3,5-dimethylphenyl)-2-methyl-2H-tetrazole and methyl 2-((S)-6-((R)-7-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate following a procedure analogous to that described in Step 5 of Intermediate 12. LC (method 11): $t_R = 1.26$ min; Mass spectrum (ESI^+): $m/z = 529$ $[\text{M}+\text{H}]^+$.

Intermediate 114

Methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-(1-methyl-1H-tetrazol-5-yl)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

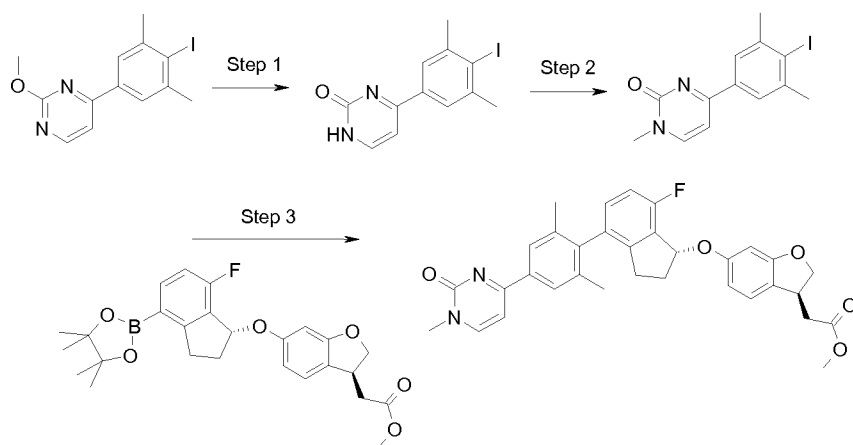


The title compound is prepared from 5-(4-bromo-3,5-dimethylphenyl)-1-methyl-1H-tetrazole and methyl 2-((S)-6-((R)-7-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate following a procedure analogous to that described in Step 5 of Intermediate 12. LC (method 11):

5 $t_R = 1.20$ min; Mass spectrum (ESI⁺): $m/z = 529$ [M+H]⁺.

Intermediate 115

Methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-(1-methyl-2-oxo-1,2-dihydropyrimidin-4-yl)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate



Step 1: 4-(4-Iodo-3,5-dimethylphenyl)pyrimidin-2(1H)-one

4-(4-Iodo-3,5-dimethylphenyl)-2-methoxypyrimidine is dissolved in 33 % solution of HBr in acetic acid (7.7 mL) and the mixture is stirred for 12 hours at room temperature. Then the mixture is diluted with water. The formed precipitate is filtered off, washed with acetone and dried. Yield: 1 g; LC (method 11): $t_R = 0.92$ min; Mass spectrum (ESI⁺): $m/z = 327$ [M+H]⁺.

Step 2: 4-(4-Iodo-3,5-dimethylphenyl)-1-methylpyrimidin-2(1H)-one

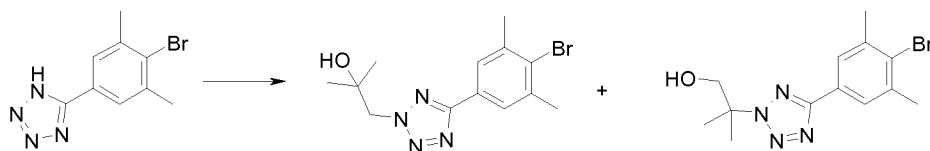
A mixture of 4-(4-iodo-3,5-dimethylphenyl)pyrimidin-2(1H)-one (500 mg), methyl iodide (165 μ L) and K₂CO₃ (254 mg) in N,N-dimethylformamide (10 mL) is stirred for 12 hours at room temperature. Then the mixture is partitioned between water and dichloromethane. The aqueous phase is extracted twice with dichloromethane and the combined organic phases are washed with brine. After drying (MgSO₄) the solvents are evaporated. The residue is triturated with diethylether. The solid is filtered off and dried to give the title compound. Yield: 380 mg; LC (method 11): $t_R = 0.96$ min; Mass spectrum (ESI⁺): $m/z = 341$ [M+H]⁺.

Step 3: Methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-(1-methyl-2-oxo-1,2-dihydropyrimidin-4-yl)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

The title compound is prepared from 4-(4-iodo-3,5-dimethylphenyl)-1-methylpyrimidin-2(1H)-one and methyl 2-((S)-6-((R)-7-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate following a procedure analogous to that described in Step 5 of Intermediate 12. LC (method 15): t_R = 1.14 min; Mass spectrum (ESI^+): m/z = 555 $[M+H]^+$.

Intermediate 116

1-(5-(4-Bromo-3,5-dimethylphenyl)-2H-tetrazol-2-yl)-2-methylpropan-2-ol and 2-(5-(4-bromo-3,5-dimethylphenyl)-2H-tetrazol-2-yl)-2-methylpropan-1-ol



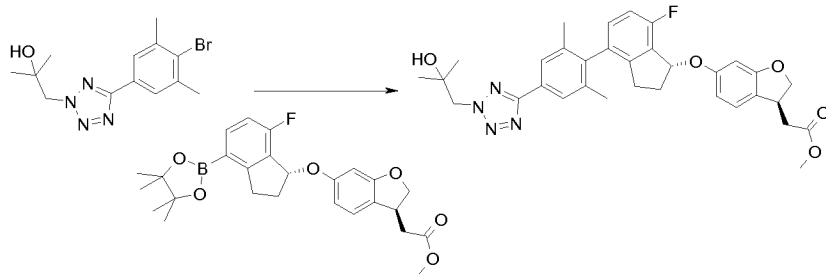
To a solution of 5-(4-bromo-3,5-dimethylphenyl)-1H-tetrazole (500 mg) in methanol (5 mL) is added Cs_2CO_3 (645 mg) and 1,1-dimethyloxirane (450 μ L). The vial is sealed and the mixture is heated to 60°C for 3 hours. Cs_2CO_3 (400 mg) and 1,1-dimethyloxirane (300 μ L) are added and the mixture is heated to 60°C for 12 hours. After addition of 1,1-dimethyloxirane (450 μ L) the mixture is heated to 80°C for 6 hours. Then the solvents are evaporated and the residue is partitioned between water and ethyl acetate. The aqueous phase is extracted twice with ethyl acetate and the combined organic phases are dried ($MgSO_4$). After concentration the residue is purified by HPLC on reversed phase to give the title compounds.

1-(5-(4-bromo-3,5-dimethylphenyl)-2H-tetrazol-2-yl)-2-methylpropan-2-ol: Yield: 310 mg; LC (method 11): t_R = 1.14 min; Mass spectrum (ESI^+): m/z = 325 $[M+H]^+$.

2-(5-(4-bromo-3,5-dimethylphenyl)-2H-tetrazol-2-yl)-2-methylpropan-1-ol: Yield: 40 mg; LC (method 11): t_R = 1.16 min; Mass spectrum (ESI^+): m/z = 325 $[M+H]^+$.

Intermediate 117

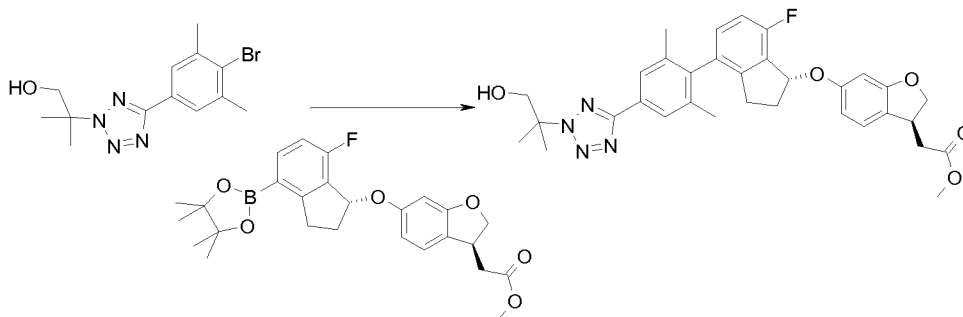
Methyl 2-((S)-6-((R)-7-fluoro-4-(4-(2-(2-hydroxy-2-methylpropyl)-2H-tetrazol-5-yl)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate



The title compound is prepared from 1-(5-(4-bromo-3,5-dimethylphenyl)-2H-tetrazol-2-yl)-2-methylpropan-2-ol and methyl 2-((S)-6-((R)-7-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate following a procedure analogous to that described in Step 5 of Intermediate 12. LC (method 15): t_R = 1.24 min; Mass spectrum (ESI⁺): m/z = 587 [M+H]⁺.

Intermediate 118

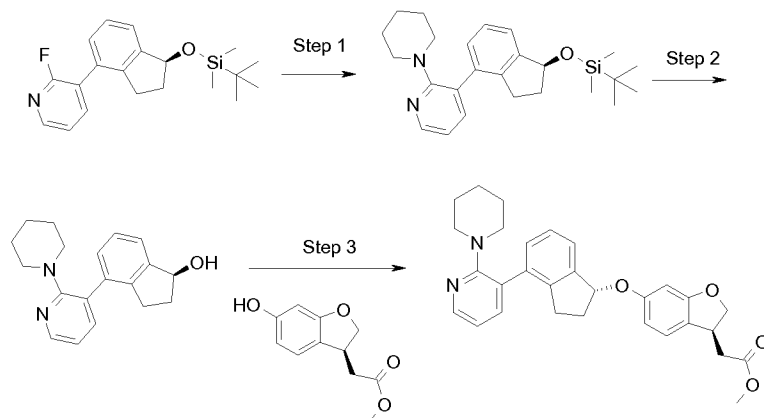
10 Methyl 2-((S)-6-((R)-7-fluoro-4-(4-(2-(1-hydroxy-2-methylpropan-2-yl)-2H-tetrazol-5-yl)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate



The title compound is prepared from 2-(5-(4-bromo-3,5-dimethylphenyl)-2H-tetrazol-2-yl)-2-methylpropan-1-ol and methyl 2-((S)-6-((R)-7-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate following a procedure analogous to that described in Step 5 of Intermediate 12. LC (method 15): t_R = 1.25 min; Mass spectrum (ESI⁺): m/z = 587 [M+H]⁺.

Intermediate 119

20 Methyl 2-((3S)-6-((1R)-4-(2-(piperidin-1-yl)pyridin-3-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate



Step 1: 3-((1S)-1-(tert-Butyldimethylsilyloxy)-2,3-dihydro-1H-inden-4-yl)-2-(piperidin-1-yl)pyridine

The title compound is prepared from piperidine and 3-((1S)-1-(tert-butyl-
 5 dimethylsilyloxy)-2,3-dihydro-1H-inden-4-yl)-2-fluoropyridine following a procedure analogous to that described in Step 3 of Intermediate 103. LC (method 7): $t_R = 1.20$ min.

Step 2: (1S)-4-(2-(Piperidin-1-yl)pyridin-3-yl)-2,3-dihydro-1H-inden-1-ol

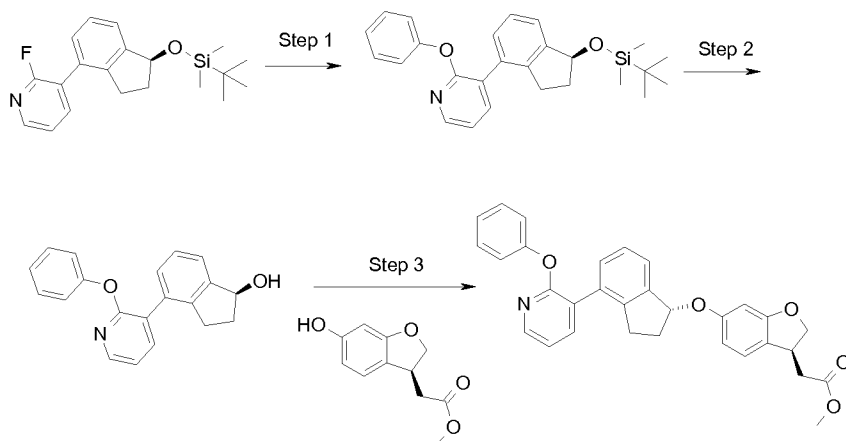
The title compound is prepared from 3-((1S)-1-(tert-butyl-
 10 dimethylsilyloxy)-2,3-dihydro-1H-inden-4-yl)-2-(piperidin-1-yl)pyridine following a procedure analogous to that described in Step 4 of Intermediate 4. LC (method 7): $t_R = 0.73$ min.

Step 3: Methyl 2-((3S)-6-((1R)-4-(2-(piperidin-1-yl)pyridin-3-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

The title compound is prepared from (1S)-4-(2-(piperidin-1-yl)pyridin-3-yl)-2,3-
 15 dihydro-1H-inden-1-ol and (S)-methyl 2-(6-hydroxy-2,3-dihydrobenzofuran-3-yl)acetate following a procedure analogous to that described in Step 3 of Intermediate 12. LC (method 7): $t_R = 0.92$ min.

Intermediate 120

Methyl 2-((3S)-6-((1R)-4-(2-phenoxypyridin-3-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-
 20 dihydrobenzofuran-3-yl)acetate



Step 1: 3-((1S)-1-(tert-Butyldimethylsilyloxy)-2,3-dihydro-1H-inden-4-yl)-2-phenoxy-pyridine

3-((1S)-1-(tert-Butyldimethylsilyloxy)-2,3-dihydro-1H-inden-4-yl)-2-fluoropyridine (220 mg) is dissolved in N-methylpyrrolidone (NMP, 2.5 mL), treated with a solution of LiOtBu in tetrahydrofuran (1 mL, 1 M) and phenole (180 mg) and heated to 200°C for 2 hours. The mixture thus obtained is directly used in the next step.

Step 2: (1S)-4-(2-Phenoxy-pyridin-3-yl)-2,3-dihydro-1H-inden-1-ol

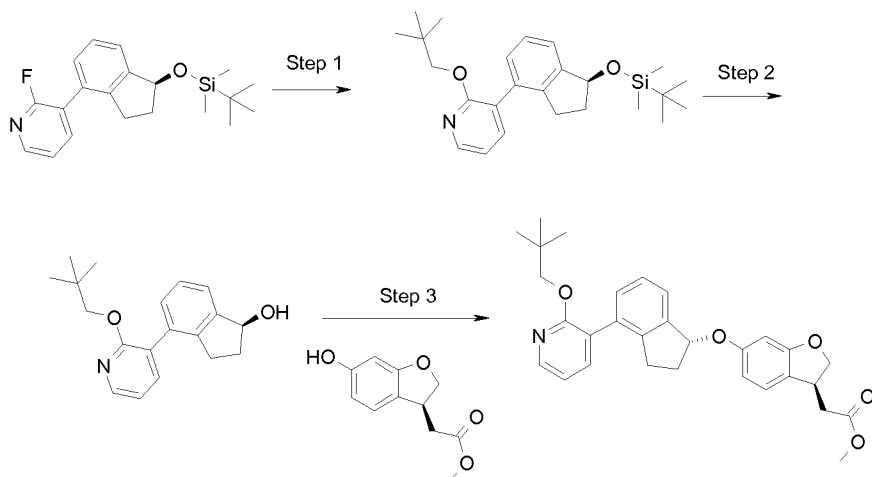
The title compound is prepared from 3-((1S)-1-(tert-butyl(dimethyl)silyloxy)-2,3-dihydro-1H-inden-4-yl)-2-phenoxy-pyridine following a procedure analogous to that described in Step 4 of Intermediate 4. LC (method 7): t_R = 0.98 min.

Step 3: Methyl 2-((3S)-6-((1R)-4-(2-phenoxy-pyridin-3-yl)-2,3-dihydro-1H-inden-1-yl)oxy)-2,3-dihydrobenzofuran-3-yl)acetate

The title compound is prepared from ((1S)-4-(2-phenoxy-pyridin-3-yl)-2,3-dihydro-1H-inden-1-ol and (S)-methyl 2-(6-hydroxy-2,3-dihydrobenzofuran-3-yl)acetate following a procedure analogous to that described in Step 3 of Intermediate 12. LC (method 9): t_R = 1.22 min.

Intermediate 121

Methyl 2-((3S)-6-((1R)-4-(2-(neopentyloxy)pyridin-3-yl)-2,3-dihydro-1H-inden-1-yl)oxy)-2,3-dihydrobenzofuran-3-yl)acetate



Step 1: 3-((1S)-1-(tert-Butyldimethylsilyloxy)-2,3-dihydro-1H-inden-4-yl)-2-(neopentyloxy)pyridine

2,2-Dimethylpropan-1-ol (59 mg) is dissolved at 0°C in N-methylpyrrolidone (NMP, 2 mL), treated with NaH (27 mg, 55% dispersion in mineral oil) and stirred for 15 minutes. The mixture is warmed to room temperature, treated with a solution of 3-((1S)-1-(tert-Butyldimethylsilyloxy)-2,3-dihydro-1H-inden-4-yl)-2-fluoropyridine (200 mg) in N-methylpyrrolidone (NMP, 1 mL) and stirred for 12 hours at 75°C. 2,2-Dimethylpropan-1-ol (59 mg) and NaH (27 mg, 55% dispersion in mineral oil) are added and the mixture is stirred for 4 hours at 80°C. The mixture thus obtained is directly used in the next step.

Step 2: (1S)-4-(2-(Neopentyloxy)pyridin-3-yl)-2,3-dihydro-1H-inden-1-ol

The title compound is prepared from 3-((1S)-1-(tert-butyldimethylsilyloxy)-2,3-dihydro-1H-inden-4-yl)-2-(neopentyloxy)pyridine following a procedure analogous to that described in Step 4 of Intermediate 4. LC (method 7): t_R = 1.11 min.

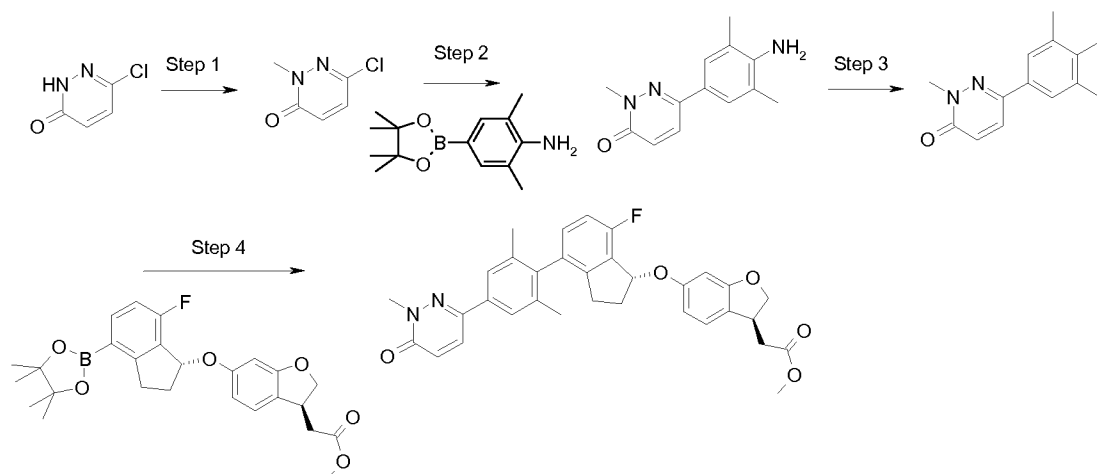
Step 3: Methyl 2-((3S)-6-((1R)-4-(2-(neopentyloxy)pyridin-3-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

The title compound is prepared from (1S)-4-(2-(neopentyloxy)pyridin-3-yl)-2,3-dihydro-1H-inden-1-ol and (S)-methyl 2-(6-hydroxy-2,3-dihydrobenzofuran-3-yl)acetate following a procedure analogous to that described in Step 3 of Intermediate 12. LC (method 15): t_R = 1.32 min.

Intermediate 122

Methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-(1-methyl-6-oxo-1,6-dihydropyridazin-3-

yl)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate



Step 1: 6-Chloro-2-methylpyridazin-3(2H)-one

The title compound is prepared from 6-chloropyridazin-3(2H)-one following a procedure analogous to that described in Step 1 of Intermediate 106.

5 Step 2: 6-(4-Amino-3,5-dimethylphenyl)-2-methylpyridazin-3(2H)-one

The title compound is prepared from 6-chloro-2-methylpyridazin-3(2H)-one and 2,6-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline following a procedure analogous to that described in Step 3 of Intermediate 5. The mixture is stirred for 12 hours at 60°C. LC (method 9): $t_R = 0.78$ min; Mass spectrum (ESI⁺): $m/z = 230$ [M+H]⁺.

10 Step 3: 6-(4-Iodo-3,5-dimethylphenyl)-2-methylpyridazin-3(2H)-one

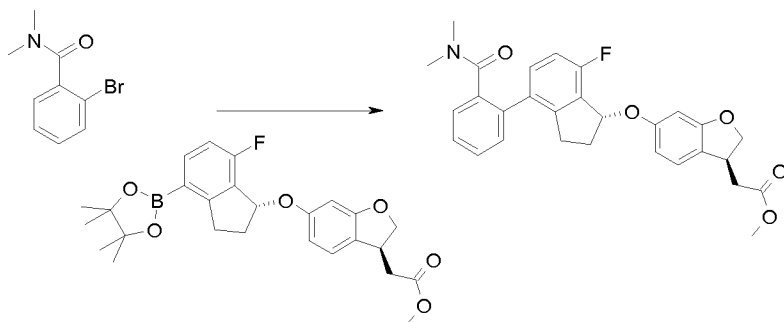
The title compound is prepared from 6-(4-amino-3,5-dimethylphenyl)-2-methylpyridazin-3(2H)-one following a procedure analogous to that described in Step 3 of Intermediate 105. LC (method 7): $t_R = 1.08$ min; Mass spectrum (ESI⁺): $m/z = 341$ [M+H]⁺.

15 Step 4: Methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-(1-methyl-6-oxo-1,6-dihydropyridazin-3-yl)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

The title compound is prepared from 6-(4-iodo-3,5-dimethylphenyl)-2-methylpyridazin-3(2H)-one and methyl 2-((S)-6-((R)-7-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate following a procedure analogous to that described in Step 5 of Intermediate 12. LC (method 9): $t_R = 1.18$ min; Mass spectrum (ESI⁺): $m/z = 555$ [M+H]⁺.

25 Intermediate 123

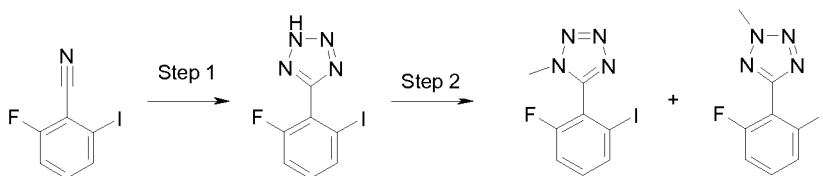
Methyl 2-((3S)-6-((1R)-4-(2-(dimethylcarbamoyl)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate



The title compound is prepared from 2-bromo-N,N-dimethylbenzamide and methyl 2-
 5 ((S)-6-((R)-7-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate following a procedure analogous to that described in Step 5 of Intermediate 12. LC (method 9): $t_R = 1.14$ min; Mass spectrum (ESI⁺): $m/z = 490$ [M+H]⁺.

10 **Intermediate 124**

5-(2-Fluoro-6-iodophenyl)-1-methyl-1H-tetrazole and 5-(2-fluoro-6-iodophenyl)-2-methyl-2H-tetrazole



Step 1: 5-(2-Fluoro-6-iodophenyl)-2H-tetrazole

15 In a microwave vial 2-fluoro-6-iodobenzonitrile (1 g) and azidotributyltin (1.12 mL) are dissolved in toluene (8.4 mL). The vial is sealed and the mixture is heated to 125°C for 72 hours. After cooling to room temperature the solvent is evaporated and the residue is purified by HPLC on reversed phase. Yield: 494 mg; Mass spectrum (ESI⁺): $m/z = 291$ [M+H]⁺.

20 Step 2: 5-(2-Fluoro-6-iodophenyl)-1-methyl-1H-tetrazole and 5-(2-fluoro-6-iodophenyl)-2-methyl-2H-tetrazole

To a solution of 5-(2-fluoro-6-iodophenyl)-2H-tetrazole (986 mg) in N,N-dimethylformamide (3.4 mL) is added K₂CO₃ (530 mg) and MeI (295 μ L) and the mixture is stirred for 12 hours at room temperature. Then the solvent is evaporated
 25 and the residue is partitioned between water and ethyl acetate. The aqueous phase

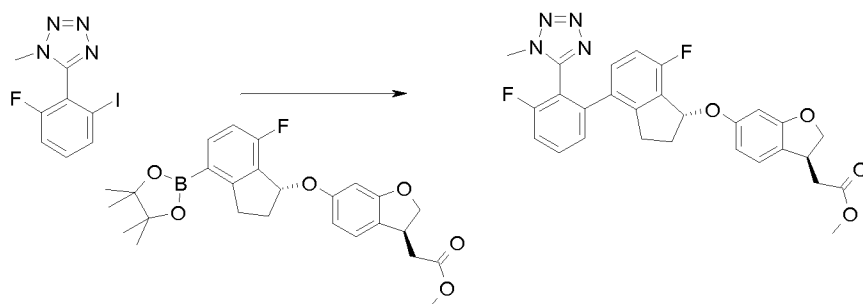
is twice extracted with ethyl acetate and the combined organic phases are washed with brine, dried (Na_2SO_4). After concentration the residue is purified by HPLC on reversed phase to give the title compounds.

5-(2-fluoro-6-iodophenyl)-1-methyl-1H-tetrazole: Yield: 547 mg; Mass spectrum (ESI⁺): $m/z = 305$ [M+H]⁺.

5-(2-fluoro-6-iodophenyl)-2-methyl-2H-tetrazole: Yield: 457 mg; Mass spectrum (ESI⁺): $m/z = 305$ [M+H]⁺.

Intermediate 125

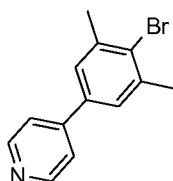
10 Methyl 2-((3S)-6-((1R)-7-fluoro-4-(3-fluoro-2-(1-methyl-1H-tetrazol-5-yl)phenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate



In a microwave vial methyl 2-((S)-6-((R)-7-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate (100 mg), 5-(2-fluoro-6-iodophenyl)-1-methyl-1H-tetrazole (78 mg), K_3PO_4 (136 mg) are suspended in 1,4-dioxane (3 mL) and purged for 10 minutes with argon. [1,3-Bis(2,6-di-3-pentylphenyl)imidazol-2-ylidene](3-chloropyridyl)palladium(II) dichloride (8.5 mg) is added, the vial is sealed and the mixture is stirred at 100°C for 12 hours. After cooling to room temperature the solvents are evaporated and the product thus obtained is used directly in the next step.

Intermediate 126

4-(4-Bromo-3,5-dimethyl-phenyl)-pyridine

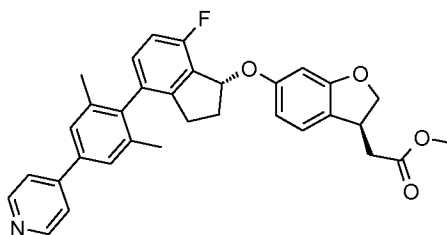


25 The title compound is prepared from 4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-pyridine and 2-bromo-5-iodo-1,3-dimethyl-benzene following a procedure analogous

to that described in Step 1 of Intermediate 96. LC (method 9): $t_R = 0.90$ min; Mass spectrum (ESI⁺): $m/z = 262/264$ (Br) [M+H]⁺.

Intermediate 127

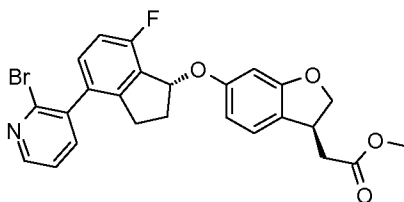
- 5 {{(S)-6-[(R)-4-(2,6-Dimethyl-4-pyridin-4-yl-phenyl)-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester



- The title compound is prepared from {{(S)-6-[(R)-7-fluoro-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester and 4-(4-bromo-3,5-dimethyl-phenyl)-pyridine following a procedure analogous to that described in Step 5 of Intermediate 12. LC (method 9): $t_R = 1.08$ min; Mass spectrum (ESI⁺): $m/z = 524$ [M+H]⁺.
- 10

Intermediate 128

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

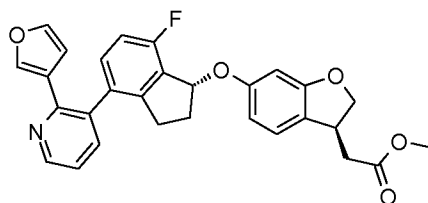


- The title compound is prepared from {{(S)-6-[(R)-7-fluoro-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester and 2-bromo-3-iodo-pyridine following a procedure analogous to that described in Step 1 of Intermediate 96. LC (method 9): $t_R = 1.15$ min; Mass spectrum (ESI⁺): $m/z = 498/500$ (Br) [M+H]⁺.
- 20

Intermediate 129

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

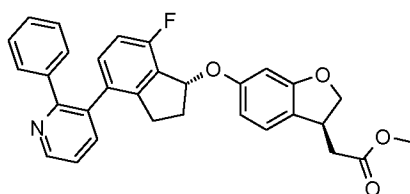
318



The title compound is prepared from {(S)-6-[(R)-4-(2-bromo-pyridin-3-yl)-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester and furan-3-boronic acid following a procedure analogous to that described in Step 1 of Intermediate 96. LC (method 9): t_R = 1.04 min; Mass spectrum (ESI^+): m/z = 486 $[M+H]^+$.

Intermediate 130

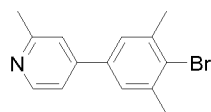
{(S)-6-[(R)-7-Fluoro-4-(2-phenyl-pyridin-3-yl)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester



The title compound is prepared from {(S)-6-[(R)-4-(2-bromo-pyridin-3-yl)-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester and phenylboronic acid following a procedure analogous to that described in Step 1 of Intermediate 96. LC (method 9): t_R = 1.15 min; Mass spectrum (ESI^+): m/z = 496 $[M+H]^+$.

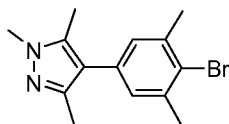
Intermediate 131

4-(4-Bromo-3,5-dimethyl-phenyl)-2-methyl-pyridine

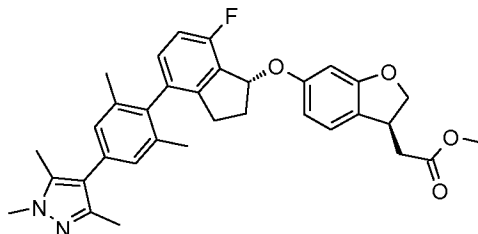


The title compound is prepared from 2-methyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-pyridine and 2-bromo-5-iodo-1,3-dimethyl-benzene following a procedure analogous to that described in Step 1 of Intermediate 96. LC (method 9): t_R = 0.87 min; Mass spectrum (ESI^+): m/z = 276/278 (Br) $[M+H]^+$.

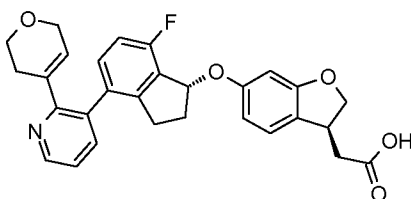
Intermediate 132

4-(4-Bromo-3,5-dimethyl-phenyl)-1,3,5-trimethyl-pyrazole

The title compound is prepared from 4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1,3,5-trimethyl-pyrazole and 2-bromo-5-iodo-1,3-dimethyl-benzene following a procedure analogous to that described in Step 1 of Intermediate 96. LC (method 7): $t_R = 1.09$ min; Mass spectrum (ESI⁺): $m/z = 293/295$ (Br) [M+H]⁺.

Intermediate 133{(S)-6-[(R)-4-(2,6-Dimethyl-4-(1,3,5-trimethyl-pyrazol-4-yl)-phenyl)-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-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester and 4-(4-bromo-3,5-dimethyl-phenyl)-1,3,5-trimethyl-pyrazole following a procedure analogous to that described in Step 5 of Intermediate 12. LC (method 9): $t_R = 1.24$ min; Mass spectrum (ESI⁺): $m/z = 555$ [M+H]⁺.

Intermediate 134{(S)-6-[(R)-7-Fluoro-4-(2-(3,6-dihydropyran-4-yl)-pyridin-3-yl)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid

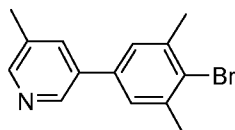
The methyl ester of the title compound is prepared from {(S)-6-[(R)-4-(2-bromopyridin-3-yl)-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester and 4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-3,6-dihydropyran following a procedure analogous to that described in Step 1 of Intermediate 96. Saponification

of the methyl ester, {(S)-6-[(R)-7-fluoro-4-(3,6-dihydropyran-4-yl-pyridin-3-yl)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester, gives the title compound following a procedure analogous to that described for Example 10. LC (method 9): t_R = 0.93 min; Mass spectrum (ESI⁺): m/z = 488 [M+H]⁺.

5

Intermediate 135

3-(4-Bromo-3,5-dimethyl-phenyl)-5-methyl-pyridine

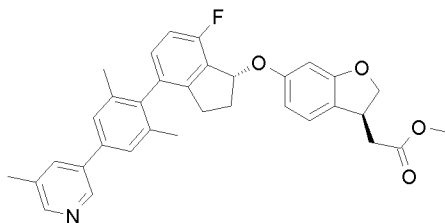


The title compound is prepared from 5-methyl-pyridine-3-boronic acid and 2-bromo-5-iodo-1,3-dimethyl-benzene following a procedure analogous to that described in Step 1 of Intermediate 96. LC (method 9): t_R = 0.93 min; Mass spectrum (ESI⁺): m/z = 276/278 (Br) [M+H]⁺.

10

Intermediate 136

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

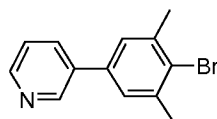


The title compound is prepared from {(S)-6-[(R)-7-fluoro-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester and 3-(4-bromo-3,5-dimethyl-phenyl)-5-methyl-pyridine following a procedure analogous to that described in Step 5 of Intermediate 12.

20

Intermediate 137

3-(4-Bromo-3,5-dimethyl-phenyl)-pyridine



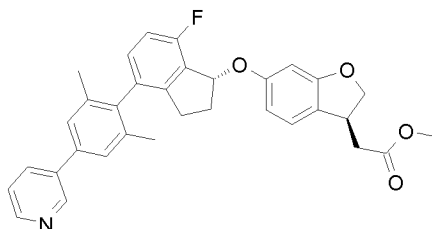
25

The title compound is prepared from pyridine-3-boronic acid and 2-bromo-5-iodo-1,3-dimethyl-benzene following a procedure analogous to that described in Step1 of Intermediate 96. LC (method 9): $t_R = 0.99$ min; Mass spectrum (ESI^+): $m/z = 262/264$ (Br) $[M+H]^+$.

5

Intermediate 138

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

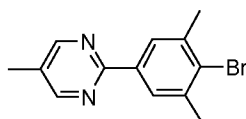


10 The title compound is prepared from {(S)-6-[(R)-7-fluoro-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester and 3-(4-bromo-3,5-dimethyl-phenyl)-pyridine following a procedure analogous to that described in Step 5 of Intermediate 12. Mass spectrum (ESI^+): $m/z = 524$ $[M+H]^+$.

15

Intermediate 139

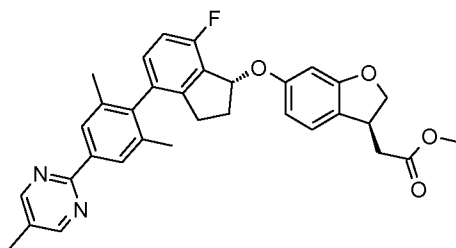
2-(4-Bromo-3,5-dimethyl-phenyl)-5-methyl-pyrimidine



20 The title compound is prepared from 2-bromo-1,3-dimethyl-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzene and 2-bromo-5-methyl-pyrimidine following a procedure analogous to that described in Step 1 of Intermediate 96. LC (method 7): $t_R = 1.20$ min; Mass spectrum (ESI^+): $m/z = 277/279$ (Br) $[M+H]^+$.

Intermediate 140

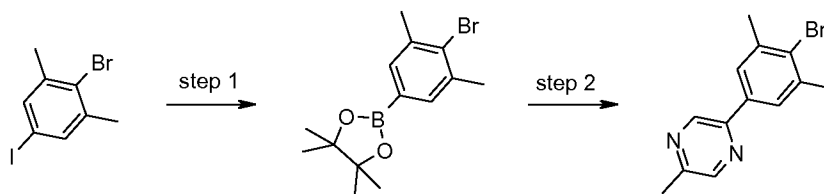
25 {{(S)-6-[(R)-4-(2,6-Dimethyl-4-(5-methyl-pyrimidin-2-yl)-phenyl)-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester



The title compound is prepared from {(S)-6-[(R)-7-fluoro-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester and 2-(4-bromo-3,5-dimethyl-phenyl)-5-methyl-pyrimidine following a procedure analogous to that described in Step 5 of Intermediate 12. LC (method 9): $t_R = 1.27$ min; Mass spectrum (ESI⁺): $m/z = 539$ [M+H]⁺.

Intermediate 141

2-(4-Bromo-3,5-dimethyl-phenyl)-5-methyl-pyrazine



Step 1: 2-bromo-1,3-dimethyl-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzene

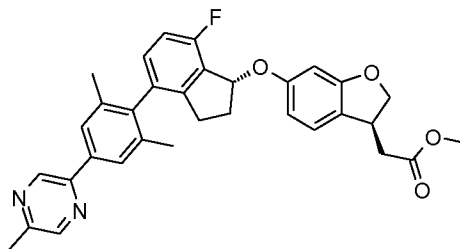
A flask charged with a stir bar, 2-bromo-5-iodo-1,3-dimethyl-benzene (1.0 g), bis-(pinacolato)-diboron (1.0 g), potassium acetate (1.1 g) and dimethyl sulfoxide (10 mL) is purged with argon for 5 min. [1,1'-Bis(diphenylphosphino)-ferrocene]-dichloropalladium(II) (0.26 g) is added at room temperature, and the mixture is stirred at 90 °C for 3 h. After cooling to room temperature, water is added and the resulting mixture is extracted with ethyl acetate. The combined extracts are dried (MgSO₄) and concentrated. The residue is chromatographed on reversed phase (HPLC; acetonitrile/water) to give the title compound. LC (method 9): $t_R = 1.30$ min; Mass spectrum (ESI⁺): $m/z = 311/313$ (Br) [M+H]⁺.

Step 2: 2-(4-bromo-3,5-dimethyl-phenyl)-5-methyl-pyrazine

The title compound is prepared from 2-bromo-1,3-dimethyl-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzene and 2-bromo-5-methyl-pyrazine following a procedure analogous to that described in Step 1 of Intermediate 96. Mass spectrum (ESI⁺): $m/z = 277/279$ (Br) [M+H]⁺.

Intermediate 142

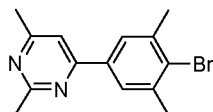
{{(S)-6-[(R)-4-(2,6-Dimethyl-4-(5-methyl-pyrazin-2-yl)-phenyl)-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester



- 5 The title compound is prepared from {{(S)-6-[(R)-7-fluoro-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester and 2-(4-bromo-3,5-dimethyl-phenyl)-5-methyl-pyrazine following a procedure analogous to that described in Step 5 of Intermediate 12.

10 Intermediate 143

4-(4-Bromo-3,5-dimethyl-phenyl)-2,6-dimethyl-pyrimidine

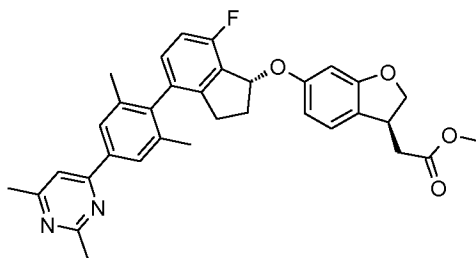


- The title compound is prepared from 2-bromo-1,3-dimethyl-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzene and 4-bromo-2,6-dimethyl-pyrimidine following a procedure analogous to that described in Step 1 of Intermediate 96. LC (method 7):
 15 $t_R = 1.01$ min; Mass spectrum (ESI⁺): $m/z = 291/293$ (Br) [M+H]⁺.

Intermediate 144

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

20

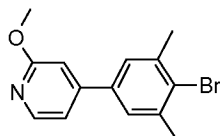


The title compound is prepared from {{(S)-6-[(R)-7-fluoro-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester and 4-(4-bromo-3,5-dimethyl-phenyl)-2,6-dimethyl-pyrimidine following a

procedure analogous to that described in Step 5 of Intermediate 12. LC (method 9): $t_R = 1.24$ min; Mass spectrum (ESI⁺): $m/z = 553$ [M+H]⁺.

Intermediate 145

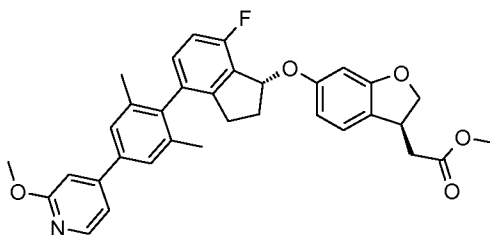
5 4-(4-Bromo-3,5-dimethyl-phenyl)-2-methoxy-pyridine



The title compound is prepared from 2-methoxy-pyridine-4-boronic acid and 2-bromo-5-iodo-1,3-dimethyl-benzene following a procedure analogous to that described in Step 1 of Intermediate 96. LC (method 9): $t_R = 1.24$ min; Mass spectrum (ESI⁺): $m/z = 293/295$ (Br) [M+H]⁺.

Intermediate 146

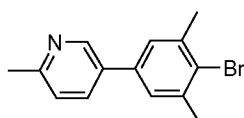
{{(S)-6-[(R)-4-(2,6-Dimethyl-4-(2-methoxy-pyridin-4-yl)-phenyl)-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester



The title compound is prepared from {{(S)-6-[(R)-7-fluoro-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester and 4-(4-bromo-3,5-dimethyl-phenyl)-2-methoxy-pyridine following a procedure analogous to that described in Step 5 of Intermediate 12. LC (method 9): $t_R = 1.30$ min; Mass spectrum (ESI⁺): $m/z = 554$ [M+H]⁺.

Intermediate 147

5-(4-Bromo-3,5-dimethyl-phenyl)-2-methyl-pyridine

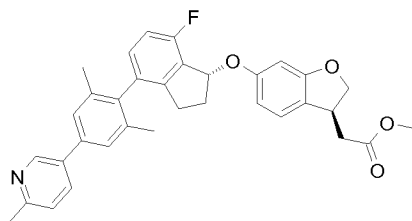


The title compound is prepared from 2-methyl-pyridine-5-boronic acid and 2-bromo-5-iodo-1,3-dimethyl-benzene following a procedure analogous to that described in Step

1 of Intermediate 96. LC (method 9): $t_R = 0.93$ min; Mass spectrum (ESI⁺): $m/z = 276/278$ (Br) [M+H]⁺.

Intermediate 148

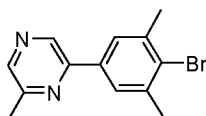
- 5 {{(S)-6-[(R)-4-(2,6-Dimethyl-4-(6-methyl-pyridin-3-yl)-phenyl)-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester}



- The title compound is prepared from {(S)-6-[(R)-7-fluoro-4-(4,4,5,5-tetramethyl-
[1,3,2]dioxaborolan-2-yl)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid
10 methyl ester and 5-(4-bromo-3,5-dimethyl-phenyl)-2-methyl-pyridine following a
procedure analogous to that described in Step 5 of Intermediate 12. LC (method 9):
 $t_R = 1.12$ min; Mass spectrum (ESI⁺): $m/z = 538$ [M+H]⁺.

Intermediate 149

- 15 2-(4-Bromo-3,5-dimethyl-phenyl)-6-methyl-pyrazine

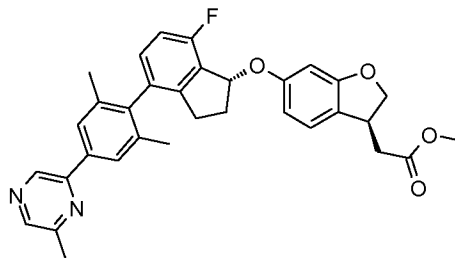


- The title compound is prepared from 2-bromo-1,3-dimethyl-5-(4,4,5,5-tetramethyl-
[1,3,2]dioxaborolan-2-yl)-benzene and 2-bromo-6-methyl-pyrazine following a
procedure analogous to that described in Step 1 of Intermediate 96. LC (method 9):
20 $t_R = 1.04$ min; Mass spectrum (ESI⁺): $m/z = 277/279$ (Br) [M+H]⁺.

Intermediate 150

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

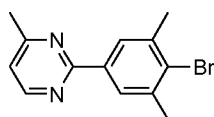
326



The title compound is prepared from {(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 and 2-(4-bromo-3,5-dimethyl-phenyl)-6-methyl-pyrazine following a procedure analogous to that described in Step 5 of Intermediate 12. LC (method 26): $t_R = 0.93$ min; Mass spectrum (ESI⁺): $m/z = 539$ [M+H]⁺.

Intermediate 151

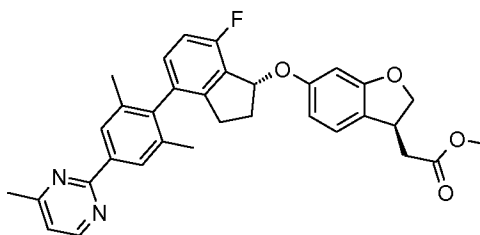
2-(4-Bromo-3,5-dimethyl-phenyl)-4-methyl-pyrimidine



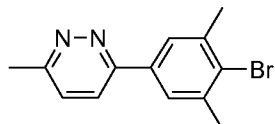
The title compound is prepared from 2-bromo-1,3-dimethyl-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzene and 2-bromo-4-methyl-pyrimidine following a procedure analogous to that described in Step 1 of Intermediate 96. LC (method 9): $t_R = 1.08$ min; Mass spectrum (ESI⁺): $m/z = 277/279$ (Br) [M+H]⁺.

Intermediate 152

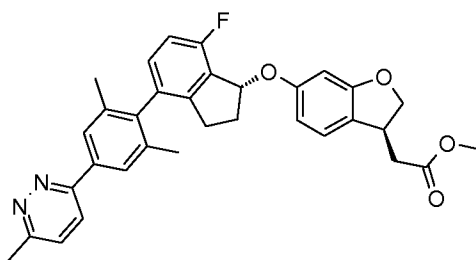
{(S)-6-[(R)-4-(2,6-Dimethyl-4-(4-methyl-pyrimidin-2-yl)-phenyl)-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester



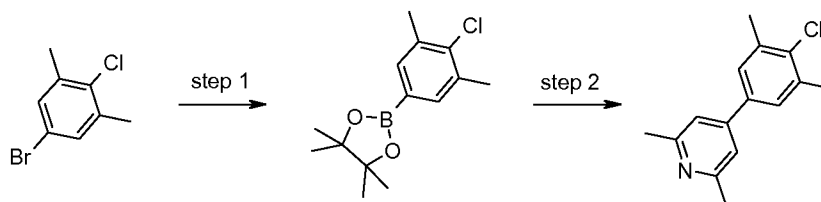
The title compound is prepared from {(S)-6-[(R)-7-fluoro-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester and 2-(4-bromo-3,5-dimethyl-phenyl)-4-methyl-pyrimidine following a procedure analogous to that described in Step 5 of Intermediate 12. LC (method 26): $t_R = 0.96$ min; Mass spectrum (ESI⁺): $m/z = 539$ [M+H]⁺.

Intermediate 1533-(4-Bromo-3,5-dimethyl-phenyl)-6-methyl-pyridazine

- 5 The title compound is prepared from 2-bromo-1,3-dimethyl-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzene and 3-bromo-6-methyl-pyridazine following a procedure analogous to that described in Step1 of Intermediate 96. LC (method 9): t_R = 1.11 min; Mass spectrum (ESI⁺): m/z = 277/279 (Br) [M+H]⁺.

Intermediate 154{(S)-6-[(R)-4-(2,6-Dimethyl-4-(6-methyl-pyridazin-3-yl)-phenyl)-7-fluoro-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-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester and 3-(4-bromo-3,5-dimethyl-phenyl)-6-methyl-pyridazine following a procedure analogous to that described in Step 5 of Intermediate 12. LC (method 26): t_R = 0.75 min; Mass spectrum (ESI⁺): m/z = 539 [M+H]⁺.

Intermediate 1554-(4-Chloro-3,5-dimethyl-phenyl)-2,6-dimethyl-pyridine

Step 1: 2-chloro-1,3-dimethyl-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzene

The title compound is prepared from 5-bromo-2-chloro-1,3-dimethyl-benzene and bis-(pinacolato)-diboron following a procedure analogous to that described in Step 1 of Intermediate **141**. LC (method 7): $t_R = 1.10$ min; Mass spectrum (ESI⁺): $m/z = 552$ [M+H]⁺.

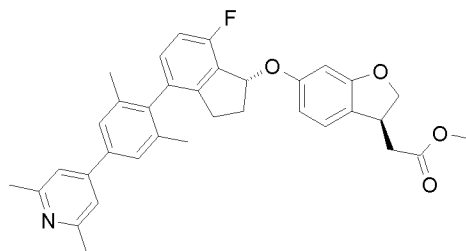
5 Step 2: 4-(4-chloro-3,5-dimethyl-phenyl)-2,6-dimethyl-pyridine

The title compound is prepared from 2-chloro-1,3-dimethyl-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzene and 4-bromo-2,6-dimethyl-pyridine following a procedure analogous to that described in Step 1 of Intermediate 96. Mass spectrum (ESI⁺): $m/z = 246/248$ (Cl) [M+H]⁺.

10

Intermediate 156

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

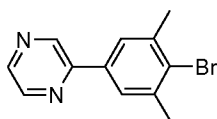


- 15 The title compound is prepared from {{(S)-6-[(R)-7-fluoro-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester and 4-(4-chloro-3,5-dimethyl-phenyl)-2,6-dimethyl-pyridine following a procedure analogous to that described in Step 5 of Intermediate 12. LC (method 7): $t_R = 1.10$ min; Mass spectrum (ESI⁺): $m/z = 552$ [M+H]⁺.

20

Intermediate 157

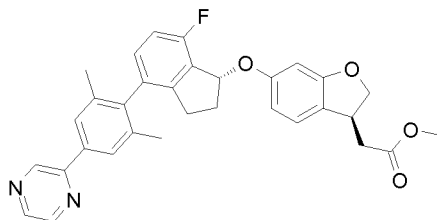
2-(4-Bromo-3,5-dimethyl-phenyl)-pyrazine



- 25 The title compound is prepared from 2-bromo-1,3-dimethyl-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzene and 2-iodo-pyrazine following a procedure analogous to that described in Step 1 of Intermediate 96. LC (method 9): $t_R = 1.12$ min; Mass spectrum (ESI⁺): $m/z = 263/265$ (Br) [M+H]⁺.

Intermediate 158

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

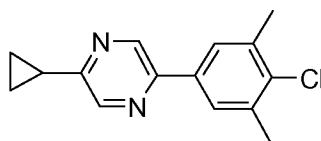


- 5 The title compound is prepared from {{(S)-6-[(R)-7-fluoro-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester and 2-(4-bromo-3,5-dimethyl-phenyl)-pyrazine following a procedure analogous to that described in Step 5 of Intermediate 12. LC (method 9): $t_R = 1.31$ min; Mass spectrum (ESI^+): $m/z = 525 [M+H]^+$.

10

Intermediate 159

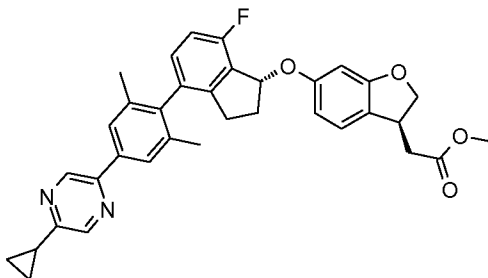
2-(4-Chloro-3,5-dimethyl-phenyl)-5-cyclopropyl-pyrazine



- 15 The title compound is prepared from 2-chloro-1,3-dimethyl-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzene and 2-bromo-5-cyclopropyl-pyrazine following a procedure analogous to that described in Step1 of Intermediate 96. LC (method 11): $t_R = 1.28$ min; Mass spectrum (ESI^+): $m/z = 259/261 (Cl) [M+H]^+$.

Intermediate 160

- 20 {{(S)-6-[(R)-4-(2,6-Dimethyl-4-(5-cyclopropyl-pyrazin-2-yl)-phenyl)-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester

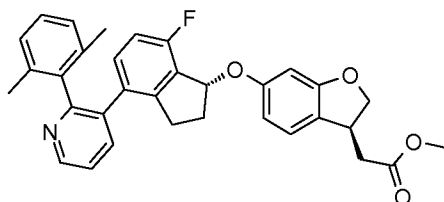


The title compound is prepared from {(S)-6-[(R)-7-fluoro-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester and 2-(4-chloro-3,5-dimethyl-phenyl)-5-cyclopropyl-pyrazine following a procedure analogous to that described in Step 5 of Intermediate 12. LC (method 7):

5 $t_R = 1.31$ min; Mass spectrum (ESI⁺): $m/z = 565$ [M+H]⁺.

Intermediate 161

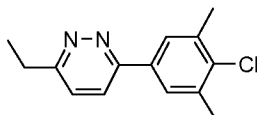
{(S)-6-[(R)-7-Fluoro-4-(2-(2,6-dimethyl-phenyl)-pyridin-3-yl)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester



10 The title compound is prepared from {(S)-6-[(R)-4-(2-bromo-pyridin-3-yl)-7-fluoro-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 in Step 5 of Intermediate 12.

Intermediate 162

3-(4-Chloro-3,5-dimethyl-phenyl)-6-ethyl-pyridazine

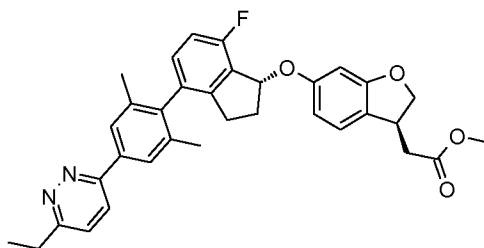


20 The title compound is prepared from 2-chloro-1,3-dimethyl-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzene and 3-bromo-6-ethyl-pyridazine following a procedure analogous to that described in Step 1 of Intermediate 96. LC (method 11): $t_R = 1.00$ min; Mass spectrum (ESI⁺): $m/z = 247/249$ (Cl) [M+H]⁺.

Intermediate 163

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

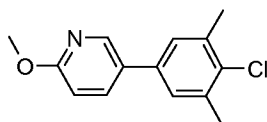
331



The title compound is prepared from {(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 and 3-(4-chloro-3,5-dimethyl-phenyl)-6-ethyl-pyridazine following a procedure analogous to that described in Step 5 of Intermediate 12. LC (method 7): $t_R = 1.14$ min; Mass spectrum (ESI^+): $m/z = 553$ $[M+H]^+$.

Intermediate 164

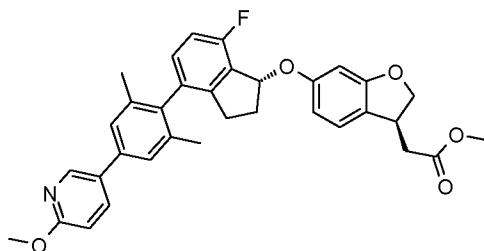
5-(4-Chloro-3,5-dimethyl-phenyl)-2-methoxy-pyridine



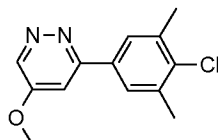
The title compound is prepared from 2-methoxy-pyridine-5-boronic acid and 5-bromo-2-chloro-1,3-dimethyl-benzene following a procedure analogous to that described in Step 1 of Intermediate 96. LC (method 7): $t_R = 1.21$ min; Mass spectrum (ESI^+): $m/z = 248/250$ (Cl) $[M+H]^+$.

Intermediate 165

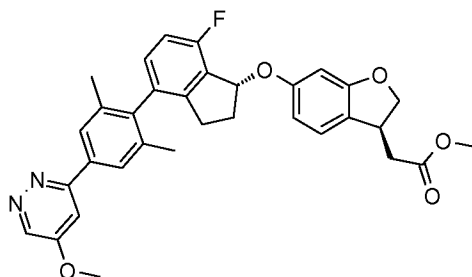
{(S)-6-[(R)-4-(2,6-Dimethyl-4-(6-methoxy-pyridin-3-yl)-phenyl)-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester



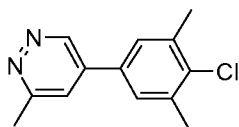
The title compound is prepared from {(S)-6-[(R)-7-fluoro-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester and 5-(4-chloro-3,5-dimethyl-phenyl)-2-methoxy-pyridine following a procedure analogous to that described in Step 5 of Intermediate 12. LC (method 7): $t_R = 1.29$ min; Mass spectrum (ESI^+): $m/z = 554$ $[M+H]^+$.

Intermediate 1663-(4-Chloro-3,5-dimethyl-phenyl)-5-methoxy-pyridazine

- 5 The title compound is prepared from 2-chloro-1,3-dimethyl-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzene and 3-chloro-5-methoxy-pyridazine following a procedure analogous to that described in Step 1 of Intermediate 96. LC (method 11): $t_R = 0.93$ min; Mass spectrum (ESI⁺): $m/z = 249/251$ (Cl) [M+H]⁺.

Intermediate 167{(S)-6-[(R)-4-(2,6-Dimethyl-4-(5-methoxy-pyridazin-3-yl)-phenyl)-7-fluoro-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-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester and 3-(4-chloro-3,5-dimethyl-phenyl)-5-methoxy-pyridazine following a procedure analogous to that described in Step 5 of Intermediate 12. LC (method 11): $t_R = 1.10$ min; Mass spectrum (ESI⁺): $m/z = 555$ [M+H]⁺.

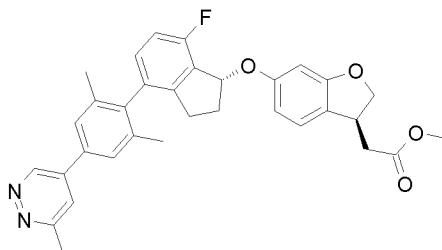
Intermediate 1685-(4-Chloro-3,5-dimethyl-phenyl)-3-methyl-pyridazine

The title compound is prepared from 3-methyl-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-pyridazine and 5-bromo-2-chloro-1,3-dimethyl-benzene

following a procedure analogous to that described in Step 1 of Intermediate 96. LC (method 11): $t_R = 0.91$ min; Mass spectrum (ESI⁺): $m/z = 233/235$ (Cl) [M+H]⁺.

Intermediate 169

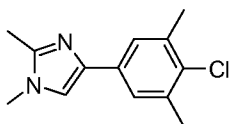
- 5 {{(S)-6-[(R)-4-(2,6-Dimethyl-4-(6-methyl-pyridazin-4-yl)-phenyl)-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester



- The title compound is prepared from {(S)-6-[(R)-7-fluoro-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester and 5-(4-chloro-3,5-dimethyl-phenyl)-3-methyl-pyridazine following a procedure analogous to that described in Step 5 of Intermediate 12. LC (method 11): $t_R = 1.09$ min; Mass spectrum (ESI⁺): $m/z = 539$ [M+H]⁺.

Intermediate 170

- 15 4-(4-Chloro-3,5-dimethyl-phenyl)-1,2-dimethyl-imidazole

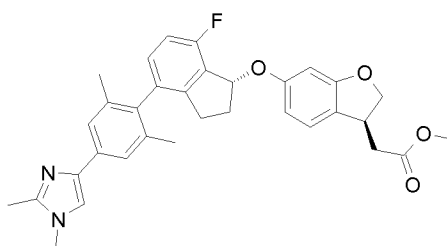


The title compound is prepared from 2-chloro-1,3-dimethyl-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzene and 4-bromo-1,2-dimethyl-imidazole following a procedure analogous to that described in Step 1 of Intermediate 96.

20

Intermediate 171

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

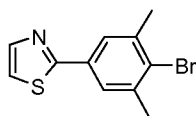


The title compound is prepared from {(S)-6-[(R)-7-fluoro-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester and 4-(4-chloro-3,5-dimethyl-phenyl)-1,2-dimethyl-imidazole following a procedure analogous to that described in Step 5 of Intermediate 12. LC (method 7):

5 $t_R = 1.06$ min; Mass spectrum (ESI⁺): $m/z = 541$ [M+H]⁺.

Intermediate 172

2-(4-Bromo-3,5-dimethyl-phenyl)-thiazole



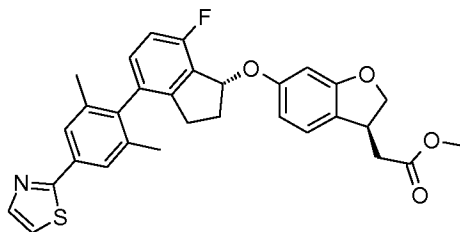
10 A mixture of 2-bromo-5-iodo-1,3-dimethyl-benzene (0.28 g), 2-thiazolylzinc bromide (0.5 mol/L in tetrahydrofuran; 1.9 mL), tetrakis(triphenylphosphine)palladium(0) (52 mg), and tetrahydrofuran (5 mL) under argon atmosphere is stirred at 100 °C for 3 h. After cooling to room temperature, water is added and the resulting mixture is extracted with ethyl acetate. The solvent is evaporated and the residue is

15 chromatographed on silica gel (cyclohexane/ethyl acetate) to give the title compound. LC (method 9): $t_R = 1.19$ min; Mass spectrum (ESI⁺): $m/z = 268/270$ (Br) [M+H]⁺.

Intermediate 173

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

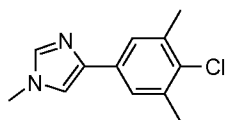
20



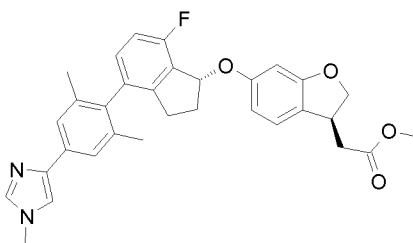
The title compound is prepared from {(S)-6-[(R)-7-fluoro-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester and 2-(4-bromo-3,5-dimethyl-phenyl)-thiazole following a procedure

25 analogous to that described in Step 5 of Intermediate 12. LC (method 7): $t_R = 1.29$ min; Mass spectrum (ESI⁺): $m/z = 530$ [M+H]⁺.

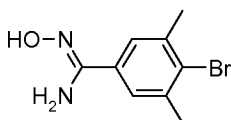
Intermediate 174

4-(4-Chloro-3,5-dimethyl-phenyl)-1-methyl-imidazole

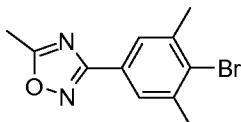
The title compound is prepared from 5-bromo-2-chloro-1,3-dimethyl-benzene and 1-methyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-imidazole following a procedure analogous to that described in Step 1 of Intermediate 96.

Intermediate 175{{(S)-6-[(R)-4-(2,6-Dimethyl-4-(1-methyl-imidazol-4-yl)-phenyl)-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-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester and 4-(4-chloro-3,5-dimethyl-phenyl)-1-methyl-imidazole following a procedure analogous to that described in Step 5 of Intermediate 12.

Intermediate 1764-Bromo-N-hydroxy-3,5-dimethyl-benzamidine

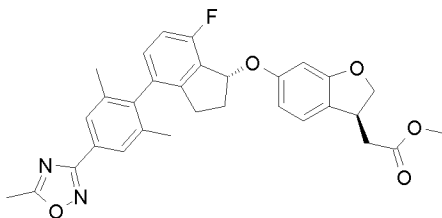
A mixture of 4-bromo-3,5-dimethyl-benzonitrile (1.50 g), hydroxylamine hydrochloride (0.90 g), triethylamine (1.8 mL) and ethanol (30 mL) is stirred at reflux temperature for 4 h. After cooling to room temperature, the mixture is concentrated, the residue is taken up in water, and the resulting mixture is extracted with ethyl acetate. The combined extract is washed with brine, dried (Na₂SO₄), and concentrated. The residue is chromatographed on silica gel (cyclohexane/ethyl acetate 7:3→3:7) to give the title compound. LC (method 11): t_R = 0.73 min; Mass spectrum (ESI⁺): m/z = 243/245 (Br) [M+H]⁺.

Intermediate 1773-(4-Bromo-3,5-dimethyl-phenyl)-5-methyl-[1,2,4]oxadiazole

- 5 Acetic anhydride (0.35 mL) is added to a solution of 4-bromo-N-hydroxy-3,5-dimethylbenzamidinium (0.30 g) in collidine (3 mL) at room temperature. The solution is stirred at room temperature for 1 h and then at 120 °C for 3 h. After cooling to room temperature, the mixture is concentrated, the residue is taken up in water and acetonitrile, and the resulting mixture is filtered. The filtrate is chromatographed on
 10 reversed phase (HPLC; acetonitrile/water/trifluoroacetic acid) to give the title compound. LC (method 11): t_R = 1.20 min; Mass spectrum (ESI^+): m/z = 267/269 (Br) $[M+H]^+$.

Intermediate 178

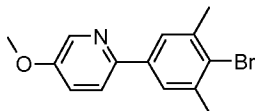
- 15 {(S)-6-[(R)-4-(2,6-Dimethyl-4-(5-methyl- [1,2,4]oxadiazol-3-yl)-phenyl)-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester



- The title compound is prepared from {(S)-6-[(R)-7-fluoro-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid
 20 methyl ester and 3-(4-bromo-3,5-dimethyl-phenyl)-5-methyl-[1,2,4]oxadiazole following a procedure analogous to that described in Step 5 of Intermediate 12. LC (method 11): t_R = 1.28 min; Mass spectrum (ESI^+): m/z = 551 $[M+Na]^+$.

Intermediate 179

- 25 2-(4-Bromo-3,5-dimethyl-phenyl)-5-methoxy-pyridine

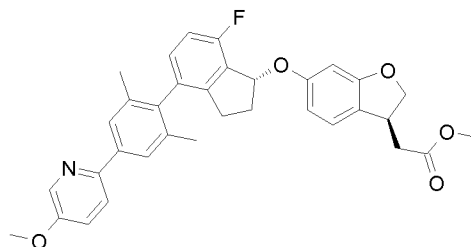


The title compound is prepared from potassium 5-methoxy-pyridine-2-trifluoroborate and 2-bromo-5-iodo-1,3-dimethyl-benzene following a procedure analogous to that described in Step 1 of Intermediate 96. LC (method 8): t_R = 0.72 min; Mass spectrum (ESI⁺): m/z = 292/294 (Br) [M+H]⁺.

5

Intermediate 180

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

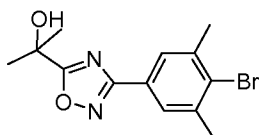


10 The title compound is prepared from {(S)-6-[(R)-7-fluoro-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester and 2-(4-bromo-3,5-dimethyl-phenyl)-5-methoxy-pyridine following a procedure analogous to that described in Step 5 of Intermediate 12. LC (method 8): t_R = 0.98 min; Mass spectrum (ESI⁺): m/z = 554 [M+H]⁺.

15

Intermediate 181

3-(4-Bromo-3,5-dimethyl-phenyl)-5-(2-hydroxy-prop-2-yl)-[1,2,4]oxadiazole



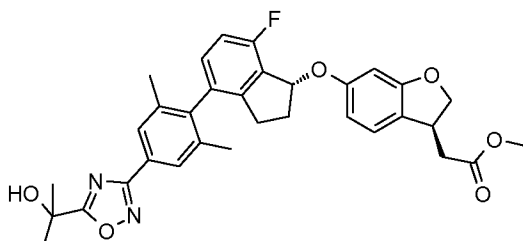
20 2-(Benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU; 0.55 g) is added to a solution of 2-hydroxy-isobutyric acid (0.18 g) and N,N-diisopropyl-ethylamine (1.4 mL) in N,N-dimethylformamide (5 mL) at room temperature. The solution is stirred at room temperature for 10 min prior to the addition of 4-bromo-N-hydroxy-3,5-dimethyl-benzamidinium (0.40 g). The solution is stirred at room temperature for another 10 min and then at 110 °C overnight. After cooling to room temperature, water is added and the resulting mixture is extracted with ethyl acetate. The combined extract is washed with brine, dried (MgSO₄), and concentrated. The residue is chromatographed on reversed phase (HPLC;

25

acetonitrile/water/trifluoroacetic acid) to give the title compound. LC (method 11): t_R = 1.16 min; Mass spectrum (ESI⁺): m/z = 313/315 (Br) [M+H]⁺.

Intermediate 182

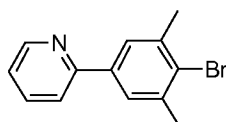
- 5 {{(S)-6-[(R)-4-(2,6-Dimethyl-4-(5-[2-hydroxy-prop-2-yl]-[1,2,4]oxadiazol-3-yl)-phenyl)-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester



- The title compound is prepared from {(S)-6-[(R)-7-fluoro-4-(4,4,5,5-tetramethyl-
[1,3,2]dioxaborolan-2-yl)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid
10 methyl ester and 3-(4-bromo-3,5-dimethyl-phenyl)-5-(2-hydroxy-prop-2-yl)-
[1,2,4]oxadiazole following a procedure analogous to that described in Step 5 of
Intermediate 12. LC (method 11): t_R = 1.25 min; Mass spectrum (ESI⁺): m/z = 573
[M+H]⁺.

15 Intermediate 183

2-(4-Bromo-3,5-dimethyl-phenyl)-pyridine

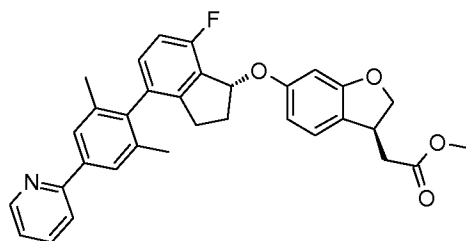


- The title compound is prepared from 2-bromo-1,3-dimethyl-5-(4,4,5,5-tetramethyl-
[1,3,2]dioxaborolan-2-yl)-benzene and 2-bromo-pyridine following a procedure
20 analogous to that described in Step 1 of Intermediate 96. LC (method 7): t_R = 0.91
min; Mass spectrum (ESI⁺): m/z = 262/264 (Br) [M+H]⁺.

Intermediate 184

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

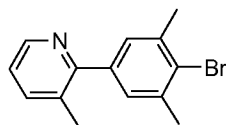
339



The title compound is prepared from {(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 and 2-(4-bromo-3,5-dimethyl-phenyl)-pyridine following a procedure
5 analogous to that described in Step 5 of Intermediate 12. LC (method 7): $t_R = 1.09$
min; Mass spectrum (ESI⁺): $m/z = 524$ [M+H]⁺.

Intermediate 185

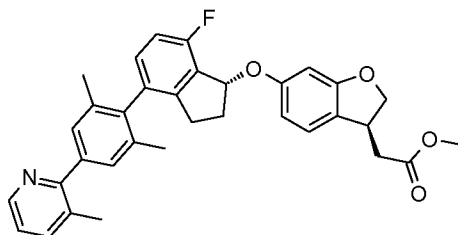
2-(4-Bromo-3,5-dimethyl-phenyl)-3-methyl-pyridine



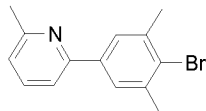
The title compound is prepared from 2-bromo-1,3-dimethyl-5-(4,4,5,5-tetramethyl-
[1,3,2]dioxaborolan-2-yl)-benzene and 2-bromo-3-methyl-pyridine following a
procedure analogous to that described in Step 1 of Intermediate 96. LC (method 7):
 $t_R = 0.88$ min; Mass spectrum (ESI⁺): $m/z = 276/278$ (Br) [M+H]⁺.

Intermediate 186

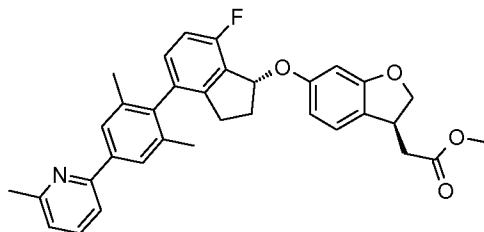
{(S)-6-[(R)-4-(2,6-Dimethyl-4-(3-methyl-pyridin-2-yl)-phenyl)-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester



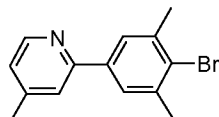
The title compound is prepared from {(S)-6-[(R)-7-fluoro-4-(4,4,5,5-tetramethyl-
[1,3,2]dioxaborolan-2-yl)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid
methyl ester and 2-(4-bromo-3,5-dimethyl-phenyl)-3-methyl-pyridine following a
procedure analogous to that described in Step 5 of Intermediate 12. LC (method 7):
20 $t_R = 1.07$ min; Mass spectrum (ESI⁺): $m/z = 538$ [M+H]⁺.

Intermediate 1872-(4-Bromo-3,5-dimethyl-phenyl)-6-methyl-pyridine

- 5 The title compound is prepared from 2-bromo-1,3-dimethyl-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzene and 2-bromo-6-methyl-pyridine following a procedure analogous to that described in Step 1 of Intermediate 96. LC (method 7): $t_R = 0.88$ min; Mass spectrum (ESI⁺): $m/z = 276/278$ (Br) [M+H]⁺.

Intermediate 188{(S)-6-[(R)-4-(2,6-Dimethyl-4-(6-methyl-pyridin-2-yl)-phenyl)-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester

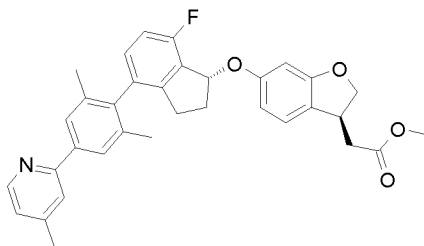
- 15 The title compound is prepared from {(S)-6-[(R)-7-fluoro-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester and 2-(4-bromo-3,5-dimethyl-phenyl)-6-methyl-pyridine following a procedure analogous to that described in Step 5 of Intermediate 12. LC (method 7): $t_R = 1.07$ min; Mass spectrum (ESI⁺): $m/z = 538$ [M+H]⁺.

Intermediate 1892-(4-Bromo-3,5-dimethyl-phenyl)-4-methyl-pyridine

- 25 The title compound is prepared from 2-bromo-1,3-dimethyl-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzene and 2-bromo-4-methyl-pyridine following a procedure analogous to that described in Step 1 of Intermediate 96. LC (method 7): $t_R = 0.90$ min; Mass spectrum (ESI⁺): $m/z = 276/278$ (Br) [M+H]⁺.

Intermediate 190

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



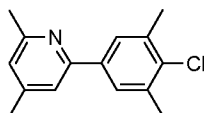
5

The title compound is prepared from {(S)-6-[(R)-7-fluoro-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester and 2-(4-bromo-3,5-dimethyl-phenyl)-4-methyl-pyridine following a procedure analogous to that described in Step 5 of Intermediate 12. LC (method 7):

10 $t_R = 1.07$ min; Mass spectrum (ESI⁺): $m/z = 538$ [M+H]⁺.

Intermediate 191

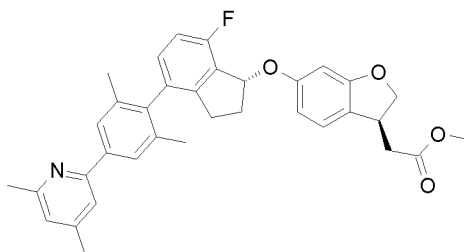
2-(4-Chloro-3,5-dimethyl-phenyl)-4,6-dimethyl-pyridine



15 The title compound is prepared from 2-chloro-1,3-dimethyl-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzene and 2-bromo-4,6-dimethyl-pyridine following a procedure analogous to that described in Step 1 of Intermediate 96. LC (method 7): $t_R = 0.89$ min; Mass spectrum (ESI⁺): $m/z = 246/248$ (Cl) [M+H]⁺.

Intermediate 192

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



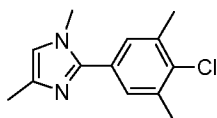
20

The title compound is prepared from {(S)-6-[(R)-7-fluoro-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester and 2-(4-chloro-3,5-dimethyl-phenyl)-4,6-methyl-pyridine following a procedure analogous to that described in Step 5 of Intermediate 12. LC (method 7):

5 $t_R = 1.02$ min; Mass spectrum (ESI⁺): $m/z = 552$ [M+H]⁺.

Intermediate 193

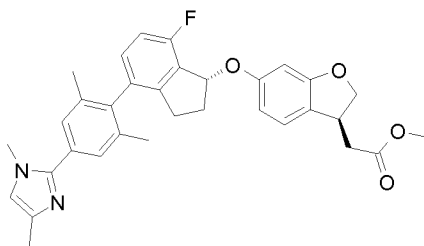
2-(4-Chloro-3,5-dimethyl-phenyl)-1,4-dimethyl-imidazole



10 The title compound is prepared from 2-chloro-1,3-dimethyl-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzene and 2-bromo-1,4-dimethyl-imidazole following a procedure analogous to that described in Step 1 of Intermediate 96. LC (method 7): $t_R = 0.82$ min; Mass spectrum (ESI⁺): $m/z = 235/237$ (Cl) [M+H]⁺.

15 Intermediate 194

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

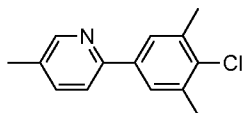


20 The title compound is prepared from {(S)-6-[(R)-7-fluoro-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester and 2-(4-chloro-3,5-dimethyl-phenyl)-1,4-dimethyl-imidazole following a procedure analogous to that described in Step 5 of Intermediate 12. LC (method 7): $t_R = 0.98$ min; Mass spectrum (ESI⁺): $m/z = 541$ [M+H]⁺.

25 Intermediate 195

2-(4-Chloro-3,5-dimethyl-phenyl)-5-methyl-pyridine

343

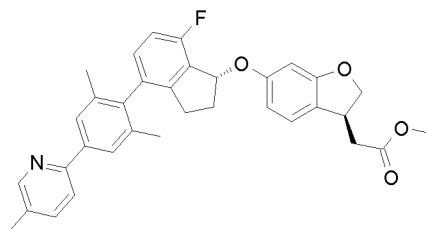


The title compound is prepared from 2-chloro-1,3-dimethyl-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzene and 2-bromo-5-methyl-pyridine following a procedure analogous to that described in Step 1 of Intermediate 96. LC (method 7):

5 $t_R = 0.90$ min; Mass spectrum (ESI⁺): $m/z = 232/234$ (Cl) [M+H]⁺.

Intermediate 196

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



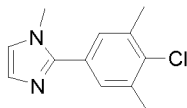
10

The title compound is prepared from {{(S)-6-[(R)-7-fluoro-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester and 2-(4-chloro-3,5-dimethyl-phenyl)-5-methyl-pyridine following a procedure analogous to that described in Step 5 of Intermediate 12. LC (method 7):

15 $t_R = 1.08$ min; Mass spectrum (ESI⁺): $m/z = 538$ [M+H]⁺.

Intermediate 197

2-(4-Chloro-3,5-dimethyl-phenyl)-1-methyl-imidazole

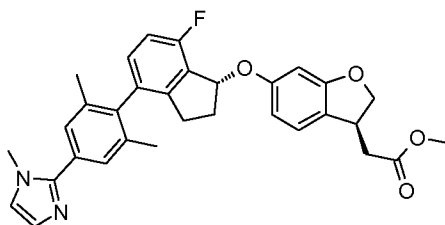


20 The title compound is prepared from 2-chloro-1,3-dimethyl-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzene and 2-iodo-1-methyl-imidazole following a procedure analogous to that described in Step 1 of Intermediate 96. LC (method 7): $t_R = 0.80$ min; Mass spectrum (ESI⁺): $m/z = 221/223$ (Cl) [M+H]⁺.

25 Intermediate 198

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

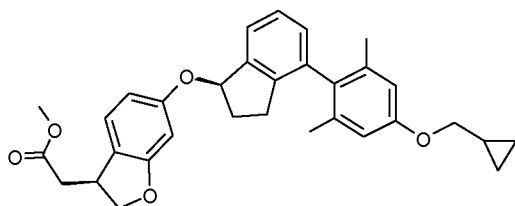
344



The title compound is prepared from {(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 and 2-(4-chloro-3,5-dimethyl-phenyl)-1-methyl-imidazole following a
5 procedure analogous to that described in Step 5 of Intermediate 12. LC (method 7):
 $t_R = 1.02$ min; Mass spectrum (ESI⁺): $m/z = 527$ [M+H]⁺.

Intermediate 199

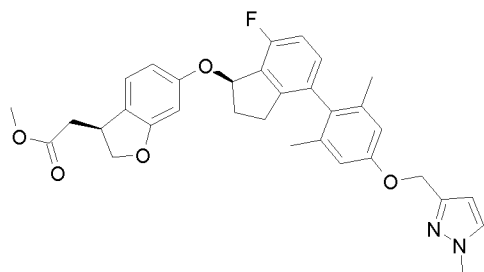
Methyl 2-((S)-6-((R)-4-(4-(cyclopropylmethoxy)-2,6-dimethylphenyl)-2,3-dihydro-1H-
10 inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate



Methyl 2-((S)-6-((R)-4-(4-hydroxy-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-
2,3-dihydrobenzofuran-3-yl)acetate (45 mg) and bromomethylcyclopropane (29.4 μ l)
15 were suspended in dimethylformamide (2 mL) and potassium carbonate (63 mg) was
added. The reaction mixture was shaken for 24 h at 60 °C and then directly
chromatographed by HPLC on reversed phase. The product fractions are collected
and lyophilized to give the title compound. Yield: 17 mg; LC (method 27): $t_R = 1.32$
min.

Intermediate 200

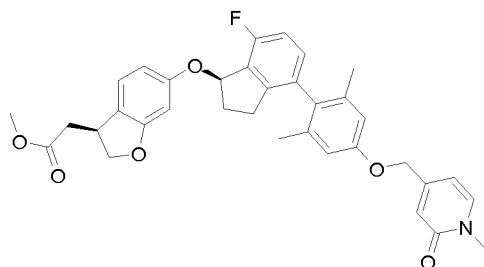
Methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-((1-methyl-1H-pyrazol-3-yl)methoxy)phenyl)-7-
20 fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate



Methyl 2-((S)-6-((R)-7-fluoro-4-(4-hydroxy-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate (Intermediate 51i) (46.3 mg) and 3-(chloromethyl)-1-methyl-1H-pyrazole (39.2 mg) were suspended in dimethylformamide (1.8 mL) and potassium carbonate (62 mg) was added. The reaction mixture was shaken for 24 h at 60 °C and then directly chromatographed by HPLC on reversed phase. The product fractions are collected and lyophilized to give the title compound. Yield: 44.5 mg; LC (method 23): t_R = 2.09 min; Mass spectrum (ESI⁺): m/z = 557 [M+H]⁺.

Intermediate 201

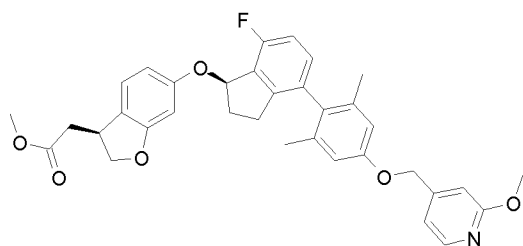
Methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-((1-methyl-2-oxo-1,2-dihydropyridin-4-yl)methoxy)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate



Methyl 2-((S)-6-((R)-7-fluoro-4-(4-hydroxy-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate (Intermediate 51i) (46.3 mg) and 4-(chloromethyl)-1-methylpyridin-2(1H)-one (47.3 mg) were suspended in dimethylformamide (1.8 mL) and potassium carbonate (62 mg) was added. The reaction mixture was shaken for 24 h at 60 °C and then directly chromatographed by HPLC on reversed phase. The product fractions are collected and lyophilized to give the title compound. Yield: 49.6 mg; LC (method 23): t_R = 1.96 min; Mass spectrum (ESI⁺): m/z = 584 [M+H]⁺.

Intermediate 202

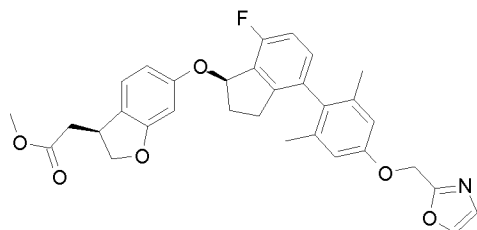
Methyl 2-((S)-6-((R)-7-fluoro-4-(4-((2-methoxypyridin-4-yl)methoxy)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate



Methyl 2-((S)-6-((R)-7-fluoro-4-(4-hydroxy-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate (Intermediate 51i) (46.3 mg) and 4-(chloromethyl)-2-methoxypyridine hydrochloride (58.2 mg) were suspended in dimethylformamide (1.8 mL) and potassium carbonate (62 mg) was added. The reaction mixture was shaken for 24 h at 60 °C and then directly chromatographed by HPLC on reversed phase. The product fractions are collected and lyophilized to give the title compound. Yield: 42 mg; LC (method 23): t_R = 2.21 min; Mass spectrum (ESI⁺): m/z = 584 [M+H]⁺.

Intermediate 203

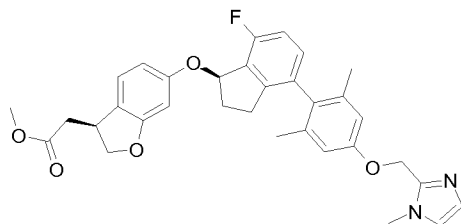
Methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-(oxazol-2-ylmethoxy)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate



Methyl 2-((S)-6-((R)-7-fluoro-4-(4-hydroxy-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate (Intermediate 51i) (46.3 mg) and 2-(chloromethyl)oxazole (25.3 mg) were suspended in dimethylformamide (2.0 mL) and potassium carbonate (62 mg) was added. The reaction mixture was shaken for 24 h at 60 °C. Another portion of 2-(chloromethyl)oxazole (25.3 mg) and potassium carbonate (62 mg) was added and the mixture was shaken again for 24 h at 60 °C and then directly chromatographed by HPLC on reversed phase. The product fractions are collected and lyophilized to give the title compound. Yield: 30.9 mg; LC (method 23): t_R = 2.09 min; Mass spectrum (ESI⁺): m/z = 544 [M+H]⁺.

Intermediate 204

Methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-((1-methyl-1H-imidazol-2-yl)methoxy)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

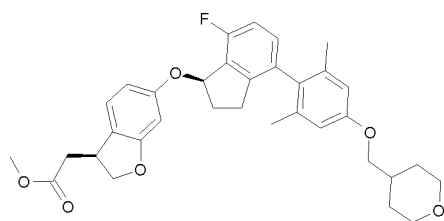


- 5 Methyl 2-((S)-6-((R)-7-fluoro-4-(4-hydroxy-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate (Intermediate 51i) (46.3 mg) and 2-(chloromethyl)-1-methyl-1H-imidazole (39.2 mg) were suspended in dimethylformamide (1.8 mL) and potassium carbonate (62 mg) was added. The reaction mixture was shaken for 24 h at 60 °C. Another portion of 2-(chloromethyl)-1-methyl-1H-imidazole (39.2 mg) and potassium carbonate (62 mg) was added and the mixture was shaken again for 24 h at 60 °C and then directly chromatographed by HPLC on reversed phase. The product fractions are collected and lyophilized to give the title compound. Yield: 31.5 mg; LC (method 23): $t_R = 1.54$ min; Mass spectrum (ESI⁺): $m/z = 557$ [M+H]⁺.

15

Intermediate 205

Methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methoxy)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

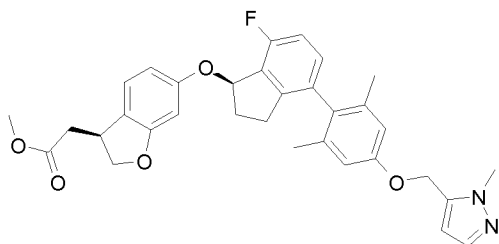


- 20 Methyl 2-((S)-6-((R)-7-fluoro-4-(4-hydroxy-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate (Intermediate 51i) (138 mg) and 4-(bromomethyl)tetrahydro-2H-pyran (160.3 mg) were suspended in dimethylformamide (5 mL) and potassium carbonate (185.7 mg) was added. The reaction mixture was shaken for 48 h at 60 °C and then directly chromatographed by HPLC on reversed phase. The product fractions are collected and lyophilized to give the title compound. Yield: 117 mg; LC (method 23): $t_R = 2.26$ min; Mass spectrum (ESI⁺): $m/z = 561$ [M+H]⁺.

25

Intermediate 206

Methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-((1-methyl-1H-pyrazol-5-yl)methoxy)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate



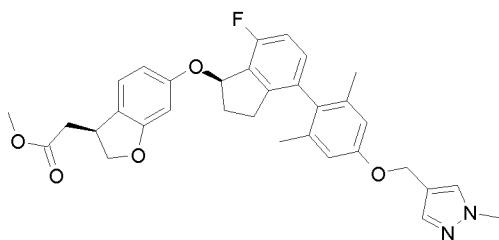
5

Methyl 2-((S)-6-((R)-7-fluoro-4-(4-hydroxy-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate (Intermediate 51i) (46.3 mg) and 5-(chloromethyl)-1-methyl-1H-pyrazole hydrochloride (50.1 mg) were suspended in dimethylformamide (1.8 mL) and potassium carbonate (62 mg) was added. The reaction mixture was shaken for 24 h at 60 °C. Another portion of 5-(chloromethyl)-1-methyl-1H-pyrazole hydrochloride (50.1 mg) and potassium carbonate (62 mg) was added and the mixture was shaken again for 24 h at 60 °C and then directly chromatographed by HPLC on reversed phase. The product fractions are collected and lyophilized to give the title compound. Yield: 27.8 mg; LC (method 11): $t_R = 1.13$ min; Mass spectrum (ESI⁺): $m/z = 557$ [M+H]⁺.

15

Intermediate 207

Methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-((1-methyl-1H-pyrazol-4-yl)methoxy)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate



20

Methyl 2-((S)-6-((R)-7-fluoro-4-(4-hydroxy-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate (Intermediate 51i) (46.3 mg) and 4-(chloromethyl)-1-methyl-1H-pyrazole dihydrochloride (61.1 mg) were suspended in dimethylformamide (1.8 mL) and potassium carbonate (124.4 mg) was added. The reaction mixture was shaken for 24 h at 60 °C and 72 h at 70 °C. Another portion of 4-(chloromethyl)-1-methyl-1H-pyrazole dihydrochloride (124.4 mg) and potassium

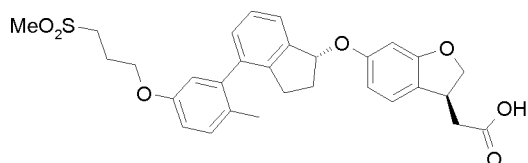
25

carbonate (124.4 mg) was added and the mixture was shaken again for 24 h at 120 °C and then directly chromatographed by HPLC on reversed phase. The product fractions are collected and lyophilized to give the title compound. Yield: 10,1 mg; LC (method 23): t_R = 2.06 min; Mass spectrum (ESI⁺): m/z = 557 [M+H]⁺.

5

Example 1

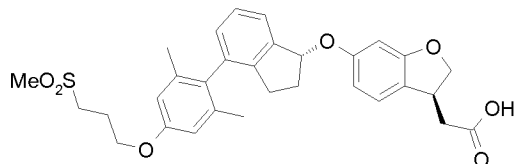
2-((3S)-6-((1R)-4-(2-methyl-5-(3-(methylsulfonyl)propoxy)phenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



- 10 4 M aqueous NaOH solution (39 μ L) is added to a solution of methyl 2-((3S)-6-((1R)-4-(2-methyl-5-(3-(methylsulfonyl)propoxy)phenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate (34 mg) in tetrahydrofuran (0.5 mL) and methanol (0.5 mL) at room temperature. The mixture is stirred at room temperature for 12 hours. The mixture is diluted with water and neutralized with 4 M aqueous HCl
- 15 solution (41 μ L). The resulting mixture is extracted with ethyl acetate, and the combined extract is washed with brine and dried (MgSO₄). The solvent is evaporated and the residue is chromatographed on silica gel (cyclohexane/ethyl acetate 70:30→10:90). The product thus obtained is dissolved in acetonitrile/water (1:1) and lyophilized to give the title compound. Yield: 25 mg; LC (method 1): t_R = 1.04 min;
- 20 Mass spectrum (ESI⁺): m/z = 537 [M+H]⁺.

Example 2

2-((S)-6-((R)-4-(2,6-dimethyl-4-(3-(methylsulfonyl)propoxy)phenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid

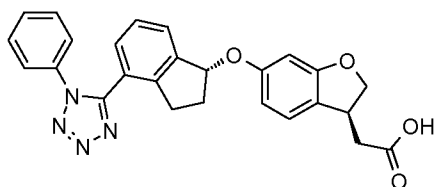


25

The title compound is prepared from methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-(3-(methylsulfonyl)propoxy)phenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate following a procedure analogous to that described in example 1. LC (method 1): t_R = 1.31 min; Mass spectrum (ESI⁺): m/z = 551 [M+H]⁺.

Example 3

2-((3S)-6-((1R)-4-(1-phenyl-1H-tetrazol-5-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



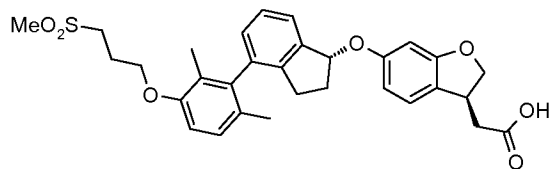
5

The title compound is prepared from methyl 2-((3S)-6-((1R)-4-(1-methyl-1H-tetrazol-5-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate following a procedure analogous to that described in example 1. The mixture is stirred for 1 hour at 35°C. The product is purified by HPLC on reversed phase. LC (method 1): t_R = 1.62 min; Mass spectrum (ESI^+): m/z = 455 $[M+H]^+$.

10

Example 4

2-((3S)-6-((1R)-4-(2,6-dimethyl-3-(3-(methylsulfonyl)propoxy)phenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



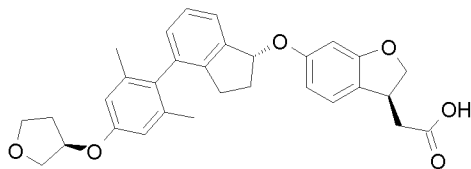
15

The title compound is prepared from methyl 2-((3S)-6-((1R)-4-(2,6-dimethyl-3-(3-(methylsulfonyl)propoxy)phenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate following a procedure analogous to that described in example 1. LC (method 1): t_R = 1.62 min; Mass spectrum (ESI^+): m/z = 551 $[M+H]^+$.

20

Example 5

2-((S)-6-((R)-4-(2,6-Dimethyl-4-((R)-tetrahydrofuran-3-yloxy)phenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid

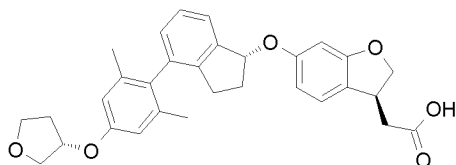


The title compound is prepared from methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-((R)-tetrahydrofuran-3-yloxy)phenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate following a procedure analogous to that described in example 1. LC (method 4): $t_R = 1.85$ min; Mass spectrum (ESI⁻): $m/z = 499$ [M-H]⁻.

5

Example 6

2-((S)-6-((R)-4-(2,6-Dimethyl-4-((S)-tetrahydrofuran-3-yloxy)phenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid

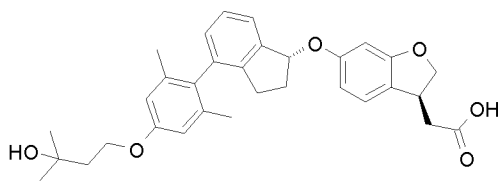


- 10 The title compound is prepared from methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-((S)-tetrahydrofuran-3-yloxy)phenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate following a procedure analogous to that described in example 1. The product is purified by HPLC on reversed phase. LC (method 4): $t_R = 1.86$ min; Mass spectrum (ESI⁻): $m/z = 499$ [M-H]⁻.

15

Example 7

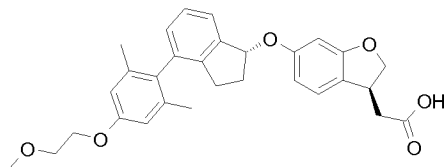
2-((S)-6-((R)-4-(4-(3-Hydroxy-3-methylbutoxy)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



- 20 In a microwave vial a mixture of methyl 2-((S)-6-((R)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate (100 mg), 4-(4-bromo-3,5-dimethylphenoxy)-2-methylbutan-2-ol (70 mg), Na₂CO₃ (1.2 mL of a 2 M aqueous solution), 1,4-dioxane (3 mL) and ethanol (1 mL) is purged for 5 minutes with argon. Tetrakis-triphenylphosphine-palladium-(0) (13 mg) is added,
25 the vial is sealed and the mixture is stirred at 90°C for 12 hours. The mixture is purified by HPLC on reversed phase to give the title compound. Yield: 23 mg; LC (method 5): $t_R = 1.48$ min; Mass spectrum (ESI⁻): $m/z = 515$ [M-H]⁻.

Example 8

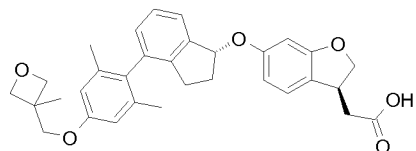
2-((S)-6-((R)-4-(4-(2-methoxyethoxy)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



- 5 1 M aqueous NaOH solution (80 μ L) is added to a solution of methyl 2-((S)-6-((R)-4-(4-(2-methoxyethoxy)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate (28 mg) in isopropanol (2 mL). The mixture is stirred at 40°C for 12 hours. After addition of 1 N hydrochloric acid (80 μ L) the mixture is diluted with diethylether and washed with water and brine. The organic phase is dried
- 10 (MgSO_4). The solvent is evaporated and the residue is chromatographed on silica gel (cyclohexane/ethyl acetate 80:20 $\rightarrow$ 0:100). The product thus obtained is dissolved in acetonitrile/water (1:1) and lyophilized to give the title compound. Yield: 18 mg; LC (method 1): t_R = 1.40 min; Mass spectrum (ESI^+): m/z = 489 $[\text{M}+\text{H}]^+$.

15 **Example 9**

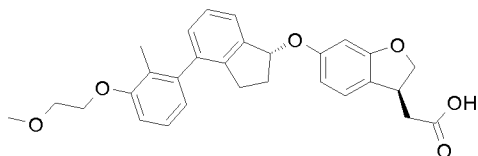
2-((S)-6-((R)-4-(2,6-dimethyl-4-((3-methyloxetan-3-yl)methoxy)phenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



- The title compound is prepared from methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-((3-methyloxetan-3-yl)methoxy)phenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate following a procedure analogous to that described in
- 20 example 8. LC (method 1): t_R = 1.44 min; Mass spectrum (ESI^+): m/z = 515 $[\text{M}+\text{H}]^+$.

Example 10

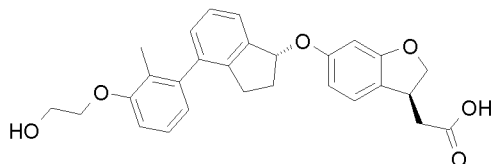
- 25 2-((3S)-6-((1R)-4-(3-(2-Methoxyethoxy)-2-methylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



1 M aqueous NaOH solution (340 μ L) is added to a solution of methyl 2-((3S)-6-((1R)-4-(3-(2-methoxyethoxy)-2-methylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate (33 mg) in tetrahydrofuran (2 mL) and methanol (2 mL) at room temperature. The mixture is stirred at room temperature for 12 hours. The organic solvents are evaporated in vacuo. The residue is diluted with water and neutralized with 1 M aqueous HCl solution (340 μ L). The mixture is stirred for 1 hour. The precipitate formed is filtered off, washed with water and dried in vacuo to give the title compound. Yield: 32 mg; LC (method 3): t_R = 1.43 min; Mass spectrum (ESI⁺): m/z = 475 [M+H]⁺.

Example 11

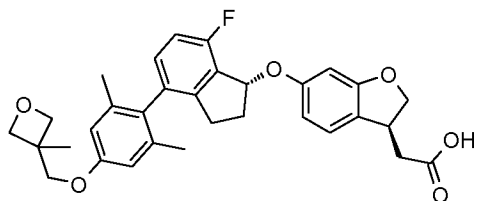
2-((3S)-6-((1R)-4-(3-(2-Hydroxyethoxy)-2-methylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



The title compound is prepared from methyl 2-((3S)-6-((1R)-4-(3-(2-hydroxyethoxy)-2-methylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate following a procedure analogous to that described in example 10. LC (method 3): t_R = 1.26 min; Mass spectrum (ESI⁺): m/z = 461 [M+H]⁺.

Example 12

2-((S)-6-((R)-4-(2,6-dimethyl-4-((3-methyloxetan-3-yl)methoxy)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid

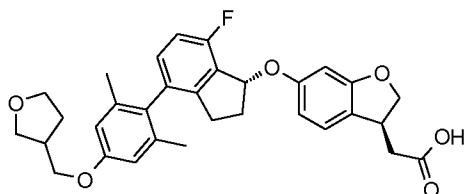


The title compound is prepared from methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-((3-methyloxetan-3-yl)methoxy)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-

dihydrobenzofuran-3-yl)acetate following a procedure analogous to that described in example 1. LC (method 4): $t_R = 1.87$ min; Mass spectrum (ESI⁺): $m/z = 533$ [M+H]⁺.

Example 13

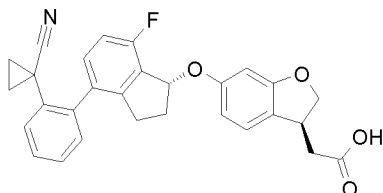
- 5 2-((3S)-6-((1R)-4-(2,6-dimethyl-4-((tetrahydrofuran-3-yl)methoxy)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



- The title compound is prepared from methyl 2-((3S)-6-((1R)-4-(2,6-dimethyl-4-((tetrahydrofuran-3-yl)methoxy)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate following a procedure analogous to that described in example 8. LC (method 1): $t_R = 1.42$ min; Mass spectrum (ESI⁺): $m/z = 533$ [M+H]⁺.

Example 14

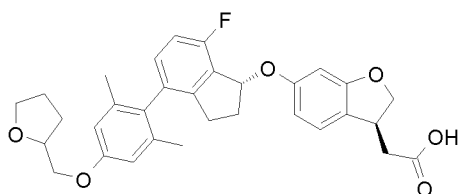
- 15 2-((3S)-6-((1R)-4-(2-(1-Cyanocyclopropyl)phenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



- The title compound is prepared from methyl 2-((3S)-6-((1R)-4-(2-(1-cyanocyclopropyl)phenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate following a procedure analogous to that described in example 10. LC (method 4): $t_R = 1.84$ min; Mass spectrum (ESI⁺): $m/z = 452$ [M+H]⁺.

Example 15

- 2-((3S)-6-((1R)-4-(2,6-dimethyl-4-((tetrahydrofuran-2-yl)methoxy)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid

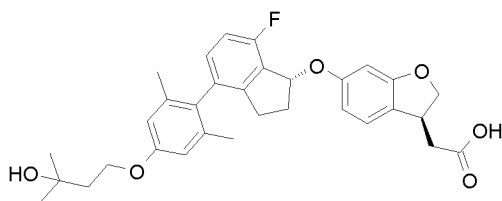


The title compound is prepared from methyl 2-((3S)-6-((1R)-4-(2,6-dimethyl-4-((tetrahydrofuran-2-yl)methoxy)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate following a procedure analogous to that described in example 8. LC (method 1): t_R = 1.42 min; Mass spectrum (ESI⁺): m/z = 533 [M+H]⁺.

5

Example 16

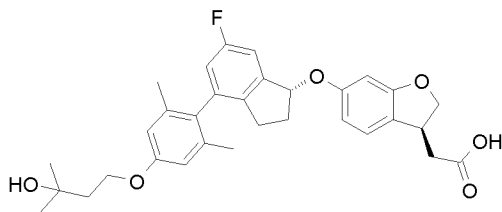
2-((S)-6-((R)-7-Fluoro-4-(4-(3-hydroxy-3-methylbutoxy)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



- 10 The title compound is prepared from methyl 2-((S)-6-((R)-7-fluoro-4-(4-(3-hydroxy-3-methylbutoxy)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate following a procedure analogous to that described in example 10. LC (method 4): t_R = 1.85 min; Mass spectrum (ESI⁺): m/z = 535 [M+H]⁺.

15 Example 17

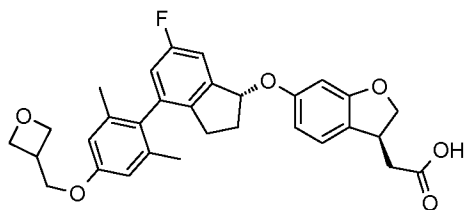
2-((S)-6-((R)-6-Fluoro-4-(4-(3-hydroxy-3-methylbutoxy)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



- 20 The title compound is prepared from methyl 2-((S)-6-((R)-6-fluoro-4-(4-(3-hydroxy-3-methylbutoxy)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate following a procedure analogous to that described in example 10. LC (method 3): t_R = 1.54 min; Mass spectrum (ESI⁺): m/z = 535 [M+H]⁺.

Example 18

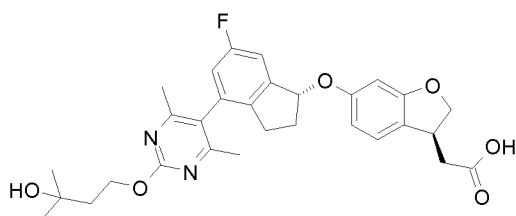
- 25 2-((S)-6-((R)-4-(2,6-Dimethyl-4-((3-methyloxetan-3-yl)methoxy)phenyl)-6-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



The title compound is prepared from methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-((3-methoxypropoxy)methoxy)phenyl)-6-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate following a procedure analogous to that described in
 5 example 10. LC (method 3): t_R = 1.56 min; Mass spectrum (ESI^+): m/z = 533 $[M+H]^+$.

Example 19

2-((S)-6-((R)-6-Fluoro-4-(2-(3-hydroxy-3-methylbutoxy)-4,6-dimethylpyrimidin-5-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid

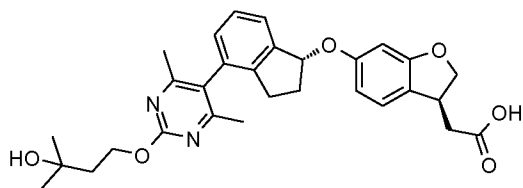


10

The title compound is prepared from methyl 2-((S)-6-((R)-6-fluoro-4-(2-(3-hydroxy-3-methylbutoxy)-4,6-dimethylpyrimidin-5-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate following a procedure analogous to that described in
 15 example 10. LC (method 3): t_R = 1.30 min; Mass spectrum (ESI^+): m/z = 537 $[M+H]^+$.

Example 20

2-((S)-6-((R)-4-(2-(3-Hydroxy-3-methylbutoxy)-4,6-dimethylpyrimidin-5-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



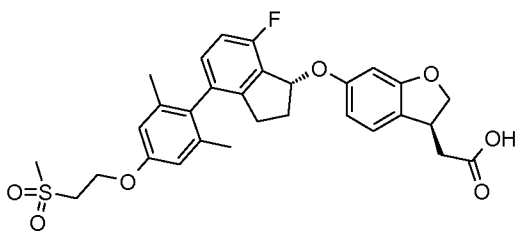
20

The title compound is prepared from methyl 2-((S)-6-((R)-4-(2-(3-hydroxy-3-methylbutoxy)-4,6-dimethylpyrimidin-5-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate following a procedure analogous to that described in
 example 10. LC (method 3): t_R = 1.24 min; Mass spectrum (ESI^+): m/z = 519 $[M+H]^+$.

1 M aqueous NaOH solution (480 μ L) is added to a solution of methyl 2-((3S)-6-((1R)-4-(2,6-dimethyl-4-(2-(methylsulfinyl)ethoxy)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate (180 mg) in methanol (5 mL) at room temperature. The mixture is stirred at room temperature for 12 hours. The mixture is neutralized with 1 M aqueous HCl solution and partitioned between diethylether and brine. The organic phase is dried (MgSO_4) and concentrated. The residue is chromatographed on silica gel (cyclohexane/ethyl acetate 60:40 $\rightarrow$ 10:90) to give the title compound. Yield: 80 mg; LC (method 4): t_R = 1.71 min; Mass spectrum (ESI^+): m/z = 539 $[\text{M}+\text{NH}_4]^+$.

Example 24

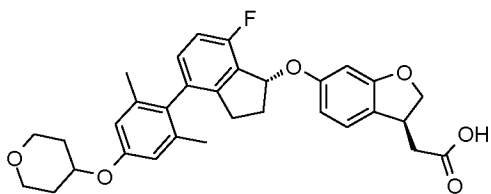
2-((S)-6-((R)-4-(2,6-Dimethyl-4-(2-(methylsulfonyl)ethoxy)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



To a solution of 2-((3S)-6-((1R)-4-(2,6-dimethyl-4-(2-(methylsulfinyl)ethoxy)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid (70 mg) in methanol (1.5 mL) and water (0.75 mL) is added potassium peroxomonosulfate (oxone[®]) (150 mg). The mixture is stirred for 3 hour at room temperature and then potassium peroxomonosulfate (oxone[®]) (80 mg) is added. After stirring for 12 hours at room temperature the mixture is partitioned between ethyl acetate and water. The organic phase is dried (MgSO_4) and concentrated. The residue is chromatographed on silica gel (cyclohexane/ethyl acetate 50:50 $\rightarrow$ 0:100). The product thus obtained is dissolved in acetonitrile/water (1:1) and lyophilized to give the title compound. Yield: 7 mg; LC (method 4): t_R = 1.71 min; Mass spectrum (ESI^+): m/z = 555 $[\text{M}+\text{H}]^+$.

Example 25

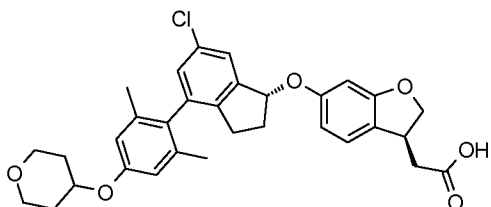
2-((S)-6-((R)-4-(2,6-Dimethyl-4-(tetrahydro-2H-pyran-4-yloxy)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



The title compound is prepared from methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-(tetrahydro-2H-pyran-4-yloxy)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate following a procedure analogous to that described in
 5 example 1. LC (method 4): $t_R = 1.90$ min; Mass spectrum (ESI⁺): $m/z = 533$ [M+H]⁺.

Example 26

2-((S)-6-((R)-6-Chloro-4-(2,6-dimethyl-4-(tetrahydro-2H-pyran-4-yloxy)phenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid

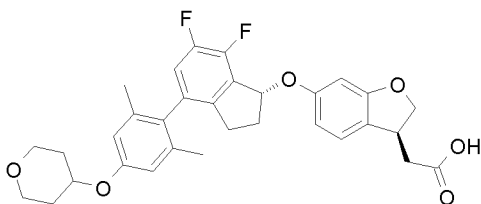


10

The title compound is prepared from methyl 2-((S)-6-((R)-6-chloro-4-(2,6-dimethyl-4-(tetrahydro-2H-pyran-4-yloxy)phenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate following a procedure analogous to that described in
 15 example 10. LC (method 8): $t_R = 0.78$ min; Mass spectrum (ESI⁺): $m/z = 549$ [M+H]⁺.

Example 27

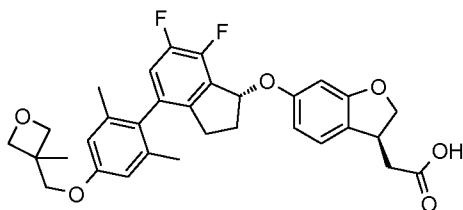
2-((S)-6-((R)-4-(2,6-Dimethyl-4-(tetrahydro-2H-pyran-4-yloxy)phenyl)-6,7-difluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



20 The title compound is prepared from methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-(tetrahydro-2H-pyran-4-yloxy)phenyl)-6,7-difluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate following a procedure analogous to that described in
 example 10. LC (method 4): $t_R = 1.89$ min; Mass spectrum (ESI⁺): $m/z = 551$ [M+H]⁺.

Example 28

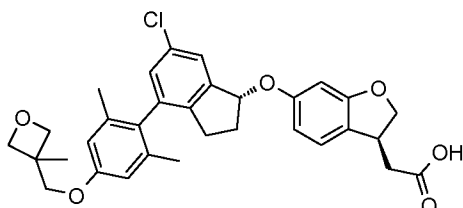
2-((S)-6-((R)-4-(2,6-Dimethyl-4-((3-methyloxetan-3-yl)methoxy)phenyl)-6,7-difluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



- 5 The title compound is prepared from methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-((3-methyloxetan-3-yl)methoxy)phenyl)-6,7-difluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate following a procedure analogous to that described in example 10. LC (method 4): t_R = 1.89 min; Mass spectrum (ESI^+): m/z = 551 $[M+H]^+$.

Example 29

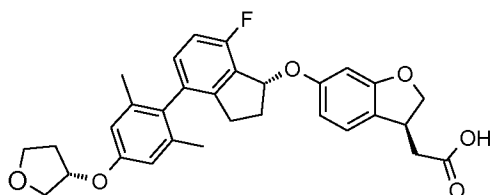
2-((S)-6-((R)-6-Chloro-4-(2,6-dimethyl-4-((3-methyloxetan-3-yl)methoxy)phenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



- 15 The title compound is prepared from methyl 2-((S)-6-((R)-6-chloro-4-(2,6-dimethyl-4-((3-methyloxetan-3-yl)methoxy)phenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate following a procedure analogous to that described in example 10. LC (method 8): t_R = 0.79 min; Mass spectrum (ESI^+): m/z = 549 $[M+H]^+$.

Example 30

- 20 2-((S)-6-((R)-4-(2,6-Dimethyl-4-((S)-tetrahydrofuran-3-yloxy)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid

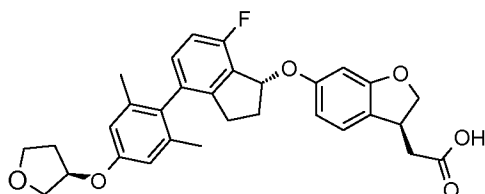


1 M aqueous NaOH solution (585 μ L) is added to a solution of methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-((S)-tetrahydrofuran-3-yloxy)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-

ylxy)-2,3-dihydrobenzofuran-3-yl)acetate (125 mg) in methanol (3 mL). The mixture is stirred at 40°C for 12 hours. After addition of 1 N hydrochloric acid (585 µL) the mixture is diluted with diethylether and washed with water and brine. The organic phase is dried (MgSO₄). The solvent is evaporated and the residue is chromatographed on silica gel (cyclohexane/ethyl acetate 70:30→20:80). The product thus obtained is dissolved in acetonitrile/water (1:1) and lyophilized to give the title compound. Yield: 55 mg; LC (method 4): t_R = 1.82 min; Mass spectrum (ESI⁺): m/z = 519 [M+H]⁺.

10 Example 31

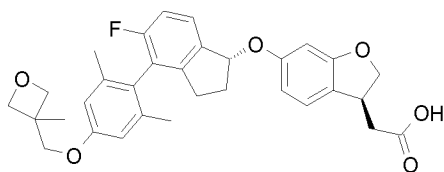
2-((S)-6-((R)-4-(2,6-Dimethyl-4-((R)-tetrahydrofuran-3-yloxy)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



The title compound is prepared from methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-((R)-tetrahydrofuran-3-yloxy)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate following a procedure analogous to that described in example 30. LC (method 4): t_R = 1.82 min; Mass spectrum (ESI⁺): m/z = 519 [M+H]⁺.

Example 32

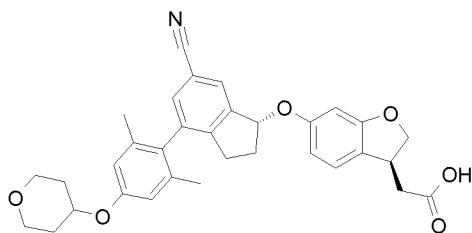
2-((S)-6-((R)-4-(2,6-Dimethyl-4-((3-methyloxetan-3-yl)methoxy)phenyl)-5-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



The title compound is prepared from methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-((3-methyloxetan-3-yl)methoxy)phenyl)-5-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate following a procedure analogous to that described in example 10. LC (method 7): t_R = 1.15 min; Mass spectrum (ESI⁻): m/z = 531 [M-H]⁻.

Example 33

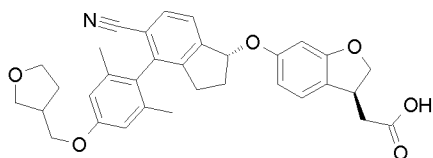
2-((S)-6-((R)-6-Cyano-4-(2,6-dimethyl-4-(tetrahydro-2H-pyran-4-yloxy)phenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



4 M aqueous NaOH solution (200 μ L) is added to a solution of methyl 2-((S)-6-((R)-6-cyano-4-(2,6-dimethyl-4-(tetrahydro-2H-pyran-4-yloxy)phenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate (34 mg) in tetrahydrofuran (1 mL) and methanol (1 mL) at room temperature. The mixture is stirred at room temperature for 3 hours. The organic solvents are evaporated and the residue is partitioned between water and ethyl acetate. 4 M Aqueous HCl solution is added to adjust the pH to 3. The phases are separated and the aqueous phase is extracted twice with ethyl acetate. The combined organic phases are washed with brine, dried (MgSO_4) and concentrated. The residue is purified by HPLC on reversed phase. Product containing fractions are pooled, the acetonitrile is evaporated and the residue acidified to pH 3 by addition of 1 M aqueous HCl solution. The precipitate is filtered off and dried to give the title compound. Yield: 9 mg; LC (method 7): t_R = 1.13 min; Mass spectrum (ESI^-): m/z = 538 $[\text{M}-\text{H}]^-$.

Example 34

2-(((3S)-6-((1R)-5-Cyano-4-(2,6-dimethyl-4-((tetrahydrofuran-3-yl)methoxy)phenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid

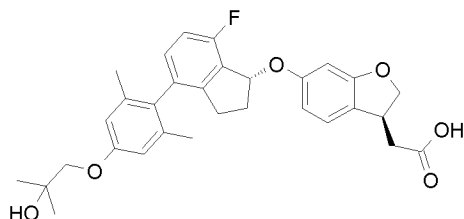


1 M Aqueous NaOH solution (37 μ L) is added to a solution of methyl 2-(((3S)-6-((1R)-5-cyano-4-(2,6-dimethyl-4-((tetrahydrofuran-3-yl)methoxy)phenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate (10 mg) in methanol (2 mL) at room temperature. The mixture is stirred at room temperature for 12 hours, treated with 1 M aqueous NaOH solution (37 μ L) and heated for 12 hours at 50°C. The mixture is neutralized by addition of 1 N aqueous HCl solution and purified by HPLC

on reversed phase to give the title compound. Yield: 2 mg; LC (method 8): t_R = 0.44 min; Mass spectrum (ESI⁺): m/z = 540 [M+H]⁺.

Example 35

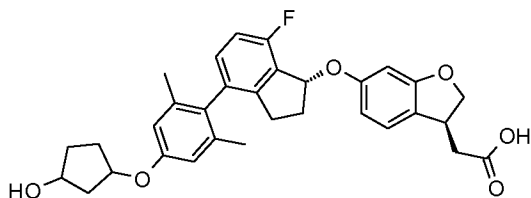
- 5 2-((S)-6-((R)-7-Fluoro-4-(4-(2-hydroxy-2-methylpropoxy)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



- The title compound is prepared from methyl 2-((S)-6-((R)-7-fluoro-4-(4-(2-hydroxy-2-methylpropoxy)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate following a procedure analogous to that described in example 10. LC (method 8): t_R = 0.50 min; Mass spectrum (ESI⁺): m/z = 521 [M+H]⁺.

Example 36

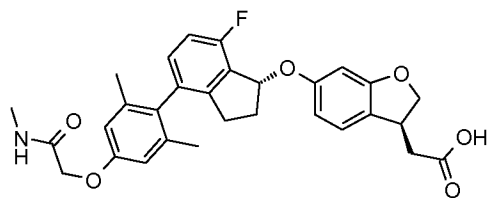
- 15 2-((3S)-6-((1R)-7-Fluoro-4-(4-(3-hydroxycyclopentyloxy)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



- The title compound is prepared from methyl 2-((3S)-6-((1R)-7-fluoro-4-(4-(3-hydroxycyclopentyloxy)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate following a procedure analogous to that described in example 10. The product is purified by chromatography on silica gel (petrole ether/ethyl acetate 50:50→0:10) to give the title compound. LC (method 8): t_R = 0.41 min; Mass spectrum (ESI⁺): m/z = 533 [M+H]⁺.

Example 37

- 25 2-((S)-6-((R)-4-(2,6-Dimethyl-4-(2-(methylamino)-2-oxoethoxy)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid

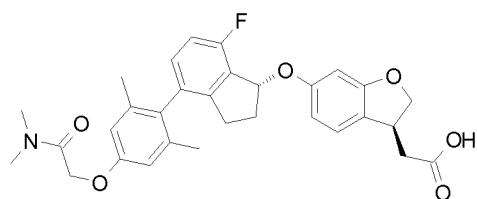


In a microwave vial 2-((S)-6-((R)-7-fluoro-4-(4-(2-methoxy-2-oxoethoxy)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid (15 mg) is dissolved in a 2 M solution of methylamin in tetrahydrofuran (1 mL).

- 5 The vial is sealed and the mixture is heated to 80°C for 12 hours. The mixture is concentrated and the residue is purified by HPLC on reversed phase. Yield: 8 mg; LC (method 9): $t_R = 1.03$ min; Mass spectrum (ESI⁺): $m/z = 520$ [M+H]⁺.

Example 38

- 10 2-((S)-6-((R)-4-(4-(2-(Dimethylamino)-2-oxoethoxy)-2,6-dimethylphenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid

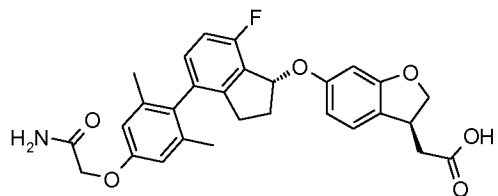


The title compound is prepared from 2-((S)-6-((R)-7-fluoro-4-(4-(2-methoxy-2-oxoethoxy)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-

- 15 dihydrobenzofuran-3-yl)acetic acid and 2 M solution of dimethylamin in tetrahydrofuran following a procedure analogous to that described in example 37. LC (method 9): $t_R = 1.06$ min; Mass spectrum (ESI⁺): $m/z = 534$ [M+H]⁺.

Example 39

- 20 2-((S)-6-((R)-4-(4-(2-Amino-2-oxoethoxy)-2,6-dimethylphenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



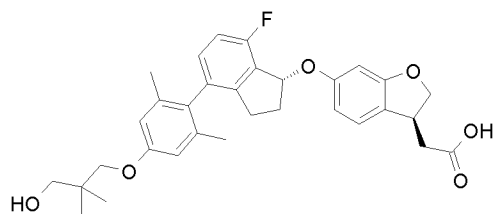
The title compound is prepared from 2-((S)-6-((R)-7-fluoro-4-(4-(2-methoxy-2-oxoethoxy)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-

- 25 dihydrobenzofuran-3-yl)acetic acid and 0.5 M solution of ammonia in 1,4-dioxane

following a procedure analogous to that described in example 37. LC (method 9): t_R = 1.01 min; Mass spectrum (ESI⁺): m/z = 506 [M+H]⁺.

Example 40

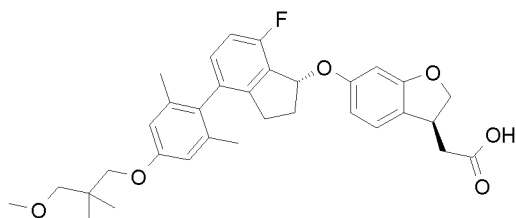
- 5 2-((S)-6-((R)-7-Fluoro-4-(4-(3-hydroxy-2,2-dimethylpropoxy)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



- The title compound is prepared from methyl 2-((S)-6-((R)-7-fluoro-4-(4-(3-hydroxy-2,2-dimethylpropoxy)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate following a procedure analogous to that described in example 30. LC (method 8): t_R = 0.67 min; Mass spectrum (ESI⁺): m/z = 535 [M+H]⁺.
- 10

Example 41

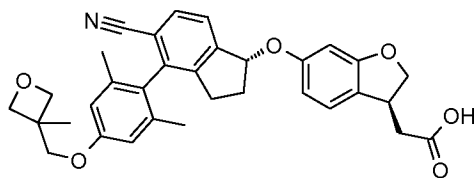
- 15 2-((S)-6-((R)-7-Fluoro-4-(4-(3-methoxy-2,2-dimethylpropoxy)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



- 1 M aqueous NaOH solution (450 μ L) is added to a solution of methyl 2-((S)-6-((R)-7-fluoro-4-(4-(3-methoxy-2,2-dimethylpropoxy)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate (82 mg) in methanol (2 mL). The mixture is stirred at room temperature for 12 hours. 1 N Hydrochloric acid (450 μ L) is added and the residue is purified by HPLC on reversed phase to give the title compound. Yield: 39 mg; LC (method 8): t_R = 0.97 min; Mass spectrum (ESI⁺): m/z = 549 [M+H]⁺.
- 20

25 Example 42

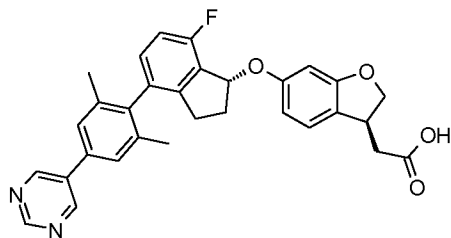
- 2-((S)-6-((R)-5-Cyano-4-(2,6-dimethyl-4-((3-methyloxetan-3-yl)methoxy)phenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



The title compound is prepared from methyl 2-((S)-6-((R)-5-cyano-4-(2,6-dimethyl-4-((3-methyloxetan-3-yl)methoxy)phenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate following a procedure analogous to that described in
 5 example 10. LC (method 8): t_R = 0.43 min; Mass spectrum (ESI⁺): m/z = 540 [M+H]⁺.

Example 43

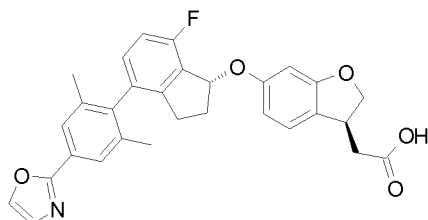
2-((S)-6-((R)-4-(2,6-Dimethyl-4-(pyrimidin-5-yl)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



1 M aqueous NaOH solution (167 μ L) is added to a solution of methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-(pyrimidin-5-yl)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate (35 mg) in methanol (3 mL). The mixture is stirred at 40°C for 1 hour. After addition of 1 N hydrochloric acid (167 μ L) the mixture is diluted
 15 with ethyl acetate and washed with brine. The organic phase is dried (MgSO₄) and concentrated. The product thus obtained is dissolved in 1,4-dioxane and lyophilized to give the title compound. Yield: 29 mg; LC (method 11): t_R = 1.14 min; Mass spectrum (ESI⁺): m/z = 511 [M+H]⁺.

Example 44

2-((S)-6-((R)-4-(2,6-Dimethyl-4-(oxazol-2-yl)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid

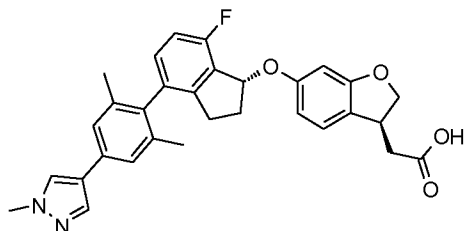


The title compound is prepared from methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-(oxazol-2-yl)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate following a procedure analogous to that described in example 43. LC (method 11): t_R = 1.19 min; Mass spectrum (ESI⁺): m/z = 500 [M+H]⁺.

5

Example 45

2-((S)-6-((R)-4-(2,6-Dimethyl-4-(1-methyl-1H-pyrazol-4-yl)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid

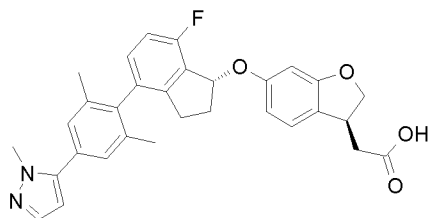


- 10 The title compound is prepared from methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-(1-methyl-1H-pyrazol-4-yl)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate following a procedure analogous to that described in example 43. LC (method 11): t_R = 1.15 min; Mass spectrum (ESI⁺): m/z = 513 [M+H]⁺.

15

Example 46

2-((S)-6-((R)-4-(2,6-Dimethyl-4-(1-methyl-1H-pyrazol-5-yl)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid

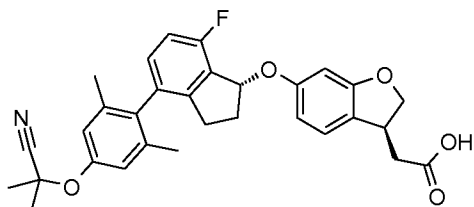


- 20 The title compound is prepared from methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-(1-methyl-1H-pyrazol-5-yl)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate following a procedure analogous to that described in example 43. LC (method 11): t_R = 1.16 min; Mass spectrum (ESI⁺): m/z = 513 [M+H]⁺.

25

Example 47

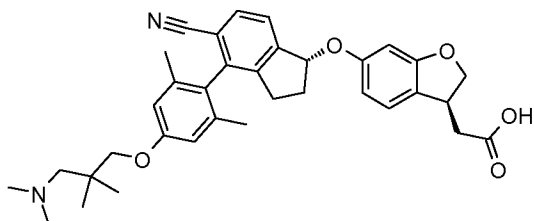
2-((S)-6-((R)-4-(4-(2-Cyanopropan-2-yloxy)-2,6-dimethylphenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



1 M aqueous LiOH solution (500 μ L) is added to a solution of methyl 2-((S)-6-((R)-4-
 5 (4-(2-cyanopropan-2-yloxy)-2,6-dimethylphenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate (130 mg) in tetrahydrofuran (2 mL). The mixture is stirred at room temperature for 48 hours. 1 N Hydrochloric acid (500 μ L) is added and the residue is purified by HPLC on reversed phase. The product thus obtained is chromatographed on silica gel (petrole ether/ethyl acetate 80:20 $\rightarrow$ 20:80)
 10 to give the title compound. Yield: 23 mg; LC (method 12): t_R = 0.67 min; Mass spectrum (ESI⁺): m/z = 516 [M+H]⁺.

Example 48

2-((S)-6-((R)-4-(4-(3-(Dimethylamino)-2,2-dimethylpropoxy)-2,6-dimethylphenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid

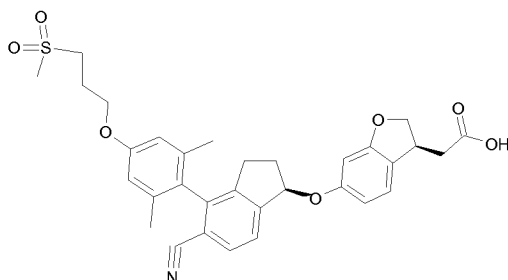


1 M Aqueous NaOH solution (70 μ L) is added to a solution of methyl 2-((S)-6-((R)-4-
 (4-(3-(dimethylamino)-2,2-dimethylpropoxy)-2,6-dimethylphenyl)-7-fluoro-2,3-dihydro-
 1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate (20 mg) in methanol (2 mL) at
 20 room temperature. The mixture is stirred at room temperature for 48 hours, treated with 1 M aqueous NaOH solution (70 μ L) and heated for 4 hours at 50°C. The mixture is neutralized by addition of 1 N aqueous HCl solution and purified by HPLC on reversed phase to give the title compound. Yield: 11 mg; LC (method 14): t_R = 0.95 min; Mass spectrum (ESI⁺): m/z = 562 [M+H]⁺.

25

Example 48a

((S)-6-((R)-5-Cyano-4-[4-(3-methanesulfonyl-propoxy)-2,6-dimethyl-phenyl]-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid



Intermediate 33a (45 mg) and 1 M water solution of NaOH (0.11 mL) are stirred in 2.5 mL of 2-propanol at room temperature for 12 h. The solvent is removed and a 10% water solution of citric acid (10 mL) is added. The reaction mixture is extracted with dichloromethane and the organic phase is separated, dried over sodium sulfate and concentrated under vacuum to give the title compound. Yield: 21 mg. LC (method 20): t_R = 6.29 min; Mass spectrum (ESI⁺): m/z = 576 [M+H]⁺.

10

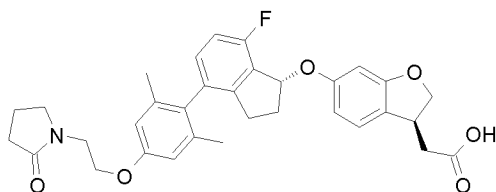
The following examples are prepared in analogy to Example 48a starting from the correspondent ester intermediates.

Example No	Starting intermediate	Structure	Name
48b	33b		((S)-6-((R)-5-Cyano-4-[4-(1,1-dioxo-hexahydro-1-thiopyran-4-ylmethoxy)-2,6-dimethyl-phenyl]-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid
48c	33c		((S)-6-((R)-5-Cyano-4-[4-((R)-1-methanesulfonyl-pyrrolidin-3-yloxy)-2,6-dimethyl-phenyl]-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid

Example No	t_R [Min]	LC method No	(ESI ⁺) or (ESI ⁻): m/z
48b	6,55	20	602 [M+H] ⁺
48c	2,63	20B	603 [M+H] ⁺

Example 49

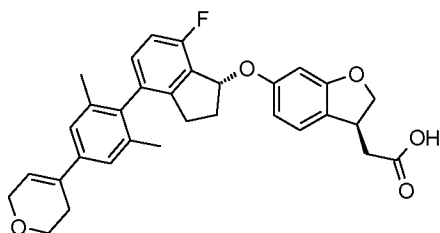
2-((S)-6-((R)-4-(2,6-Dimethyl-4-(2-(2-oxopyrrolidin-1-yl)ethoxy)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



The title compound is prepared from methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-(2-(2-oxopyrrolidin-1-yl)ethoxy)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate following a procedure analogous to that described in example 10. LC (method 8): t_R = 0.35 min; Mass spectrum (ESI^+): m/z = 560 $[M+H]^+$.

Example 50

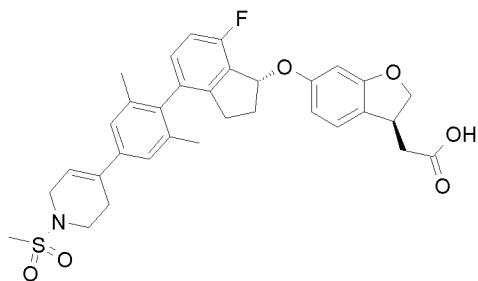
2-((S)-6-((R)-4-(4-(3,6-dihydro-2H-pyran-4-yl)-2,6-dimethylphenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



The title compound is prepared from methyl 2-((S)-6-((R)-4-(4-(3,6-dihydro-2H-pyran-4-yl)-2,6-dimethylphenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate following a procedure analogous to that described in example 10. The reaction is run for 12 hours at room temperature and for 3 hours at 50°C. LC (method 8): t_R = 0.71 min; Mass spectrum (ESI^+): m/z = 515 $[M+H]^+$.

Example 51

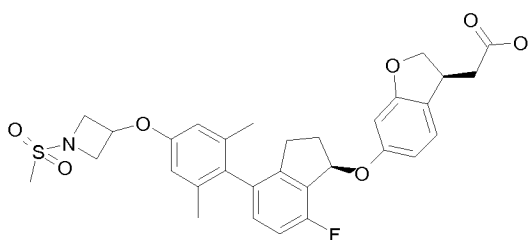
2-((S)-6-((R)-4-(2,6-dimethyl-4-(1-(methylsulfonyl)-1,2,3,6-tetrahydropyridin-4-yl)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



The title compound is prepared from methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-(1-(methylsulfonyl)-1,2,3,6-tetrahydropyridin-4-yl)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate following a procedure analogous to that described in example 10. The reaction is run for 12 hours at room temperature and for 3 hours at 50°C. LC (method 8): $t_R = 0.51$ min; Mass spectrum (ESI⁺): $m/z = 592$ [M+H]⁺.

Example 52

2-((S)-6-((R)-4-(2,6-Dimethyl-4-(1-(methylsulfonyl)azetidin-3-yloxy)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid

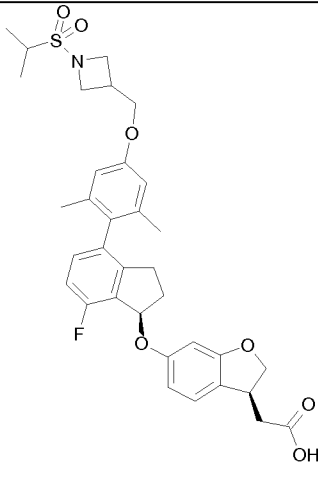
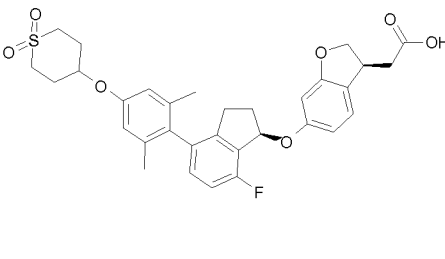
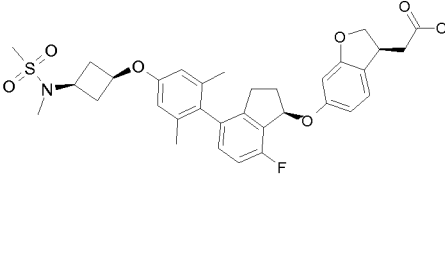
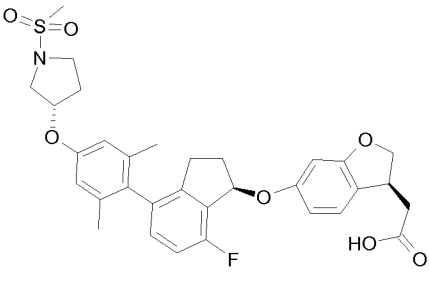


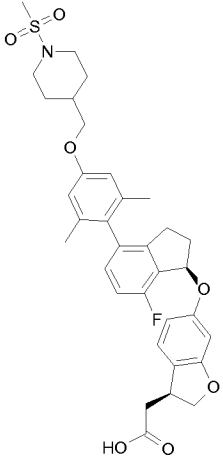
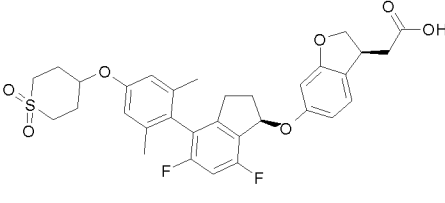
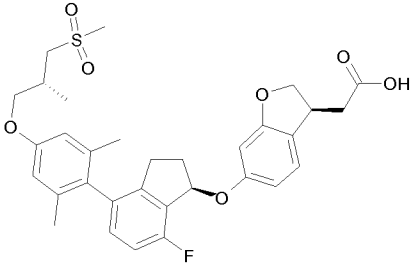
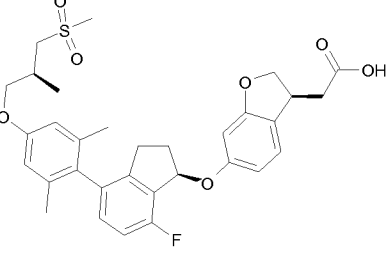
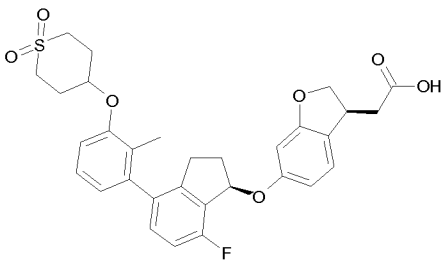
Aqueous NaOH solution (1 M; 39 μ L) is added to a solution of methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-(1-(methylsulfonyl)azetidin-3-yloxy)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate (Intermediate 51a, 50 mg) in water (0.5 mL) and isopropanol (0.5 mL) at ambient temperature. The mixture is stirred at ambient temperature for 12 hours. The mixture is concentrated and acidified with 10% aqueous citric acid solution. The resulting mixture is extracted with dichloromethane, and the extract dried (MgSO₄). The solvent is evaporated and the residue is chromatographed on silica gel (cyclohexane/ethyl acetate 80:30→0:100) to give the title compound. Yield: 35 mg.

LC (method 20): $t_R = 6.19$ min; Mass spectrum (ESI⁻): $m/z = 580$ [M-H]⁻.

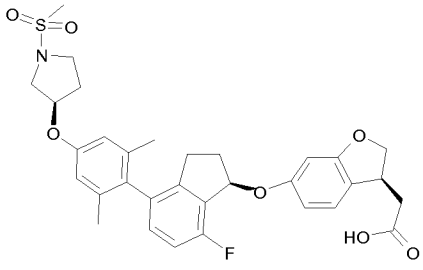
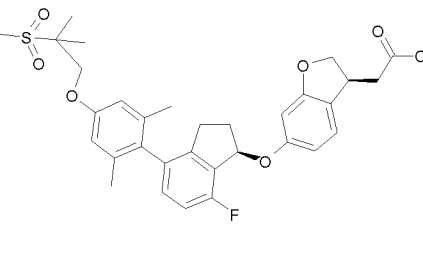
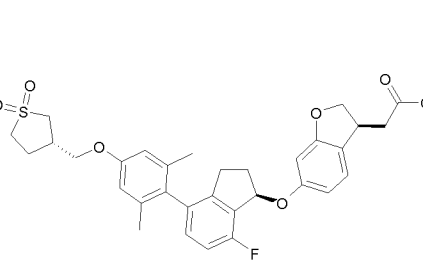
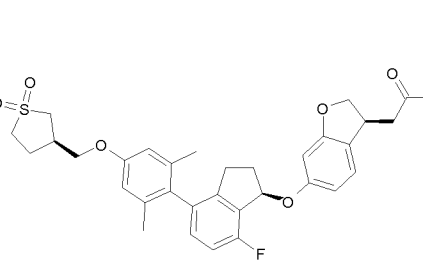
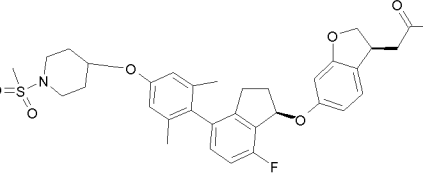
The examples in the following table are prepared from the corresponding starting ester intermediates following a procedure analogous to that described for Example 52.

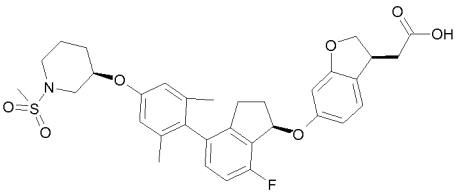
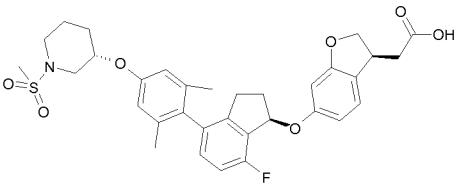
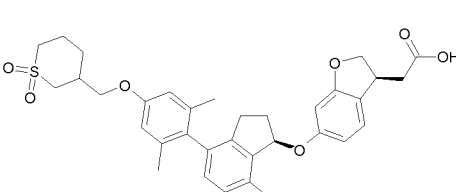
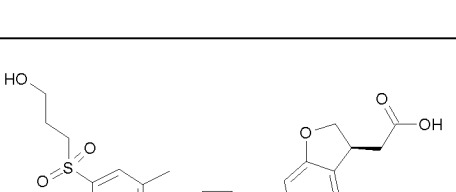
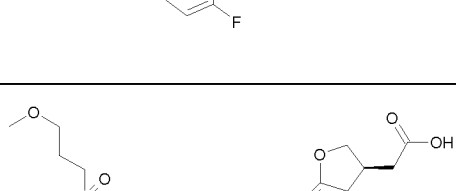
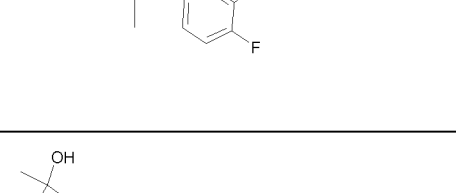
Example No	Starting intermediate	Structure	Name
53	51b		2-((3S)-6-((1R)-4-(2,6-Dimethyl-4-((1,1-dioxo-tetrahydrothiophen-3-yl)methoxy)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid
54	51c		2-((S)-6-((R)-4-(2,6-Dimethyl-4-((1,1-dioxo-tetrahydro-2H-thiopyran-4-yl)methoxy)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid
55	51d		2-((S)-6-((R)-4-(2,6-Dimethyl-4-((1-(methylsulfonyl)azetidin-3-yl)methoxy)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid
56	51e		2-((S)-6-((R)-4-(4-((1-(Ethylsulfonyl)azetidin-3-yl)methoxy)-2,6-dimethylphenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid

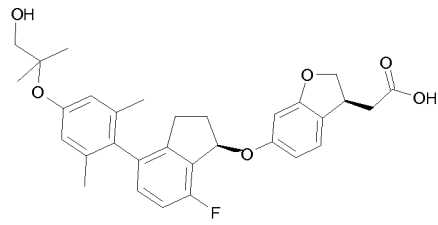
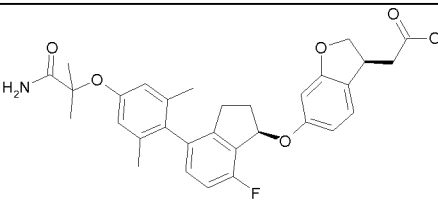
57	51f		2-((S)-6-((R)-7-Fluoro-4-(4-((1-(isopropylsulfonyl)azetidin-3-yl)methoxy)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid
58	51g		2-((S)-6-((R)-4-(2,6-Dimethyl-4-(1,1-dioxo-tetrahydro-2H-thiopyran-4-yloxy)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid
59	51h		2-((S)-6-((R)-4-(2,6-Dimethyl-4-((1s,3S)-3-(N-methylmethylsulfonamido)cyclobutoxy)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid
60	51i		2-((S)-6-((R)-4-(2,6-Dimethyl-4-((S)-1-(methylsulfonyl)pyrrolidin-3-yloxy)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid

61	51k		2-((S)-6-((R)-4-(2,6-Dimethyl-4-((1-(methylsulfonyl)piperidin-4-yl)methoxy)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid
62	51l		2-((S)-6-((R)-4-(2,6-Dimethyl-4-(1,1-dioxo-tetrahydro-2H-thiopyran-4-yloxy)phenyl)-5,7-difluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid
62a	51n		((S)-6-((R)-7-Fluoro-4-[4-((R)-3-methanesulfonyl-2-methylpropoxy)-2,6-dimethyl-phenyl]-indan-1-yloxy}-2,3-dihydro-benzofuran-3-yl)-acetic acid
62b	51o		((S)-6-((R)-7-Fluoro-4-[4-((S)-3-methanesulfonyl-2-methylpropoxy)-2,6-dimethyl-phenyl]-indan-1-yloxy}-2,3-dihydro-benzofuran-3-yl)-acetic acid
62c	51p		((S)-6-((R)-4-[3-(1,1-Dioxo-hexahydro-1-thiopyran-4-yloxy)-2-methyl-phenyl]-7-fluoro-indan-1-yloxy}-2,3-dihydro-benzofuran-3-yl)-acetic acid

62d	51q		((S)-6-((R)-7-Fluoro-4-[4-(1-methanesulfonyl-3-methyl-azetidin-3-ylmethoxy)-2,6-dimethyl-phenyl]-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid
62e	51r		[(S)-6-((R)-4-{4-[2-(1,1-Dioxo-1-isothiazolidin-2-yl)-ethoxy]-2,6-dimethyl-phenyl}-7-fluoro-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl]-acetic acid
62f	51s		((S)-6-((R)-4-[4-(1,1-Dioxo-1-[1,2]thiazinan-4-yloxy)-2,6-dimethyl-phenyl]-7-fluoro-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid
62g	51t		((S)-6-((R)-4-[2,6-Dimethyl-4-(2-methyl-1,1-dioxo-1-[1,2]thiazinan-4-yloxy)-phenyl]-7-fluoro-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid
62h	51u		((S)-6-((R)-7-Fluoro-4-[4-(4-methanesulfonyl-butoxy)-2,6-dimethyl-phenyl]-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid
62i	51la		((S)-6-((R)-5,7-Difluoro-4-[4-(1-methanesulfonyl-azetidin-3-ylmethoxy)-2,6-dimethyl-phenyl]-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid

62j	51v		((S)-6-((R)-7-Fluoro-4-[4-((R)-1-methanesulfonyl-pyrrolidin-3-yloxy)-2,6-dimethyl-phenyl]-indan-1-yloxy}-2,3-dihydro-benzofuran-3-yl)-acetic acid
62k	51w		((S)-6-((R)-7-Fluoro-4-[4-(2-methanesulfonyl-2-methyl-propoxy)-2,6-dimethyl-phenyl]-indan-1-yloxy}-2,3-dihydro-benzofuran-3-yl)-acetic acid
62l	51x		((S)-6-((R)-4-[4-((S)-1,1-Dioxotetrahydro-1-thiophen-3-ylmethoxy)-2,6-dimethyl-phenyl]-indan-1-yloxy}-2,3-dihydro-benzofuran-3-yl)-acetic acid. Absolute configuration unknown
62m	51y		((S)-6-((R)-4-[4-((R)-1,1-Dioxotetrahydro-1-thiophen-3-ylmethoxy)-2,6-dimethyl-phenyl]-indan-1-yloxy}-2,3-dihydro-benzofuran-3-yl)-acetic acid Absolute configuration unknown
62n	51z		((S)-6-((R)-7-Fluoro-4-[4-(1-methanesulfonyl-piperidin-4-yloxy)-2,6-dimethyl-phenyl]-indan-1-yloxy}-2,3-dihydro-benzofuran-3-yl)-acetic acid

62o	51za		((S)-6-{{(R)-7-Fluoro-4-[4-((R)-1-methanesulfonyl-piperidin-3-yloxy)-2,6-dimethyl-phenyl]-indan-1-yloxy}-2,3-dihydro-benzofuran-3-yl)-acetic acid
62p	51zb		((S)-6-{{(R)-7-Fluoro-4-[4-((S)-1-methanesulfonyl-piperidin-3-yloxy)-2,6-dimethyl-phenyl]-indan-1-yloxy}-2,3-dihydro-benzofuran-3-yl)-acetic acid
62q	51zc		((S)-6-{{(R)-4-[4-(1,1-Dioxo-hexahydro-1-thiopyran-3-ylmethoxy)-2,6-dimethyl-phenyl]-7-fluoro-indan-1-yloxy}-2,3-dihydro-benzofuran-3-yl)-acetic acid
62r	51zf		((S)-6-{{(R)-7-Fluoro-4-[4-(3-hydroxy-propane-1-sulfonyl)-2,6-dimethyl-phenyl]-indan-1-yloxy}-2,3-dihydro-benzofuran-3-yl)-acetic acid
62s	51zg		((S)-6-{{(R)-7-Fluoro-4-[4-(3-methoxy-propane-1-sulfonyl)-2,6-dimethyl-phenyl]-indan-1-yloxy}-2,3-dihydro-benzofuran-3-yl)-acetic acid
62t	66a		((S)-6-{{(R)-7-Fluoro-4-[4-(2-hydroxy-2-methyl-propylcarbamoyl)-2,6-dimethyl-phenyl]-indan-1-yloxy}-2,3-dihydro-benzofuran-3-yl)-acetic acid

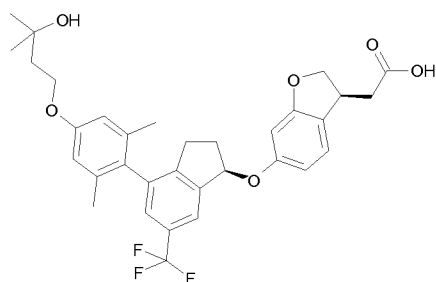
62u	51zd		((S)-6-((R)-7-Fluoro-4-[4-(2-hydroxy-1,1-dimethylethoxy)-2,6-dimethylphenyl]indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid
62w	51ze		((S)-6-((R)-4-[4-(1-carbamoyl-1-methylethoxy)-2,6-dimethylphenyl]-7-fluoroindan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid

Example No	t _R [Min]	LC method No	(ESI ⁺) or (ESI ⁻): m/z
53	6.44	20	579 [M-H] ⁻
54	6.52	20	593 [M-H] ⁻
55	6.45	20	596 [M+H] ⁺
56	6.67	20	608 [M-H] ⁻
57	13.48	21	624 [M+H] ⁺
58	6.33	20	579 [M-H] ⁻
59	6.93	20	610 [M+H] ⁺
60	12.8	21	596 [M+H] ⁺
61	6.93	20	624 [M+H] ⁺
62	12.61	21	599 [M+H] ⁺
62a	6,88	20	583 [M+H] ⁺
62b	6,92	20	583 [M+H] ⁺
62c	8,73	20A	567 [M+H] ⁺
62d	7,07	20	608 [M-H] ⁻
62e	6,33	20	596 [M+H] ⁺
62f	6,35	20	580 [M-H] ⁻
62g	6,81	20	594 [M-H] ⁻
62h	6,84	20	583 [M+H] ⁺
62i	6,38	20	614 [M+H] ⁺
62j	6,47	20	596 [M+H] ⁺
62k	6,53	20	583 [M+H] ⁺
62l	6,73	20	579 [M-H] ⁻
62m	6,83	20	579 [M+H] ⁺

62n	7,20	20	608 [M-H]-
62o	7,10	20	610 [M+H]+
62p	7,18	20	610 [M+H]+
62q	7,04	20	593 [M-H]-
62r	5,66	20	533 [M-H]-
62s	6,50	20	569 [M-H]-
62t	7,78	20A	548 [M-H]-
62u	6,88	20	519 [M-H]-
62w	6,57	20	532 [M-H]-

Example 62aa

2-((S)-6-((R)-4-(4-(3-Hydroxy-3-methylbutoxy)-2,6-dimethylphenyl)-6-(trifluoromethyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



5

The title compound is prepared in analogy to Example 52, starting from Intermediate 52caa.

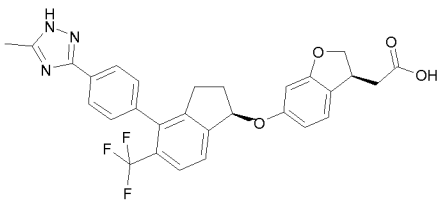
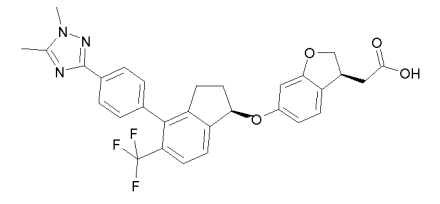
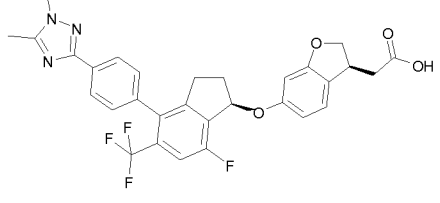
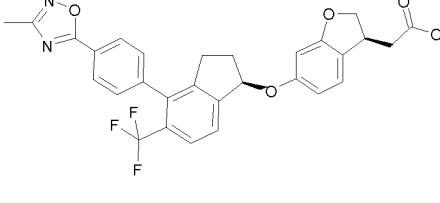
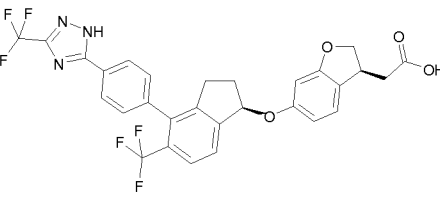
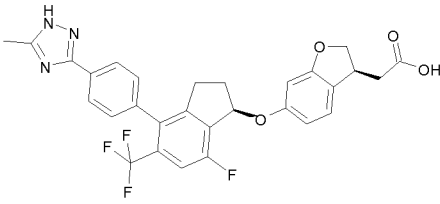
The following examples are prepared in analogy to Example 52, starting from the correspondent ester intermediates.

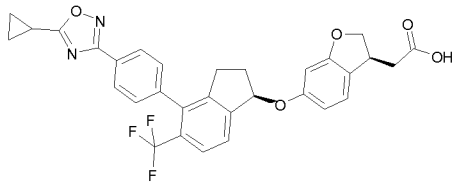
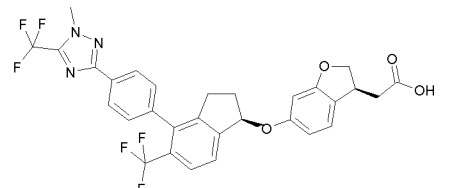
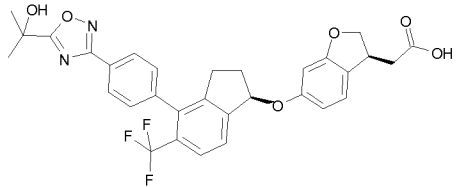
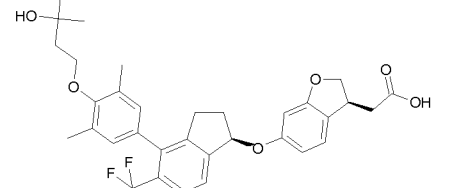
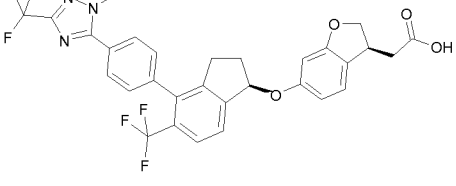
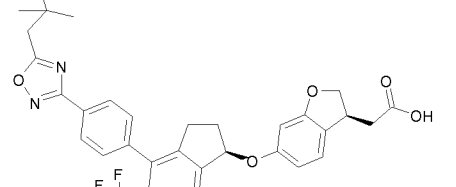
10

Example No	Starting intermediate	Structure	Name
62ab	52cab		((S)-6-((R)-4-[4-(1,1-Dioxohexahydro-1-thiopyran-4-ylmethoxy)-2,6-dimethylphenyl]-6-trifluoromethyl-indan-1-yloxy)-2,3-dihydrobenzofuran-3-yl)-acetic acid

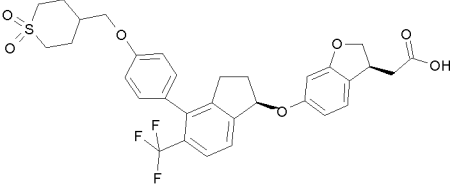
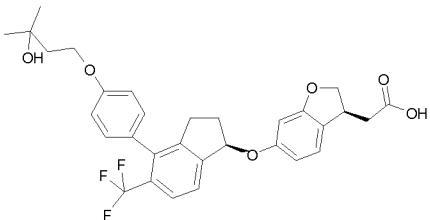
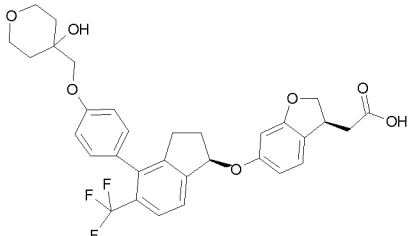
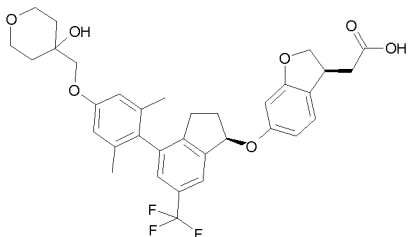
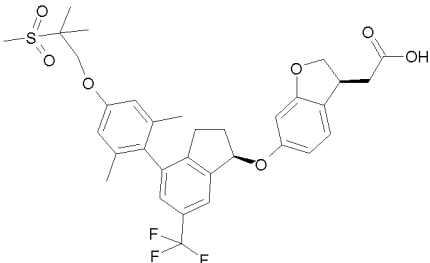
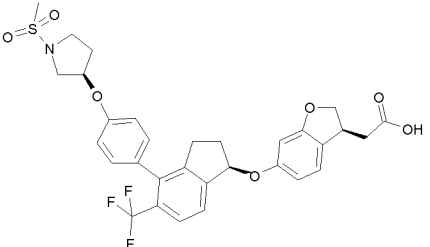
62ac	52ha		[(S)-6-((R)-4-{4-[1-(2-Hydroxy-2-methyl-propyl)-1H-pyrazol-4-yl]-phenyl}-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl]-acetic acid
62ad	52hb		((S)-6-{(R)-5-Trifluoromethyl-4-[4-(5-trifluoromethyl-isoxazol-3-yl)-phenyl]-indan-1-yloxy}-2,3-dihydro-benzofuran-3-yl)-acetic acid
62ae	52ib		((S)-6-{(R)-7-Fluoro-5-trifluoromethyl-4-[4-(5-trifluoromethyl-isoxazol-3-yl)-phenyl]-indan-1-yloxy}-2,3-dihydro-benzofuran-3-yl)-acetic acid
62af	52hc		((S)-6-{(R)-4-[4-(5-Methyl-isoxazol-3-yl)-phenyl]-5-trifluoromethyl-indan-1-yloxy}-2,3-dihydro-benzofuran-3-yl)-acetic acid
62ag	52cac		((S)-6-{(R)-4-[4-(4-Hydroxy-1,1-dioxo-hexahydro-1-thiopyran-4-ylmethoxy)-2,6-dimethyl-phenyl]-6-trifluoromethyl-indan-1-yloxy}-2,3-dihydro-benzofuran-3-yl)-acetic acid
62ah	52dad		((S)-6-{(R)-7-Fluoro-4-[4-(3-hydroxy-3-methyl-butoxy)-2,6-dimethyl-phenyl]-6-trifluoromethyl-indan-1-yloxy}-2,3-dihydro-benzofuran-3-yl)-acetic acid

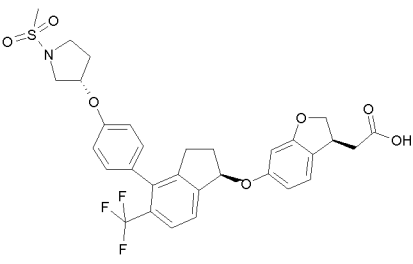
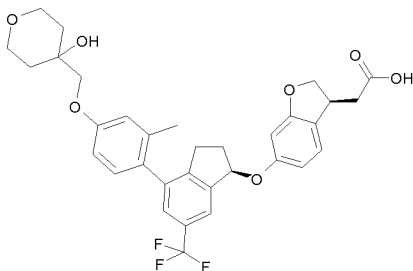
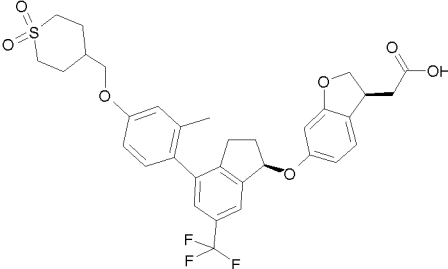
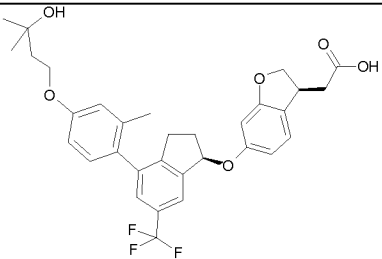
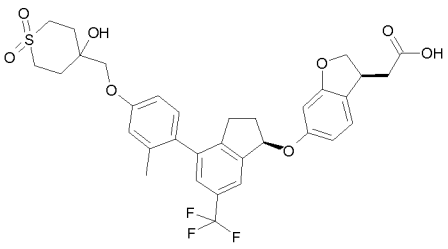
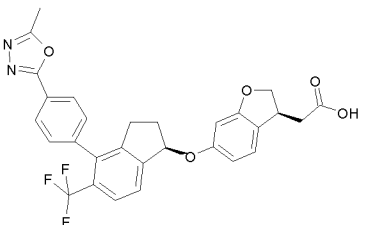
62ai	52daa		((S)-6-((R)-4-[4-(1,1-Dioxo-hexahydro-1-thiopyran-4-ylmethoxy)-2,6-dimethyl-phenyl]-7-fluoro-6-trifluoromethyl-indan-1-yloxy}-2,3-dihydro-benzofuran-3-yl)-acetic acid
62aj	52dab		((S)-6-((R)-7-Fluoro-4-[4-(4-hydroxy-1,1-dioxo-hexahydro-1-thiopyran-4-ylmethoxy)-2,6-dimethyl-phenyl]-6-trifluoromethyl-indan-1-yloxy}-2,3-dihydro-benzofuran-3-yl)-acetic acid
62ak	52dac		2-((S)-6-((R)-7-fluoro-4-(4-((4-hydroxytetrahydro-2H-pyran-4-yl)methoxy)-2,6-dimethylphenyl)-6-(trifluoromethyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid
62al	52hzp		((S)-6-((R)-4-[5-(3-Hydroxy-3-methyl-butoxy)-pyrimidin-2-yl]-5-trifluoromethyl-indan-1-yloxy}-2,3-dihydro-benzofuran-3-yl)-acetic acid
62am	52hd		((S)-6-((R)-4-[4-(5-Methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-5-trifluoromethyl-indan-1-yloxy}-2,3-dihydro-benzofuran-3-yl)-acetic acid
62an	52ic		((S)-6-((R)-7-Fluoro-4-[4-(5-methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-5-trifluoromethyl-indan-1-yloxy}-2,3-dihydro-

			benzofuran-3-yl)-acetic acid
62ao	52he		((S)-6-((R)-4-[4-(5-Methyl-1H-[1,2,4]triazol-3-yl)-phenyl]-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid
62ap	52hf		((S)-6-((R)-4-[4-(1,5-Dimethyl-1H-[1,2,4]triazol-3-yl)-phenyl]-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid
62aq	52ie		((S)-6-((R)-4-[4-(1,5-Dimethyl-1H-[1,2,4]triazol-3-yl)-phenyl]-7-fluoro-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid
62ar	52hg		((S)-6-((R)-4-[4-(3-Methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid
62as	52hh		((S)-6-((R)-5-Trifluoromethyl-4-[4-(5-trifluoromethyl-2H-[1,2,4]triazol-3-yl)-phenyl]-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid
62at	52id		((S)-6-((R)-7-Fluoro-4-[4-(5-methyl-1H-[1,2,4]triazol-3-yl)-phenyl]-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid

62au	52hi		((S)-6-((R)-4-[4-(5-Cyclopropyl- [1,2,4]oxadiazol-3-yl)-phenyl]- 5-trifluoromethyl-indan-1- yloxy}-2,3-dihydro-benzofuran- 3-yl)-acetic acid
62aw	52hj		((S)-6-((R)-4-[4-(1-Methyl-5- trifluoromethyl-1H- [1,2,4]triazol-3-yl)-phenyl]-5- trifluoromethyl-indan-1-yloxy)- 2,3-dihydro-benzofuran-3-yl)- acetic acid
62ax	52hk		[(S)-6-((R)-4-[4-[5-(1-Hydroxy- 1-methyl-ethyl)- [1,2,4]oxadiazol-3-yl]- phenyl]-5-trifluoromethyl- indan-1-yloxy)-2,3-dihydro- benzofuran-3-yl]-acetic acid
62ay	52hzf		((S)-6-((R)-4-[4-(3-Hydroxy-3- methyl-butoxy)-3,5-dimethyl- phenyl]-5-trifluoromethyl- indan-1-yloxy)-2,3-dihydro- benzofuran-3-yl)-acetic acid
62az	52hl		((S)-6-((R)-4-[4-(2-Methyl-5- trifluoromethyl-2H- [1,2,4]triazol-3-yl)-phenyl]-5- trifluoromethyl-indan-1-yloxy)- 2,3-dihydro-benzofuran-3-yl)- acetic acid
62ba	52hka		[(S)-6-((R)-4-[4-[5-(2-Hydroxy- 2-methyl-propyl)- [1,2,4]oxadiazol-3-yl]-phenyl]- 5-trifluoromethyl-indan-1- yloxy)-2,3-dihydro-benzofuran- 3-yl]-acetic acid

62bb	52hzm		((S)-6-((R)-4-[3,5-Difluoro-4-(5-methyl-[1,3,4]oxadiazol-2-yl)-phenyl]-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid
62bc	52hzn		((S)-6-((R)-4-[3,5-Difluoro-4-(5-methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid
62be	52hze		[(S)-6-((R)-4-[4-[5-(1-Hydroxy-1-methyl-ethyl)-1-methyl-1H-[1,2,4]triazol-3-yl]-phenyl]-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl]-acetic acid
62bf	52eaa		((S)-6-((R)-4-[4-(4-Hydroxy-tetrahydro-pyran-4-ylmethoxy)-2,6-dimethyl-phenyl]-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid
62bg	52eac		((S)-6-((R)-4-[4-(3-Hydroxy-3-methyl-butoxy)-2,6-dimethyl-phenyl]-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid
62bh	52ead		((S)-6-((R)-4-[4-(2-Hydroxy-2-methyl-propoxy)-2,6-dimethyl-phenyl]-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid

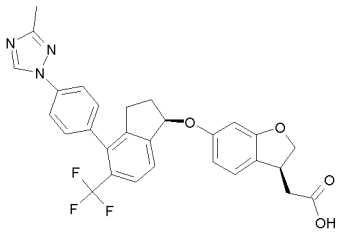
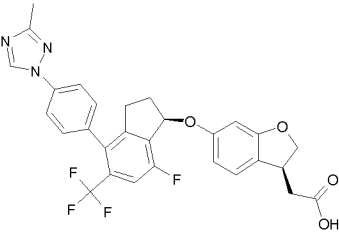
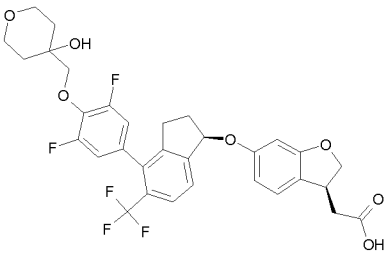
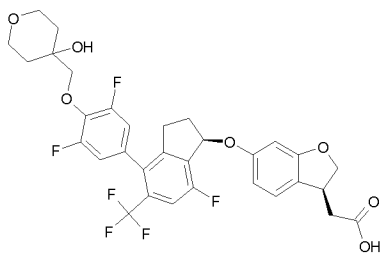
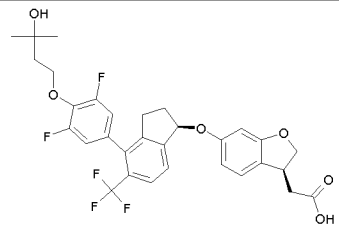
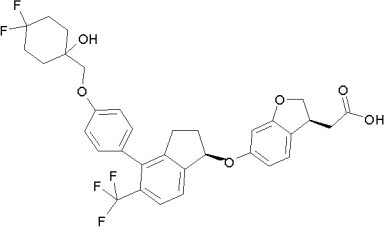
62bi	52aaa		((S)-6-((R)-4-[4-(1,1-Dioxohexahydro-1-thiopyran-4-ylmethoxy)-phenyl]-5-trifluoromethyl-indan-1-yloxy}-2,3-dihydro-benzofuran-3-yl)-acetic acid
62bj	52aaj		((S)-6-((R)-4-[4-(3-Hydroxy-3-methyl-butoxy)-phenyl]-5-trifluoromethyl-indan-1-yloxy}-2,3-dihydro-benzofuran-3-yl)-acetic acid
62bk	52aan		((S)-6-((R)-4-[4-(4-Hydroxy-tetrahydro-pyran-4-ylmethoxy)-phenyl]-5-trifluoromethyl-indan-1-yloxy}-2,3-dihydro-benzofuran-3-yl)-acetic acid
62bl	52cad		((S)-6-((R)-4-[4-(4-Hydroxy-tetrahydro-pyran-4-ylmethoxy)-2,6-dimethyl-phenyl]-6-trifluoromethyl-indan-1-yloxy}-2,3-dihydro-benzofuran-3-yl)-acetic acid
62bm	52cae		((S)-6-((R)-4-[4-(2-Methanesulfonyl-2-methyl-propoxy)-2,6-dimethyl-phenyl]-6-trifluoromethyl-indan-1-yloxy}-2,3-dihydro-benzofuran-3-yl)-acetic acid
62bn	52aab		((S)-6-((R)-4-[4-((R)-1-Methanesulfonyl-pyrrolidin-3-yloxy)-phenyl]-5-trifluoromethyl-indan-1-yloxy}-2,3-dihydro-benzofuran-3-yl)-acetic acid

62bo	52aac		((S)-6-((R)-4-[4-((S)-1-Methanesulfonyl-pyrrolidin-3-yloxy)-phenyl]-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid
62bp	52caf		((S)-6-((R)-4-[4-(4-Hydroxy-tetrahydro-pyran-4-ylmethoxy)-2-methyl-phenyl]-6-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid
62bq	52cag		((S)-6-((R)-4-[4-(1,1-Dioxo-hexahydro-1-thiopyran-4-ylmethoxy)-2-methyl-phenyl]-6-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid
62br	52cah		((S)-6-((R)-4-[4-(3-Hydroxy-3-methyl-butoxy)-2-methyl-phenyl]-6-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid
62bs	52cai		((S)-6-((R)-4-[4-(4-Hydroxy-1,1-dioxo-hexahydro-1-thiopyran-4-ylmethoxy)-2-methyl-phenyl]-6-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid
62bt	52hla		((S)-6-((R)-4-[4-(5-Methyl-[1,3,4]oxadiazol-2-yl)-phenyl]-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid

62bu	52aap		((S)-6-((R)-4-[4-(1,1-Dioxo-hexahydro-1-thiopyran-4-ylmethoxy)-2-fluoro-phenyl]-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid
62bw	52aad		((S)-6-((R)-4-[4-(1-Methanesulfonyl-piperidin-4-yloxy)-phenyl]-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid
62bx	52aae		((S)-6-((R)-4-[4-(3-Methanesulfonyl-propoxy)-phenyl]-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid
62by	52hm		((S)-6-((R)-4-[4-(1-Methyl-1H-pyrazol-4-yl)-phenyl]-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid
62bz	52hn		((S)-6-((R)-4-[4-(2,5-Dimethyl-2H-pyrazol-3-yl)-phenyl]-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid
62ca	52ho		((S)-6-((R)-4-[4-(2-Methyl-2H-pyrazol-3-yl)-phenyl]-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid
62cb	52aai		((S)-6-((R)-4-[4-(Tetrahydro-pyran-4-yloxy)-phenyl]-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid

			acetic acid
62cc	52hp		(S)-6-[(R)-4-(4-Pyrimidin-5-yl-phenyl)-5-trifluoromethyl-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl]-acetic acid
62cd	52aak		[(S)-6-((R)-4-{4-[(R)-(Tetrahydro-furan-3-yl)oxy]-phenyl}-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl]-acetic acid
62ce	52aal		[(S)-6-((R)-4-{4-[(S)-(Tetrahydro-furan-3-yl)oxy]-phenyl}-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl]-acetic acid
62cf	52hra;		((S)-6-{(R)-4-[4-(3-Methyl-pyrazol-1-yl)-phenyl]-5-trifluoromethyl-indan-1-yloxy}-2,3-dihydro-benzofuran-3-yl)-acetic acid
62cg	52hrb		((S)-6-{(R)-4-[4-(5-Methyl-pyrazol-1-yl)-phenyl]-5-trifluoromethyl-indan-1-yloxy}-2,3-dihydro-benzofuran-3-yl)-acetic acid
62ch	52aaf		[(S)-6-((R)-4-{4-[(S)-1-(Tetrahydro-furan-2-yl)methoxy]-phenyl}-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl]-acetic acid
62ci	52aag		[(S)-6-((R)-4-{4-[(R)-1-(Tetrahydro-furan-2-yl)methoxy]-phenyl}-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl]-acetic acid

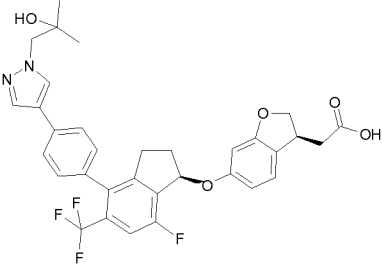
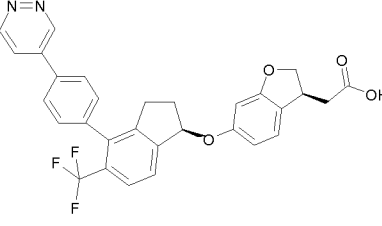
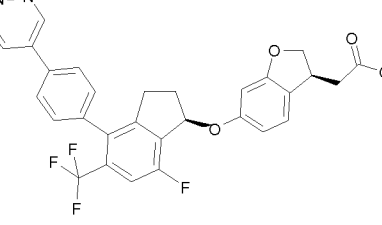
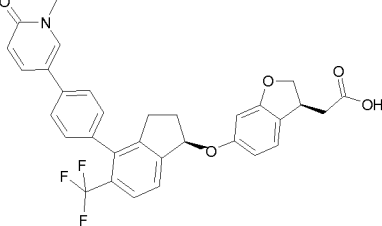
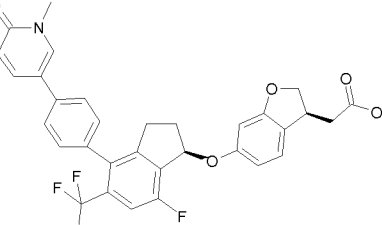
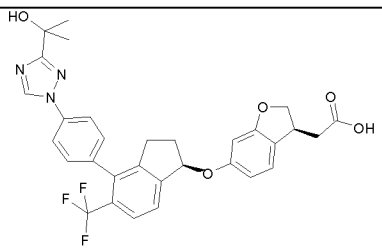
			acetic acid
62cj	52aam		((S)-6-((R)-4-[4-(Tetrahydro-pyran-4-ylmethoxy)-phenyl]-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid
62ck	52ii		{(S)-6-[(R)-7-Fluoro-4-(4-pyrimidin-5-yl-phenyl)-5-trifluoromethyl-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid
62cl	52ij		((S)-6-((R)-7-Fluoro-4-[4-(3-methyl-pyrazol-1-yl)-phenyl]-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid
62cm	52aah		[(S)-6-((R)-4-{4-[(R)-1-(Tetrahydro-furan-3-yl)methoxy]-phenyl}-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl]-acetic acid
62cn	52ik		((S)-6-((R)-7-Fluoro-5-trifluoromethyl-4-[4-(3-trifluoromethyl-pyrazol-1-yl)-phenyl]-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid
62co	52hs		((S)-6-((R)-5-Trifluoromethyl-4-[4-(3-trifluoromethyl-pyrazol-1-yl)-phenyl]-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid

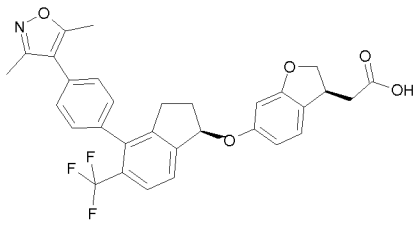
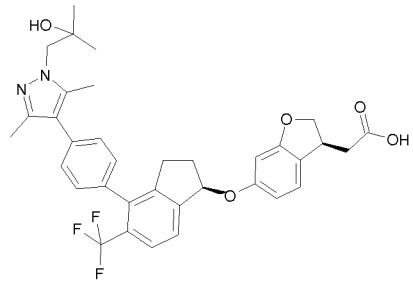
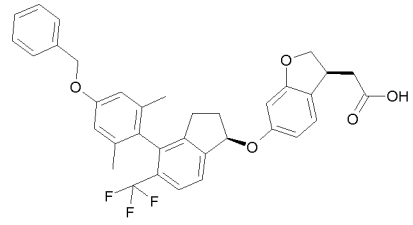
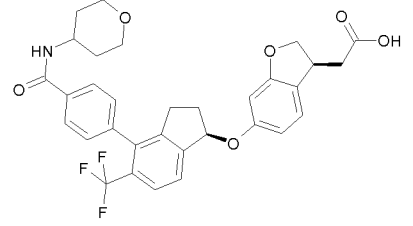
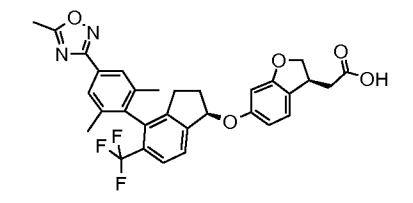
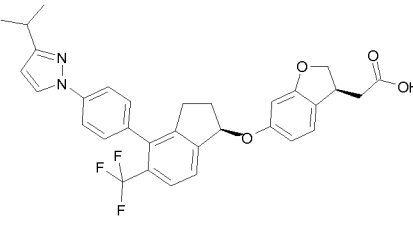
62cp	52ht		((S)-6-((R)-4-[4-(3-Methyl-[1,2,4]triazol-1-yl)-phenyl]-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid
62cq	52il		((S)-6-((R)-7-Fluoro-4-[4-(3-methyl-[1,2,4]triazol-1-yl)-phenyl]-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid
62cr	52hzg		((S)-6-((R)-4-[3,5-Difluoro-4-(4-hydroxy-tetrahydro-pyran-4-ylmethoxy)-phenyl]-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid
62cs	52io		((S)-6-((R)-4-[3,5-Difluoro-4-(4-hydroxy-tetrahydro-pyran-4-ylmethoxy)-phenyl]-7-fluoro-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid
62ct	52hzi		((S)-6-((R)-4-[3,5-Difluoro-4-(3-hydroxy-3-methyl-butoxy)-phenyl]-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid
62cu	52aao		((S)-6-((R)-4-[4-(4,4-Difluoro-1-hydroxy-cyclohexylmethoxy)-phenyl]-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid

62cw	52hu		((S)-6-((R)-4-[4-(5-Ethyl-1,2,4-oxadiazol-3-yl)-phenyl]-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid
62cx	52hw		((S)-6-((R)-4-[4-(5-Isopropyl-1,2,4-oxadiazol-3-yl)-phenyl]-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid
62cy	52hzi		((S)-6-((R)-4-[3,5-Difluoro-4-(3-methanesulfonyl-propoxy)-phenyl]-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid
62cz	52hzh		((S)-6-((R)-4-[3,5-Difluoro-4-(2-hydroxy-2-methyl-propoxy)-phenyl]-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid
62da	52hzj		[(S)-6-((R)-4-[3,5-Difluoro-4-((R)-(tetrahydro-furan-3-yl)oxy)-phenyl]-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl]-acetic acid
62db	52hzk		[(S)-6-((R)-4-[3,5-Difluoro-4-((S)-(tetrahydro-furan-3-yl)oxy)-phenyl]-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl]-acetic acid
62dc	52hxx		((S)-6-((R)-4-[4-(2-Methyl-2H-tetrazol-5-yl)-phenyl]-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid

62dd	52hzo		[(S)-6-((R)-4-{3,5-Difluoro-4-[1-(2-hydroxy-2-methyl-propyl)-1H-pyrazol-4-yl]-phenyl}-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl]-acetic acid
62de	52eab		((S)-6-((R)-4-[4-(4-Hydroxy-1,1-dioxo-hexahydro-1-thiopyran-4-ylmethoxy)-2,6-dimethyl-phenyl]-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid
62df	52eae		((S)-6-((R)-4-[2,6-Dimethyl-4-(tetrahydro-pyran-4-yloxy)-phenyl]-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid
62dg	52bac		((S)-6-((R)-7-Fluoro-4-[4-(3-hydroxy-3-methyl-butoxy)-phenyl]-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid
62dh	52baa		((S)-6-((R)-4-[4-(1,1-Dioxo-hexahydro-1-thiopyran-4-ylmethoxy)-phenyl]-7-fluoro-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid
62di	52bab		((S)-6-((R)-7-Fluoro-4-[4-((S)-1-methanesulfonyl-pyrrolidin-3-yloxy)-phenyl]-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid

62dj	52baf		((S)-6-((R)-4-[4-((S)-2,3-Dihydroxy-3-methyl-butoxy)-phenyl]-7-fluoro-5-trifluoromethyl-indan-1-yloxy}-2,3-dihydro-benzofuran-3-yl)-acetic acid Absolute configuration unknown
62dk	52bag		((S)-6-((R)-4-[4-((R)-2,3-Dihydroxy-3-methyl-butoxy)-phenyl]-7-fluoro-5-trifluoromethyl-indan-1-yloxy}-2,3-dihydro-benzofuran-3-yl)-acetic acid Absolute configuration unknown
62dl	52ig		((S)-6-((R)-7-Fluoro-4-[4-(1-methyl-1H-pyrazol-4-yl)-phenyl]-5-trifluoromethyl-indan-1-yloxy}-2,3-dihydro-benzofuran-3-yl)-acetic acid
62dm	52ih		((S)-6-((R)-4-[4-(2,5-Dimethyl-2H-pyrazol-3-yl)-phenyl]-7-fluoro-5-trifluoromethyl-indan-1-yloxy}-2,3-dihydro-benzofuran-3-yl)-acetic acid
62dn	52if		((S)-6-((R)-7-Fluoro-4-[4-(5-methyl-[1,3,4]oxadiazol-2-yl)-phenyl]-5-trifluoromethyl-indan-1-yloxy}-2,3-dihydro-benzofuran-3-yl)-acetic acid

62do	52ia		[(S)-6-((R)-7-Fluoro-4-{4-[1-(2-hydroxy-2-methyl-propyl)-1H-pyrazol-4-yl]-phenyl}-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl]-acetic acid
62dp	52hy		{(S)-6-[(R)-4-(4-Pyridazin-4-yl-phenyl)-5-trifluoromethyl-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid
62dq	52im		{(S)-6-[(R)-7-Fluoro-4-(4-pyridazin-4-yl-phenyl)-5-trifluoromethyl-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid
62dr	52hz		((S)-6-((R)-4-[4-(1-Methyl-6-oxo-1,6-dihydro-pyridin-3-yl)-phenyl]-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid
62ds	52in		((S)-6-((R)-7-Fluoro-4-[4-(1-methyl-6-oxo-1,6-dihydro-pyridin-3-yl)-phenyl]-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid
62dt	52hza		[(S)-6-((R)-4-{4-[3-(1-Hydroxy-1-methyl-ethyl)-[1,2,4]triazol-1-yl]-phenyl}-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl]-acetic acid

62du	52hzb		((S)-6-((R)-4-[4-(3,5-Dimethyl-isoxazol-4-yl)-phenyl]-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid
62dw	52hzc		[(S)-6-((R)-4-{4-[1-(2-Hydroxy-2-methyl-propyl)-3,5-dimethyl-1H-pyrazol-4-yl]-phenyl]-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl]-acetic acid
62dx	Step 7 in the preparation of 52ea		{(S)-6-[(R)-4-(4-Benzyloxy-2,6-dimethyl-phenyl)-5-trifluoromethyl-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl)-acetic acid
62dy	52hzb		((S)-6-((R)-4-[4-(Tetrahydropyran-4-ylcarbonyl)-phenyl]-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid
62dz	52eaf		((S)-6-((R)-4-[2,6-Dimethyl-4-(5-methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid
62ea	52hzb		((S)-6-((R)-4-[4-(3-Isopropyl-pyrazol-1-yl)-phenyl]-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid

Example No	t _R [Min]	LC method No	(ESI ⁺) or (ESI ⁻): m/z
62ab	3,27	20B	643 [M-H]-
62ac	2,85	20B	593 [M+H]+

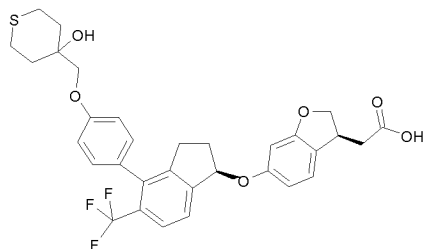
62ad	8,09	20B	588 [M-H]-
62ae	3,93	20B	606 [M-H]-
62af	3,56	20B	536 [M+H]+
62ag	2,83	20B	659 [M-H]-
62ah	3,60	20B	603 [M+H]+
62ai	3,28	20B	663 [M+H]+
62aj	2,89	20B	679 [M+H]+
62ak	3,22	20B	631 [M+H]+
62al	2,58	20B	559 [M+H]+
62am	3,37	20B	537 [M+H]+
62an	3,16	20B	553 [M-H]-
62ao	2,52	20B	536 [M+H]+
62ap	2,74	20B	550 [M+H]+
62aq	2,83	20B	568 [M+H]+
62ar	3,35	20B	537 [M+H]+
62as	3,13	20B	590 [M+H]+
62at	2,57	20B	554 [M+H]+
62au	4,00	20B	563 [M+H]+
62aw	3,76	20B	604 [M+H]+
62ax	3,25	20B	581 [M+H]+
62ay	3,28	20B	585 [M+H]+
62az	3,32	20B	604 [M+H]+
62ba	3,00	20B	595 [M+H]+
62bb	2,82	20B	573 [M+H]+
62bc	3,15	20B	573 [M+H]+
62be	3,06	20B	594 [M+H]+
62bf	2,90	20B	611 [M-H]-
62bg	3,23	20B	583 [M-H]-
62bh	3,10	20B	569 [M-H]-
62bi	6,52	20C	615 [M+H]+
62bj	3,15	20B	555 [M-H]-
62bk	2,77	20B	583 [M-H]-
62bl	3,00	20B	613 [M+H]+
62bm	3,34	20B	633 [M+H]+
62bn	3,04	20B	618 [M+H]+

62bo	3,02	20B	618 [M+H] ⁺
62bp	2,99	20B	597 [M+H] ⁺
62bq	3,20	20B	629 [M+H] ⁺
62br	4,33	20D	571 [M+H] ⁺
62bs	4,01	20E	647 [M+H] ⁺
62bt	2,83	20B	537 [M+H] ⁺
62bu	3,00	20B	635 [M+H] ⁺
62bw	3,23	20B	630 [M+H] ⁺
62bx	3,13	20B	589 [M-H] ⁻
62by	3,13	20B	535 [M+H] ⁺
62bz	3,39	20B	549 [M+H] ⁺
62ca	3,13	20B	535 [M+H] ⁺
62cb	3,31	20B	553 [M-H] ⁻
62cc	2,86	20B	531 [M-H] ⁻
62cd	3,12	20B	539 [M-H] ⁻
62ce	3,12	20B	539 [M-H] ⁻
62cf	3,40	20B	535 [M+H] ⁺
62cg	3,23	20B	535 [M+H] ⁺
62ch	3,40	20B	555 [M+H] ⁺
62ci	3,42	20B	555 [M+H] ⁺
62cj	3,65	20B	569 [M+H] ⁺
62ck	2,97	20B	551 [M+H] ⁺
62cl	3,63	20B	553 [M+H] ⁺
62cm	3,28	20B	555 [M+H] ⁺
62cn	3,68	20B	605 [M-H] ⁻
62co	3,72	20B	587 [M-H] ⁻
62cp	2,80	20B	536 [M+H] ⁺
62cq	2,80	20B	554 [M+H] ⁺
62cr	2,94	20B	619 [M-H] ⁻
62cs	2,99	20B	637[M-H] ⁻
62ct	3,23	20B	591 [M-H] ⁻
62cu	4,34	20F	617 [M-H] ⁻
62cw	4,05	20B	551 [M+H] ⁺
62cx	3,74	20B	565 [M+H] ⁺
62cy	2,87	20B	625 [M-H] ⁻

62cz	3,05	20B	577 [M-H]-
62da	3,26	20B	577 [M+H]+
62db	3,22	20B	577 [M+H]+
62dc	3,10	20B	537 [M+H]+
62dd	3,08	20B	629 [M+H]+
62de	2,81	20B	659 [M-H]-
62df	3,44	20B	581 [M-H]-
62dg	3,17	20B	575 [M+H]+
62dh	4,28	20D	635 [M+H]+
62di	4,28	20E	636 [M+H]+
62dj	2,76	20B	591 [M+H]+
62dk	2,76	20B	591 [M+H]+
62dl	4,15	20D	553 [M+H]+
62dm	4,26	20D	567 [M+H]+
62dn	2,82	20B	555 [M+H]+
62do	4,08	20B	611 [M+H]+
62dp	2,71	20B	533 [M+H]+
62dq	2,69	20B	551 [M+H]+
62dr	3,15	20B	562 [M+H]+
62ds	3,13	20B	580 [M+H]+
62dt	2,65	20B	580 [M+H]+
62du	3,43	20B	550 [M+H]+
62dw	6,68	20C	621 [M+H]+
62dx	4,17	20B	589 [M+H]+
62dy	2,65	20B	582 [M+H]+
62dz	3,38	20B	565 [M+H]+
62ea	3,95	20B	563 [M+H]+

Example 62eb

((S)-6-((R)-4-[4-(4-Hydroxy-tetrahydro-thiopyran-4-ylmethoxy)-phenyl]-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid



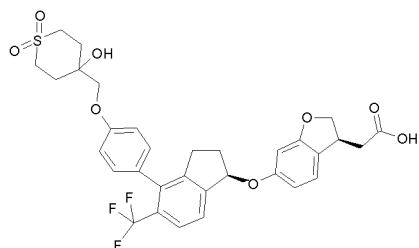
The title compound is prepared following a procedure analogous to that described for Step 1 in the preparation of Intermediate 50bc, starting from Intermediate 52aa'.

LC (method 20C): $t_R = 7.15$ min; Mass spectrum (ESI⁺): $m/z = 601$ [M+H]⁺.

5

Example 62ec

((S)-6-((R)-4-[4-(4-Hydroxy-1,1-dioxo-hexahydro-1-thiopyran-4-ylmethoxy)-phenyl]-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid

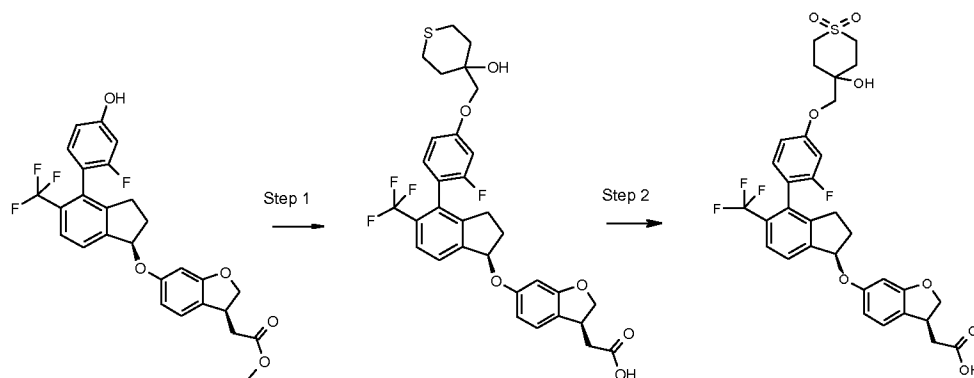


- 10 The title compound is prepared following a analogous procedure analogous to that described for Step 2 in the preparation of Intermediate 50bc, starting from Example 62eb.

LC (method 20B): $t_R = 2.33$ min; Mass spectrum (ESI⁺): $m/z = 633$ [M+H]⁺.

15 Example 62ed

((S)-6-((R)-4-[2-Fluoro-4-(4-hydroxy-1,1-dioxo-hexahydro-1-thiopyran-4-ylmethoxy)-phenyl]-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid



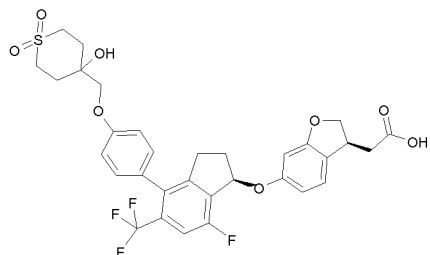
The title compound is prepared following a procedure analogous to that described in the preparation of Intermediate 50bc, starting from Intermediate 52aa''.

20

LC (method 20B): t_R = 2.71 min; Mass spectrum (ESI⁺): m/z = 651 [M+H]⁺.

Example 62ee

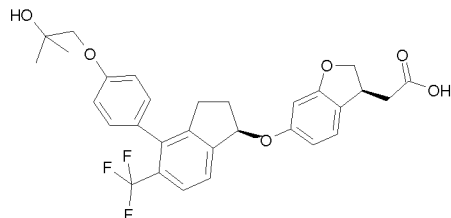
((S)-6-((R)-7-Fluoro-4-[4-(4-hydroxy-1,1-dioxo-hexahydro-1-thiopyran-4-ylmethoxy)-phenyl]-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid



The title compound is prepared in analogy to Example 62ed, starting from Intermediate 52ba. LC (method 20B): t_R = 2.71 min; Mass spectrum (ESI⁺): m/z = 651 [M+H]⁺.

Example 62ef

((S)-6-((R)-4-[4-(2-Hydroxy-2-methyl-propoxy)-phenyl]-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid

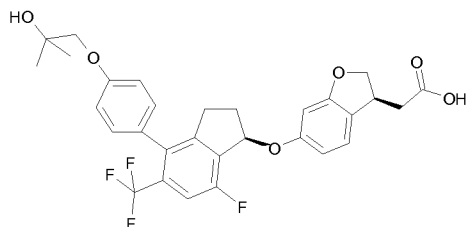


Intermediate 52aa (90 mg) and cesium carbonate (120 g) are suspended in 2 mL of N,N-dimethylformamide, Isobutylene oxide (20 g) is added and the reaction mixture is stirred at 100 °C 3 h. Water is added and the mixture is extracted with ethyl acetate, the organic phase is separated, dried over sodium sulfate and concentrated under vacuum. The residue is chromatographed on silica gel (cyclohexane/ethyl acetate 100:0→60:40) to give the title compound. Yield: 22 mg

LC (method 20B): t_R = 3.09 min; Mass spectrum (ESI⁺): m/z = 541 [M+H]⁺.

Example 62eg

((S)-6-((R)-7-Fluoro-4-[4-(2-hydroxy-2-methyl-propoxy)-phenyl]-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid



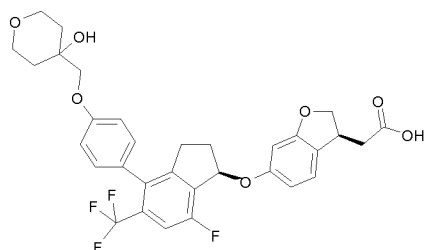
The title compound is prepared in analogy to Intermediate 62ef starting from Intermediate 52ba.

LC (method 20D): t_R = 4.00 min; Mass spectrum (ESI⁺): m/z = 561 [M+H]⁺.

5

Example 62eh

((S)-6-((R)-7-Fluoro-4-[4-(4-hydroxy-tetrahydro-pyran-4-ylmethoxy)-phenyl]-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid

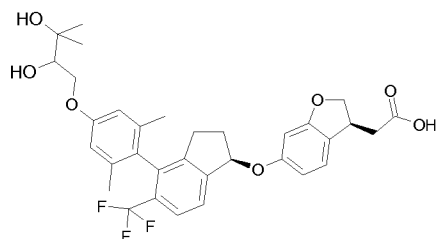


10 The title compound is prepared in analogy to example 62ef, starting from Intermediate 52ba and 1,6-dioxaspiro[2.5]octane (US2012/46304 A1, 2012).

LC (method 20B): t_R = 2.76 min; Mass spectrum (ESI⁺): m/z = 603[M+H]⁺.

Example 62ei

15 ((S)-6-((R)-4-[4-(2,3-Dihydroxy-3-methyl-butoxy)-2,6-dimethyl-phenyl]-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid



Intermediate 52ea (128 mg I), 2-oxiranyl-propan-2-ol (64 mg) and cesium carbonate (179 mg) are suspended in dry N,N-dimethylformamide and stirred at 100 °C for 5 hours. The mixture is diluted with water, acidified with 1 M aqueous hydrochloric acid and extracted with ethyl acetate. The organic phase is washed with magnesium sulfate and the solvent removed under vacuum. The residue is purified by flash chromatography

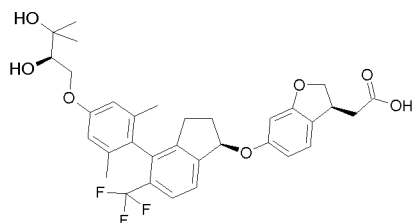
20

(dichloromethane/methanol/acetic acid 90:1:1) to give the title compound (Yield 45 mg).

LC (method 20B): t_R = 2.97 min; Mass spectrum (ESI⁻): m/z = 599 [M-H]⁻.

5 Example 62ej

((S)-6-((R)-4-[4-((R)-2,3-Dihydroxy-3-methyl-butoxy)-2,6-dimethyl-phenyl]-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid methyl ester



Example 62ei is separated by preparative chiral HPLC to give the title compound.

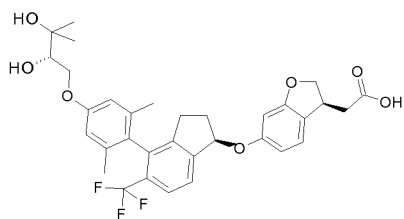
10 Chiral HPLC (method 1c): t_R = 7.75 min

LC (method 20B): t_R = 2.82. Mass spectrum (ESI⁻): m/z = 599 [M-H]⁻.

Absolute configuration unknown.

Example 62ek

15 ((S)-6-((R)-4-[4-((S)-2,3-Dihydroxy-3-methyl-butoxy)-2,6-dimethyl-phenyl]-5-trifluoromethyl-indan-1-yloxy)-2,3-dihydro-benzofuran-3-yl)-acetic acid



The title compound is obtained from further elution in the chiral HPLC chromatography for the preparation of Example 62ej,

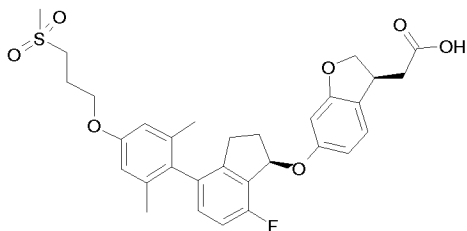
20 Chiral HPLC (method 1c): t_R = 7.84 min

LC (method 20B): t_R = 2.83. Mass spectrum (ESI⁻): m/z = 599 [M-H]⁻.

Absolute configuration unknown

Example 63

25 2-((S)-6-((R)-4-(2,6-Dimethyl-4-(3-(methylsulfonyl)propoxy)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid

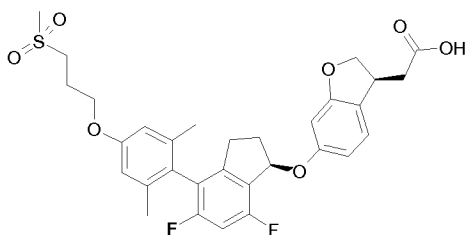


Methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-(3-(methylsulfonyl)propoxy)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate (Intermediate 53; 9 mg) is suspended in ethanol (1 mL) and aqueous NaOH (1 M; 0.2 mL) is added.

5 The mixture is stirred for 1 hour then concentrated under vacuum, acidified with aqueous HCl (1 M) and extracted twice with dichloromethane. The combined organic extracts are dried and the solvent is removed to give the title compound (8.5 mg). LC (method 20): t_R = 6.37 min; Mass spectrum (ESI⁻): m/z = 567 [M-H]⁻.

10 Example 64

2-((S)-6-((R)-4-(2,6-Dimethyl-4-(3-(methylsulfonyl)propoxy)phenyl)-5,7-difluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid

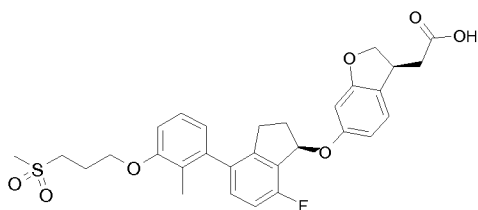


The title compound is prepared from methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-(3-(methylsulfonyl)propoxy)phenyl)-5,7-difluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate (Intermediate 54; 29 mg) following a procedure analogous to that described in Example 63. Yield 25 mg.

15 LC (method 20): t_R = 6.20 min; Mass spectrum: m/z = 587 [M+H]⁺.

20 Example 65

2-((3S)-6-((1R)-7-Fluoro-4-(2-methyl-3-(3-(methylsulfonyl)propoxy)phenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid

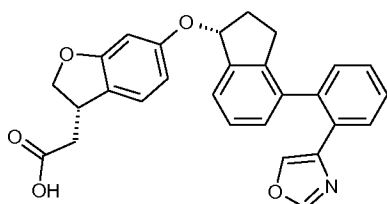


Methyl 2-((3S)-6-((1R)-7-fluoro-4-(2-methyl-3-(3-(methylsulfonyl)propoxy)phenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate (Intermediate 51m; 64 mg) in methanol (3 mL) and aqueous NaOH (1 M; 0.5 mL) is stirred for 16 hours, concentrated under vacuum, acidified with aqueous HCl (1 M) and extracted with diethyl ether. A precipitate that forms is collected by filtration, washed with some n-hexane, dried and subsequently triturated with a mixture of n-hexane and diethyl ether to give the title compound (30 mg).

LC (method 20): $t_R = 6.15$ min; Mass spectrum: $m/z = 555$ $[M+H]^+$.

10 Example 66

2-((3S)-6-((1R)-4-(2-(oxazol-4-yl)phenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



Intermediate 55 (15.7 mg) is dissolved in methanol (1 mL) and tetrahydrofuran (1 mL) and aqueous sodium hydroxide solution (0.084 mL, 1 Mol/L) is added. The reaction mixture is shaken over night at room temperature and half of the solvent is removed under reduced pressure. Aqueous hydrochloric acid (0.084 mL, 1 Mol/L) and water are added. The precipitated product is collected and washed with water. The organic phase is extracted with ethyl acetate, evaporated and the residue is chromatographed by HPLC on reversed phase to yield additional product. Yield 7 mg, LC (method 22): $t_R = 1,6$ min; Mass spectrum (ESI^+): $m/z = 454$ $[M+H]^+$.

The examples in the following table are prepared from the corresponding starting ester intermediates following a procedure analogous to that described for Example 66.

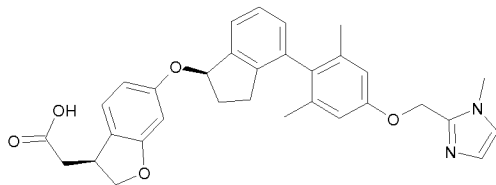
Example No	Structure	Name

67		2-((3S)-6-((1R)-4-(2-(oxazol-5-yl)phenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid
68		2-((3S)-6-((1R)-4-(2-(2-oxopyrrolidin-1-yl)phenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid
69		2-((3S)-6-((1R)-4-(2-(isoxazol-5-yl)phenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid
70		2-((S)-6-((R)-4-(4-carbamoyl-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid

Example No	t_R [Min]	LC method No	(ESI ⁺): m/z
67	1.03	11	454 [M+H] ⁺ .
68	0.94	11	470 [M+H] ⁺ .
69	0.49	14	454 [M+H] ⁺ .
70	0.59	14	458 [M+H] ⁺ .

Example 71

5 2-((S)-6-((R)-4-(2,6-dimethyl-4-((1-methyl-1H-imidazol-2-yl)methoxy)phenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



2-Chloromethyl-1-methyl-1H-imidazole (39 mg) is suspended with a solution of methyl 2-((S)-6-((R)-4-(4-hydroxy-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate (45 mg) in dimethylformamide (2 mL) and solid

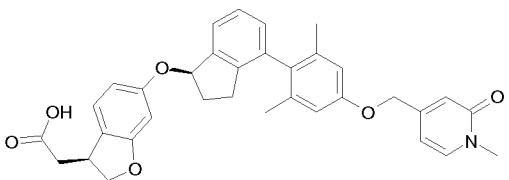
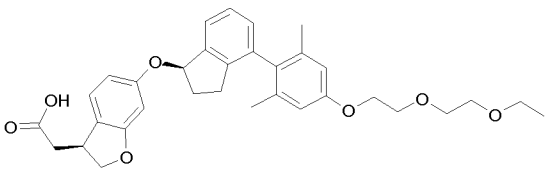
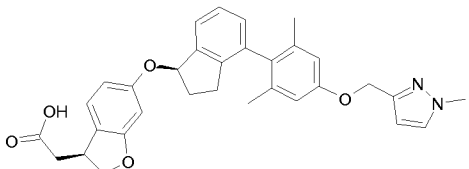
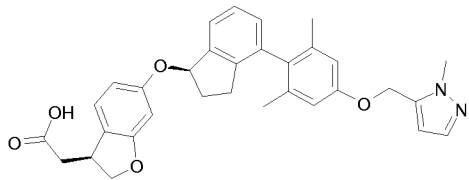
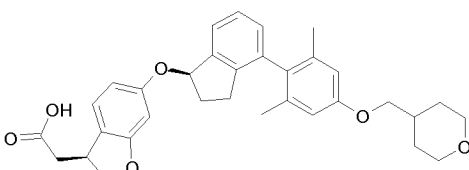
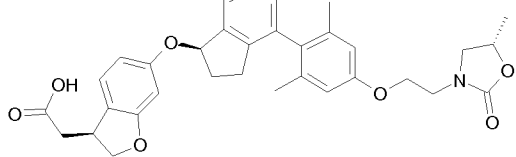
K₂CO₃ (63 mg) is added. The reaction mixture is heated at 60°C and shaken for 24 hours. The reaction mixture is acidified with aqueous trifluoroacetic acid, filtrated and chromatographed by HPLC on reversed phase. The product fractions are collected and lyophilized to give the methylester of title compound.

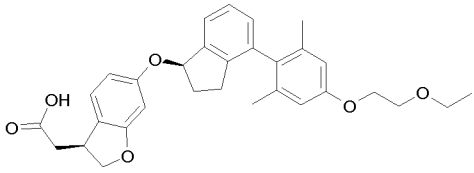
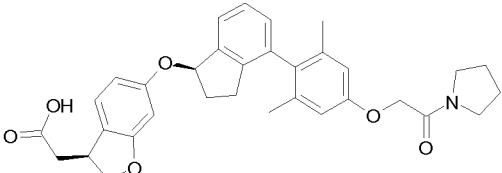
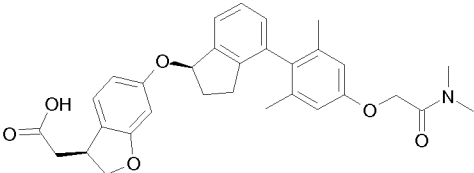
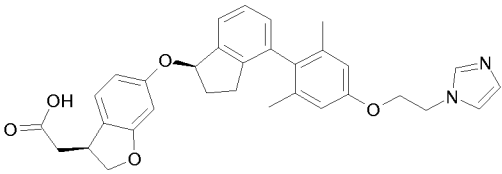
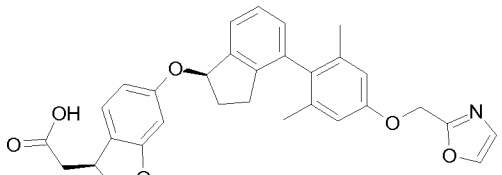
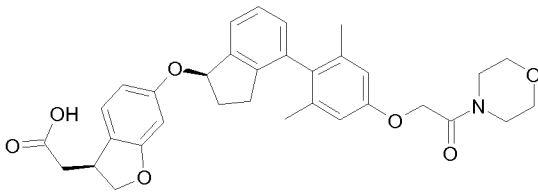
- 5 The ester is dissolved in methanol (1mL) and tetrahydrofuran (1 mL) and aqueous NaOH solution (0.2 mL, 1 Mol/L) was added. The reaction mixture is shaken for 72 hours at room temperature. Aqueous hydrochloric acid (0.2 mL, 1 Mol/L) and dimethylformamide (1 mL) are added and the product is purified by HPLC on reversed phase. The product fractions are collected and lyophilized to give the title compound. LC (method 24): t_R = 0.75 min; Mass spectrum (ESI⁺): m/z = 525 [M+H]⁺.
- 10

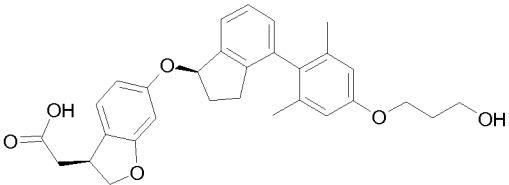
The examples in the following table are prepared analogous to example 71 starting from 2-((S)-6-((R)-4-(4-hydroxy-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate by alkylation with the respective alkylhalide and subsequent saponification of the ester.

15

Example No	Structure	Name
72		2-((S)-6-((R)-4-(2,6-dimethyl-4-(2-morpholinoethoxy)-phenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydro-benzofuran-3-yl)acetic acid
73		2-((S)-6-((R)-4-(4-(2-(2-methoxyethoxy)ethoxy)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid
74		2-((S)-6-((R)-4-(2,6-dimethyl-4-(3-morpholinopropoxy)-phenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid

75		2-((S)-6-((R)-4-(2,6-dimethyl-4-((1-methyl-2-oxo-1,2-dihydropyridin-4-yl)methoxy)phenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid
76		2-((S)-6-((R)-4-(4-(2-(2-ethoxyethoxy)ethoxy)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid
77		2-((S)-6-((R)-4-(2,6-dimethyl-4-((1-methyl-1H-pyrazol-3-yl)methoxy)phenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid
78		2-((S)-6-((R)-4-(2,6-dimethyl-4-((1-methyl-1H-pyrazol-5-yl)methoxy)phenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid
79		2-((S)-6-((R)-4-(2,6-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methoxy)phenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid
80		2-((S)-6-((R)-4-(2,6-dimethyl-4-(2-((S)-5-methyl-2-oxooxazolidin-3-yl)ethoxy)phenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid

		acid
81		2-((S)-6-((R)-4-(4-(2-ethoxyethoxy)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid
82		2-((S)-6-((R)-4-(2,6-dimethyl-4-(2-oxo-2-(pyrrolidin-1-yl)ethoxy)phenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid
83		2-((S)-6-((R)-4-(4-(2-(dimethylamino)-2-oxoethoxy)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid
84		2-((S)-6-((R)-4-(4-(2-(1H-imidazol-1-yl)ethoxy)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid
85		2-((S)-6-((R)-4-(2,6-dimethyl-4-(oxazol-2-ylmethoxy)phenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid
86		2-((S)-6-((R)-4-(2,6-dimethyl-4-(2-morpholino-2-oxoethoxy)phenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid

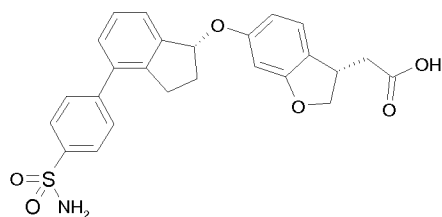
87		2-((S)-6-((R)-4-(4-(3-hydroxypropoxy)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid

Example No	t _R [Min]	LC method No	(ESI ⁺): m/z
72	0.76	24	544 [M+H] ⁺ .
73	0,79	24	533 [M+H] ⁺ .
74	0.80	24	558 [M+H] ⁺ .
75	0.74	24	552 [M+H] ⁺ .
76	0.83	24	569 [M+Na] ⁺ .
77	0.79	24	525 [M+H] ⁺ .
78	0.79	24	525 [M+H] ⁺ .
79	0.86	24	529 [M+H] ⁺ .
80	0.77	24	558 [M+H] ⁺ .
81	0.84	24	503 [M+H] ⁺ .
82	0.75	24	542 [M+H] ⁺ .
83	0.72	24	516 [M+H] ⁺ .
84	0.75	24	525 [M+H] ⁺ .
85	0.79	24	512 [M+H] ⁺ .
86	0.72	24	558 [M+H] ⁺ .
87	0.74	24	489 [M+H] ⁺ .

Example 88

2-((S)-6-((R)-4-(4-Sulfamoylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid

5



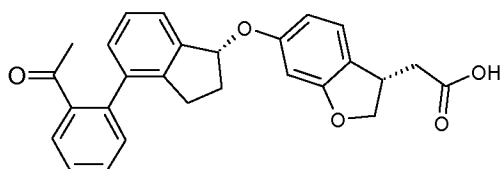
Methyl 2-((S)-6-((R)-4-(4-sulfamoylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydro benzofuran-3-yl)acetate (4.8 mg) is dissolved in methanol (1mL) and tetrahydrofuran (1 mL) and aqueous sodium hydroxide solution (0.2 mL, 1 Mol/L) is added. The

reaction mixture is shaken for 36 hours at room temperature and half of the solvent is removed under reduced pressure. Aqueous hydrochloric acid (0.2 mL, 1 Mol/L) and N,N-dimethylformamide are added and the product is purified by HPLC on reversed phase. The product fractions are collected and lyophilized to give the title compound.

5 Yield 2.6 mg, LC (method 14): t_R = 0.54 min; Mass spectrum (ESI⁻): m/z = 464 [M-H]⁻.

Example 89

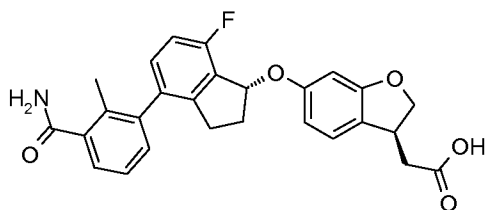
2-((3S)-6-((1R)-4-(2-Acetylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



10 Methyl 2-((3S)-6-((1R)-4-(2-acetylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate (5.9 mg) is dissolved in methanol (1mL) and tetrahydrofuran (1 mL) and aqueous sodium hydroxide solution (0.2 mL, 1 Mol/L) is added. The reaction mixture is shaken for 36 hours at room temperature and half of the solvent is removed under reduced pressure. Aqueous hydrochloric acid (0.2 mL, 1 Mol/L) and N,N-dimethylformamide are added and the product is purified by HPLC on reversed phase. The product fractions are collected and lyophilized to give the title compound.
15 Yield 5.4 mg, LC (method 14): t_R = 0.65 min; Mass spectrum (ESI⁻): m/z = 427 [M-H]⁻.

Example 90

2-((3S)-6-((1R)-4-(3-Carbamoyl-2-methylphenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



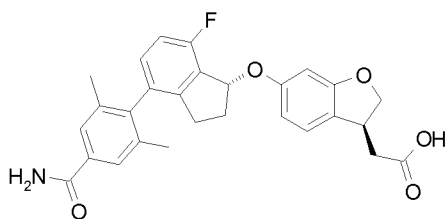
30% Aqueous NH₃ solution (4.2 mL) and 35% aqueous H₂O₂ solution (1.4 ml) are added at 0°C to a solution of 2-((3S)-6-((1R)-4-(3-cyano-2-methylphenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid (30 mg) in ethanol (5 mL). The mixture is stirred at room temperature for 12 hours, while warming to room temperature. The mixture is concentrated, diluted with water and
25

neutralized with 4 M aqueous HCl solution. The resulting mixture is extracted with dichloromethane. The organic phase is dried (MgSO₄). The solvent is evaporated to give the title compound. Yield: 29 mg; LC (method 20): t_R = 5.02 min; Mass spectrum (ESI⁺): m/z = 462 [M+H]⁺.

5

Example 91

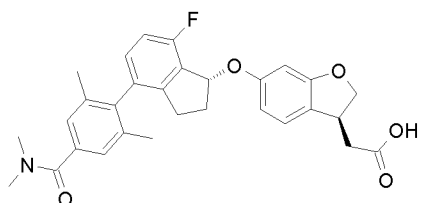
2-((S)-6-((R)-4-(4-Carbamoyl-2,6-dimethylphenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



- 10 30% Aqueous NH₃ solution (250 µL) and 35% aqueous H₂O₂ solution (83 µl) are added at 0°C to a solution of 2-((S)-6-((R)-4-(4-cyano-2,6-dimethylphenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid (19 mg) in ethanol (2 mL). The mixture is stirred at room temperature for 12 hours, while warming to room temperature. The mixture is concentrated, diluted with water and
- 15 neutralized with 4 M aqueous HCl solution. The resulting mixture is extracted with dichloromethane. The organic phase is dried (MgSO₄). The solvent is evaporated to give the title compound. Yield: 19 mg; LC (method 20): t_R = 5.33 min; Mass spectrum (ESI⁺): m/z = 476 [M+H]⁺.

20 **Example 92**

2-((S)-6-((R)-4-(4-(Dimethylcarbamoyl)-2,6-dimethylphenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



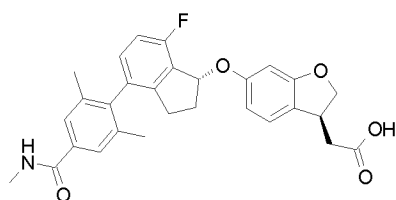
- LiOH·H₂O (11 mg) is added to a solution of methyl 2-((S)-6-((R)-4-(4-(dimethylcarbamoyl)-2,6-dimethylphenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate (70 mg) in ethanol (2.6 mL) and water (0.5 mL) and the mixture is stirred for 24 hours at room temperature. After concentration the
- 25

mixture is diluted with water, acidified with aqueous citric acid solution and extracted with dichloromethane. After concentration the mixture is partitioned between dichloromethane and citric acid. The organic phase is dried (MgSO_4) and concentrated to give the title compound. Yield 21 mg, LC (method 20): $t_R = 5.87$ min;

5 Mass spectrum (ESI^+): $m/z = 504$ $[\text{M}+\text{H}]^+$.

Example 93

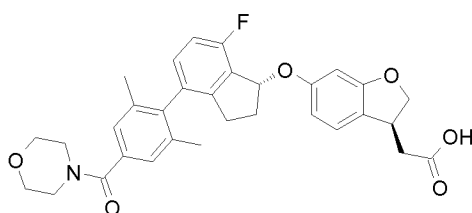
2-((S)-6-((R)-4-(2,6-Dimethyl-4-(methylcarbamoyl)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



10 $\text{LiOH}\cdot\text{H}_2\text{O}$ (3 mg) is added to a solution of methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-(methylcarbamoyl)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate (20 mg) in ethanol (0.77 mL) and water (0.5 mL) and the mixture is stirred for 24 hours at room temperature. After concentration the
15 mixture is diluted with water, acidified with aqueous citric acid solution and extracted with dichloromethane. The organic phase is dried (MgSO_4) and the residue chromatographed on silica gel (cyclohexane/ethyl acetate 100:0→60:40) to give the title compound. Yield 11 mg, LC (method 20): $t_R = 5.54$ min; Mass spectrum (ESI^+): $m/z = 490$ $[\text{M}+\text{H}]^+$.

Example 94

2-((S)-6-((R)-4-(2,6-Dimethyl-4-(morpholine-4-carbonyl)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid

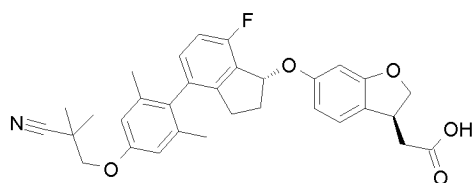


25 $\text{LiOH}\cdot\text{H}_2\text{O}$ (4.1 mg) is added to a solution of methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-(morpholine-4-carbonyl)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate (55 mg) in ethanol (1.9 mL) and water (0.5 mL) and

the mixture is stirred for 24 hours at room temperature. After concentration the mixture is diluted with water, acidified with aqueous citric acid solution and extracted with dichloromethane. The organic phase is dried (MgSO_4) and concentrated. The residue is chromatographed on silica gel (cyclohexane/ethyl acetate 50:50) to give the title compound. Yield 10 mg, LC (method 20): $t_R = 5.73$ min; Mass spectrum (ESI^+): $m/z = 546$ $[\text{M}+\text{H}]^+$.

Example 95

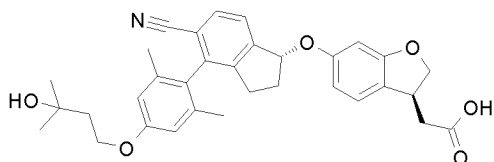
2-((S)-6-((R)-4-(4-(2-Cyano-2-methylpropoxy)-2,6-dimethylphenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



The title compound is prepared from methyl 2-((S)-6-((R)-4-(4-(2-cyano-2-methylpropoxy)-2,6-dimethylphenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate following a procedure analogous to that described in example 10. LC (method 8): $t_R = 0.70$ min; Mass spectrum (ESI^+): $m/z = 530$ $[\text{M}+\text{H}]^+$.

Example 96

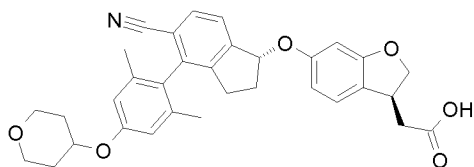
2-((S)-6-((R)-5-Cyano-4-(4-(3-hydroxy-3-methylbutoxy)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



The title compound is prepared from methyl 2-((S)-6-((R)-5-cyano-4-(4-(3-hydroxy-3-methylbutoxy)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate following a procedure analogous to that described in example 1. The mixture is stirred for 2 days. The product is purified by HPLC on reversed phase. LC (method 7): $t_R = 1.08$ min; Mass spectrum (ESI^+): $m/z = 559$ $[\text{M}+\text{NH}_4]^+$.

Example 97

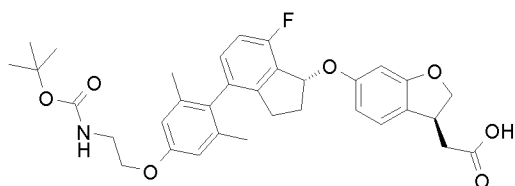
2-((S)-6-((R)-5-Cyano-4-(2,6-dimethyl-4-(tetrahydro-2H-pyran-4-yloxy)phenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



The title compound is prepared from methyl 2-((S)-6-((R)-5-cyano-4-(2,6-dimethyl-4-(tetrahydro-2H-pyran-4-yloxy)phenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate following a procedure analogous to that described in example 1. The mixture is stirred for 2 days at room temperature and for 2 hours at 50°C. The product is purified by HPLC on reversed phase. LC (method 7): $t_R = 1.10$ min; Mass spectrum (ESI⁺): $m/z = 540$ [M+H]⁺.

Example 98

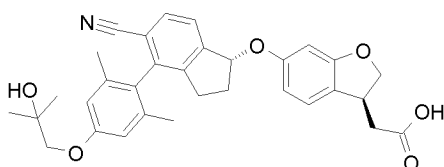
2-((S)-6-((R)-4-(4-(2-(tert-Butoxycarbonylamino)ethoxy)-2,6-dimethylphenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



The title compound is prepared from methyl 2-((S)-6-((R)-4-(4-(2-(tert-butoxycarbonylamino)ethoxy)-2,6-dimethylphenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate following a procedure analogous to that described in example 10. The mixture is stirred for 2 days at 50°C. The product is purified by HPLC on reversed phase. LC (method 8): $t_R = 0.73$ min; Mass spectrum (ESI⁺): $m/z = 592$ [M+H]⁺.

Example 99

2-((S)-6-((R)-5-Cyano-4-(4-(2-hydroxy-2-methylpropoxy)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid

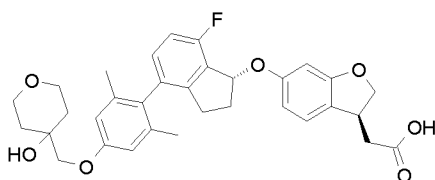


The title compound is prepared from methyl 2-((S)-6-((R)-5-cyano-4-(4-(3-hydroxy-3-methylbutoxy)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate following a procedure analogous to that described in example 1. The mixture is stirred for 2 days. The product is purified by HPLC on reversed phase.

5 LC (method 7): t_R = 1.07 min; Mass spectrum (ESI⁺): m/z = 545 [M+NH₄]⁺.

Example 100

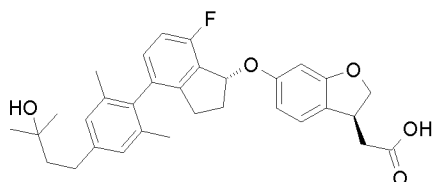
2-((S)-6-((R)-7-Fluoro-4-(4-((4-hydroxytetrahydro-2H-pyran-4-yl)methoxy)-2,6-
dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic
 10 acid



The title compound is prepared from methyl 2-((S)-6-((R)-7-fluoro-4-(4-((4-hydroxytetrahydro-2H-pyran-4-yl)methoxy)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate following a procedure analogous to that described in example 10. TLC: r_f = 0.2 (silicagel, ethyl acetate); Mass spectrum (ESI⁺): m/z = 563 [M+H]⁺.

Example 101

2-((S)-6-((R)-7-Fluoro-4-(4-(3-hydroxy-3-methylbutyl)-2,6-dimethylphenyl)-2,3-
 20 dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid

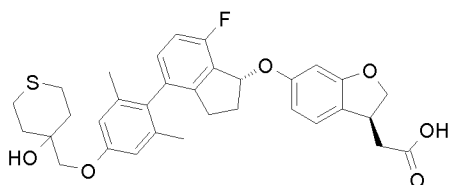


1 M aqueous NaOH solution (310 μ L) is added to a solution of methyl 2-((S)-6-((R)-7-fluoro-4-(4-(3-hydroxy-3-methylbutyl)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate (110 mg) in methanol (4 mL). The mixture is stirred at room temperature for 12 hours and at 50°C for 2 days. 1 M aqueous NaOH solution (100 μ L) is added and the mixture is stirred at 50°C for 1 hour. Methanol is evaporated in vacuo, the residue is diluted with water and neutralized with 1 M aqueous HCl. The resulting mixture is extracted with ethyl acetate, and the

combined organic phases are washed with brine and dried (MgSO_4). The solvent is evaporated to give the title compound. Yield: 80 mg; LC (method 8): $t_R = 0.59$ min; Mass spectrum (ESI^+): $m/z = 519$ $[\text{M}+\text{H}]^+$.

5 Example 102

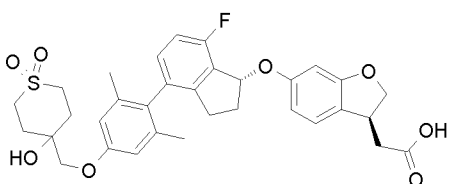
2-((S)-6-((R)-7-Fluoro-4-(4-(4-hydroxytetrahydro-2H-thiopyran-4-yl)methoxy)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



- 10 To a solution of methyl 2-((S)-6-((R)-7-fluoro-4-(4-hydroxy-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate (100 mg) in N,N-dimethylformamide (2 mL) is added Cs_2CO_3 (106 mg) and 1-oxa-6-thiaspiro[2.5]octane (37 mg). The mixture is stirred for 12 hour at 100°C . The mixture is diluted with water, acidified with 1 M aqueous HCl solution and extracted twice with
- 15 ethyl acetate. The combined organic phases are washed with water and brine, dried (MgSO_4) and concentrated. The residue is chromatographed on silica gel (cyclohexane/ethyl acetate/methanol 80:20:0 $\rightarrow$ 0:80:20) to give the title compound. Yield: 31 mg; LC (method 7): $t_R = 1.16$ min; Mass spectrum (ESI^+): $m/z = 579$ $[\text{M}+\text{H}]^+$.

20 Example 103

2-((S)-6-((R)-7-Fluoro-4-(4-((1,1-dioxo-4-hydroxytetrahydro-2H-thiopyran-4-yl)methoxy)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid

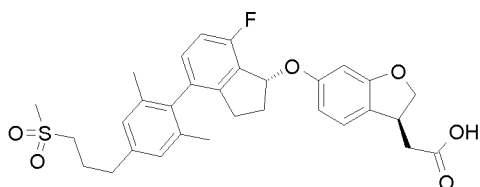


- 25 1 M aqueous NaOH solution (250 μL) is added to a solution of methyl 2-((S)-6-((R)-7-fluoro-4-(4-((1,1-dioxo-4-hydroxytetrahydro-2H-thiopyran-4-yl)methoxy)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate (85 mg) in tetrahydrofuran (4 mL). The mixture is stirred at room temperature for 12

hours. Then the mixture is diluted with ethyl acetate and neutralized with 1 M aqueous HCl solution. The resulting mixture is diluted with saturated aqueous NaCl solution and the phases are separated. The organic phase is dried (MgSO₄) and concentrated to give the title compound. Yield: 80 mg; LC (method 7): t_R = 1.04 min; Mass spectrum (ESI⁺): m/z = 611 [M+H]⁺.

Example 104

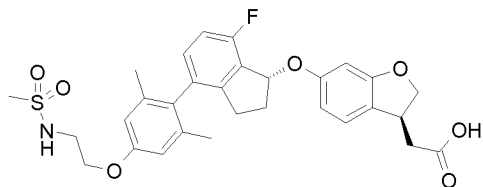
2-((S)-6-((R)-4-(2,6-Dimethyl-4-(3-(methylsulfonyl)propyl)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



1 M aqueous NaOH solution (50 µL) is added to a solution of methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-(3-(methylsulfonyl)propyl)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate (20 mg) in methanol (2 mL). The mixture is stirred at room temperature for 12 hours and at 50°C for 2 days. 1 M aqueous NaOH solution (18 µL) is added and the mixture is stirred at 50°C for 2 hours. Methanol is evaporated in vacuo, the residue is diluted with water and neutralized with 1 M aqueous HCl. The resulting mixture is extracted with ethyl acetate, and the organic phase is dried (MgSO₄). The solvent is evaporated and the residue is purified by HPLC on reversed phase to give the title compound. Yield: 7 mg; LC (method 8): t_R = 0.34 min; Mass spectrum (ESI⁺): m/z = 553 [M+H]⁺.

Example 105

2-((S)-6-((R)-4-(2,6-Dimethyl-4-(2-(methylsulfonamido)ethoxy)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid

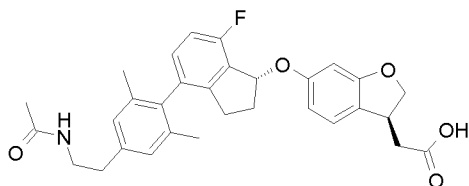


The title compound is prepared from methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-(2-(methylsulfonamido)ethoxy)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate following a procedure analogous to that described in

example 10. The mixture is stirred for 2 days at 50°C. The product is purified by HPLC on reversed phase. LC (method 7): $t_R = 1.05$ min; Mass spectrum (ESI^+): $m/z = 570$ $[M+H]^+$.

5 Example 106

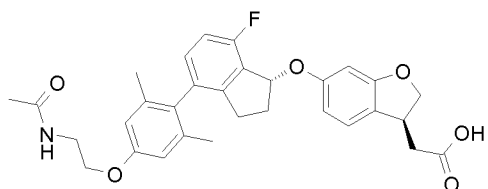
2-((S)-6-((R)-4-(4-(2-Acetamidoethyl)-2,6-dimethylphenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



The title compound is prepared from methyl 2-((S)-6-((R)-4-(4-(2-acetamidoethyl)-2,6-dimethylphenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate following a procedure analogous to that described in example 10. The mixture is stirred for 12 hours at 50°C. The product is purified by HPLC on reversed phase. LC (method 7): $t_R = 1.04$ min; Mass spectrum (ESI^+): $m/z = 518$ $[M+H]^+$.

15 Example 107

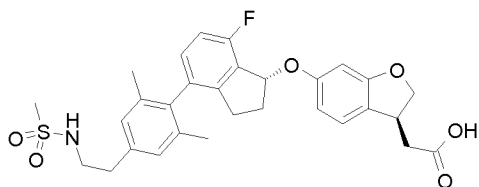
2-((S)-6-((R)-4-(4-(2-Acetamidoethoxy)-2,6-dimethylphenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



The title compound is prepared from methyl 2-((S)-6-((R)-4-(4-(2-acetamidoethoxy)-2,6-dimethylphenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate following a procedure analogous to that described in example 10. The mixture is stirred for 5 hours at 50°C. The product is purified by HPLC on reversed phase. LC (method 7): $t_R = 1.03$ min; Mass spectrum (ESI^+): $m/z = 534$ $[M+H]^+$.

25 Example 108

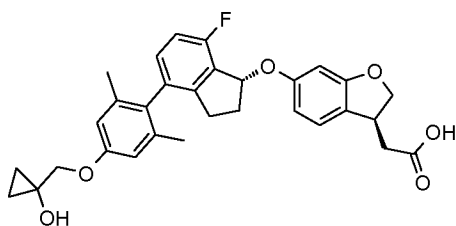
2-((S)-6-((R)-4-(2,6-dimethyl-4-(2-(methylsulfonamido)ethyl)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



The title compound is prepared from methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-(2-(methylsulfonamido)ethyl)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate following a procedure analogous to that described in
 5 example 10. The mixture is stirred for 20 hours at 50°C. The product is purified by HPLC on reversed phase. LC (method 7): t_R = 1.06 min; Mass spectrum (ESI⁺): m/z = 554 [M+H]⁺.

Example 109

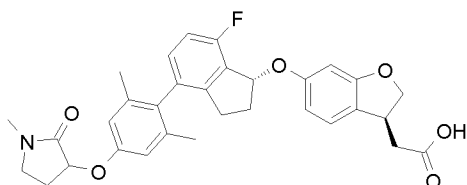
10 2-((S)-6-((R)-7-Fluoro-4-(4-((1-hydroxycyclopropyl)methoxy)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



Ethylmagnesium chloride (380 μ L of a 1 M solution in tetrahydrofurane) is added dropwise under argon to a solution of 2-((S)-6-((R)-7-fluoro-4-(4-(2-methoxy-2-oxoethoxy)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid in tetrahydrofurane (4 mL). The mixture is stirred
 15 at room temperature for 30 minutes. Ti(OiPr)₄ (120 μ L) is added dropwise and after stirring for 30 minutes ethylmagnesium chloride (1.15 mL of a 1 M solution in tetrahydrofurane) is added dropwise. The mixture is stirred for 2 hours, partitioned
 20 between ethylacetate and saturated aqueous NH₄Cl solution and stirred vigorously for 30 minutes. After filtering over celite the phases are separated, the aqueous phase is extracted with diethylether and the combined organic phases are washed with brine and dried (MgSO₄). The solvents are evaporated and the residue is purified by HPLC on reversed phase. Yield: 38 mg; LC (method 8): t_R = 0.38 min;
 25 Mass spectrum (ESI⁺): m/z = 519 [M+H]⁺.

Example 110

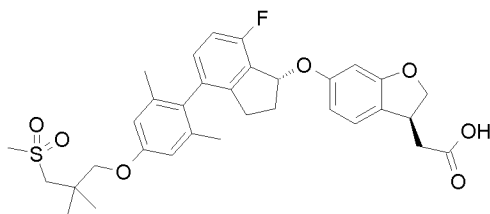
2-((3S)-6-((1R)-4-(2,6-Dimethyl-4-(1-methyl-2-oxopyrrolidin-3-yloxy)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



The title compound is prepared from methyl 2-((3S)-6-((1R)-4-(2,6-dimethyl-4-(1-methyl-2-oxopyrrolidin-3-yloxy)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate following a procedure analogous to that described in example 10. The mixture is stirred for 12 hours at 50°C. The product is purified by HPLC on reversed phase. LC (method 7): t_R = 1.06 min; Mass spectrum (ESI⁺): m/z = 546 [M+H]⁺.

Example 111

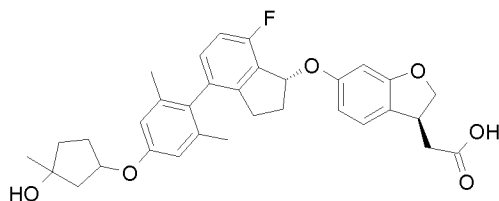
2-((S)-6-((R)-4-(4-(2,2-Dimethyl-3-(methylsulfonyl)propoxy)-2,6-dimethylphenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



The title compound is prepared from methyl 2-((S)-6-((R)-4-(4-(2,2-dimethyl-3-(methylsulfonyl)propoxy)-2,6-dimethylphenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate following a procedure analogous to that described in example 10. The mixture is stirred for 3 hours at 50°C. The product is purified by HPLC on reversed phase. LC (method 7): t_R = 1.14 min; Mass spectrum (ESI⁺): m/z = 597 [M+H]⁺.

Example 112

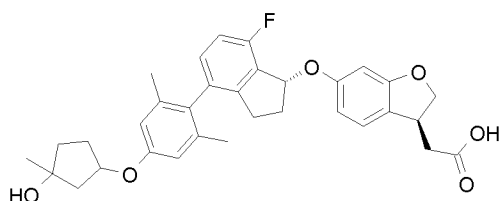
2-((3S)-6-((1R)-7-Fluoro-4-(4-(3-hydroxy-3-methylcyclopentyloxy)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid (diastereomer 1)



The title compound is prepared from methyl 2-((3S)-6-((1R)-7-fluoro-4-(4-(3-hydroxy-3-methylcyclopentyloxy)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate (diastereomer 1) following a procedure analogous to that described in example 1. LC (method 8): t_R = 0.54 min; Mass spectrum (ESI⁺): m/z = 547 [M+H]⁺.

Example 113

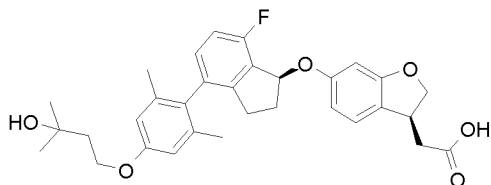
2-((3S)-6-((1R)-7-Fluoro-4-(4-(3-hydroxy-3-methylcyclopentyloxy)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid (diastereomer 2)



The title compound is prepared from methyl 2-((3S)-6-((1R)-7-fluoro-4-(4-(3-hydroxy-3-methylcyclopentyloxy)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate (diastereomer 2) following a procedure analogous to that described in example 1. LC (method 8): t_R = 0.56 min; Mass spectrum (ESI⁺): m/z = 547 [M+H]⁺.

Example 114

2-((S)-6-((S)-7-Fluoro-4-(4-(3-hydroxy-3-methylbutoxy)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



1 M aqueous NaOH solution (39 μ L) is added to a solution of methyl 2-((3S)-6-(7-fluoro-4-(4-(3-hydroxy-3-methylbutoxy)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate (48 mg) in tetrahydrofuran (2 mL). The

mixture is stirred at room temperature for 12 hours. The mixture is diluted with water and neutralized with 4 M aqueous HCl solution (41 μ L). The resulting mixture is extracted with ethyl acetate, and the combined extracts are washed with brine and dried (MgSO₄). After evaporation of the solvents the diastereomers are separated by

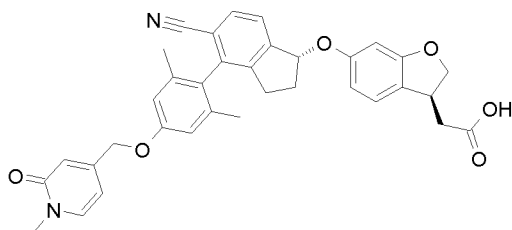
5 SFC on chiral phase (column: Daicel ADH, 5 μ m, 250 mm x 10 mm; eluent: scCO₂/(methanol+0.2% diethylamine) 80:20, 10 mL/min):

2-((S)-6-((R)-7-fluoro-4-(4-(3-hydroxy-3-methylbutoxy)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid (diastereomer 1): t_R = 22.1 min; Yield: 15 mg; Mass spectrum (ESI⁺): m/z = 535 [M+H]⁺.

10 2-((S)-6-((S)-7-fluoro-4-(4-(3-hydroxy-3-methylbutoxy)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid (diastereomer 2): t_R = 31.1 min; Yield: 10 mg; Mass spectrum (ESI⁺): m/z = 535 [M+H]⁺.

Example 115

15 2-((S)-6-((R)-5-Cyano-4-(2,6-dimethyl-4-((1-methyl-2-oxo-1,2-dihydropyridin-4-yl)methoxy)phenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid

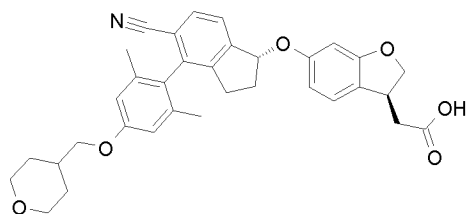


The title compound is prepared from methyl 2-((S)-6-((R)-5-cyano-4-(2,6-dimethyl-4-((1-methyl-2-oxo-1,2-dihydropyridin-4-yl)methoxy)phenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate following a procedure analogous to that described in example 10. The mixture is stirred for 2 days at room temperature and for 2 hours at 50°C. LC (method 9): t_R = 1.01 min; Mass spectrum (ESI⁺): m/z = 577 [M+H]⁺.

25

Example 116

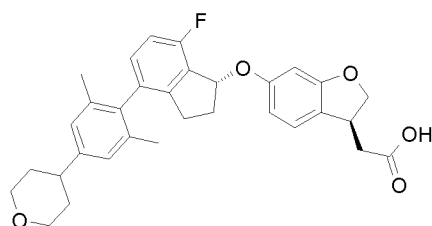
2-((S)-6-((R)-5-Cyano-4-(2,6-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methoxy)phenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



The title compound is prepared from methyl 2-((S)-6-((R)-5-cyano-4-(2,6-dimethyl-4-
((tetrahydro-2H-pyran-4-yl)methoxy)phenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-
dihydrobenzofuran-3-yl)acetate following a procedure analogous to that described in
5 example 10. The mixture is stirred for 2 days at room temperature. LC (method 9): t_R
= 1.14 min; Mass spectrum (ESI^+): m/z = 554 $[M+H]^+$.

Example 117

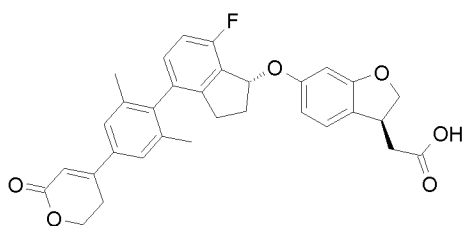
2-((S)-6-((R)-4-(2,6-Dimethyl-4-(tetrahydro-2H-pyran-4-yl)phenyl)-7-fluoro-2,3-
10 dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



The title compound is prepared from methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-
(tetrahydro-2H-pyran-4-yl)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-
dihydrobenzofuran-3-yl)acetate following a procedure analogous to that described in
15 example 1. LC (method 26): t_R = 0.79 min; Mass spectrum (ESI^+): m/z = 517 $[M+H]^+$.

Example 118

2-((S)-6-((R)-4-(2,6-Dimethyl-4-(6-oxo-3,6-dihydro-2H-pyran-4-yl)phenyl)-7-fluoro-
2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid

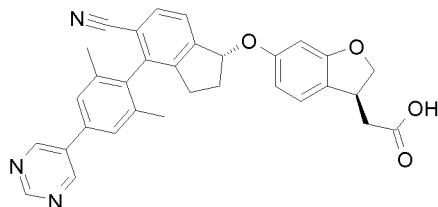


The title compound is prepared from methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-(6-oxo-
3,6-dihydro-2H-pyran-4-yl)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydro
benzofuran-3-yl)acetate following a procedure analogous to that described in

example 1. The product is purified by HPLC on reversed phase. LC (method 9): t_R = 0.96 min; Mass spectrum (ESI⁺): m/z = 529 [M+H]⁺.

Example 119

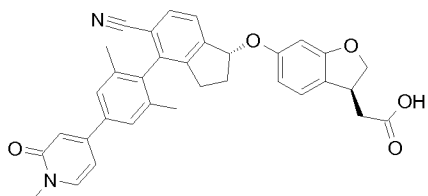
- 5 2-((S)-6-((R)-5-Cyano-4-(2,6-dimethyl-4-(pyrimidin-5-yl)phenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



- The title compound is prepared from methyl 2-((S)-6-((R)-5-cyano-4-(2,6-dimethyl-4-(pyrimidin-5-yl)phenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate following a procedure analogous to that described in example 10. The mixture is stirred for 12 hours at 50°C. LC (method 9): t_R = 1.04 min; Mass spectrum (ESI⁺): m/z = 518 [M+H]⁺.

Example 120

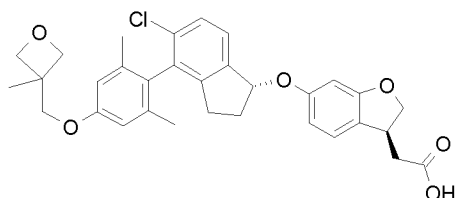
- 15 2-((S)-6-((R)-5-Cyano-4-(2,6-dimethyl-4-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)phenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



- The title compound is prepared from methyl 2-((S)-6-((R)-5-cyano-4-(2,6-dimethyl-4-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)phenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate following a procedure analogous to that described in example 1. The mixture is stirred for 4 hours at 50°C. The product is purified by HPLC on reversed phase. LC (method 9): t_R = 1.00 min; Mass spectrum (ESI⁺): m/z = 547 [M+H]⁺.

- 25 **Example 121**

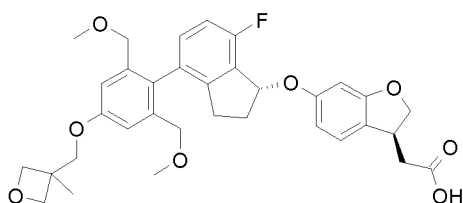
2-((S)-6-((R)-5-Chloro-4-(2,6-dimethyl-4-((3-methyloxetan-3-yl)methoxy)phenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



The title compound is prepared from methyl 2-((S)-6-((R)-5-chloro-4-(2,6-dimethyl-4-
 5 ((3-methyloxetan-3-yl)methoxy)phenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate following a procedure analogous to that described in example 10. LC (method 8): t_R = 0.71 min; Mass spectrum (ESI^+): m/z = 549 $[M+H]^+$.

Example 122

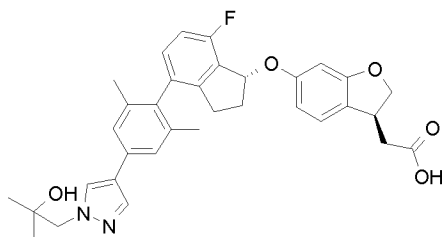
10 2-((S)-6-((R)-4-(2,6-Bis(methoxymethyl)-4-((3-methyloxetan-3-yl)methoxy)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



The title compound is prepared from methyl 2-((S)-6-((R)-4-(2,6-bis(methoxymethyl)-
 4-((3-methyloxetan-3-yl)methoxy)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-
 15 dihydrobenzofuran-3-yl)acetate following a procedure analogous to that described in example 10. LC (method 8): t_R = 0.43 min; Mass spectrum (ESI^+): m/z = 593 $[M+H]^+$.

Example 123

20 2-((S)-6-((R)-7-Fluoro-4-(4-(1-(2-hydroxy-2-methylpropyl)-1H-pyrazol-4-yl)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid

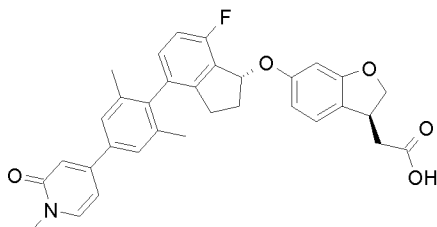


The title compound is prepared from methyl 2-((S)-6-((R)-7-fluoro-4-(4-(1-(2-hydroxy-
 2-methylpropyl)-1H-pyrazol-4-yl)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-

2,3-dihydrobenzofuran-3-yl)acetate following a procedure analogous to that described in example 10. LC (method 11): $t_R = 1.13$ min; Mass spectrum (ESI^+): $m/z = 571$ $[M+H]^+$.

5 **Example 124**

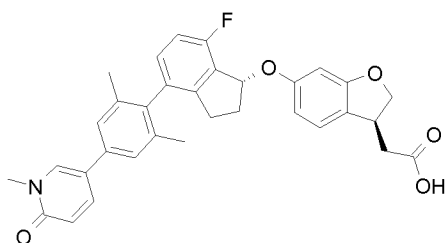
2-((S)-6-((R)-4-(2,6-Dimethyl-4-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



The title compound is prepared from methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-(1-methyl-
10 2-oxo-1,2-dihydropyridin-4-yl)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate following a procedure analogous to that described in example 10. LC (method 11): $t_R = 1.09$ min; Mass spectrum (ESI^+): $m/z = 540$ $[M+H]^+$.

15 **Example 125**

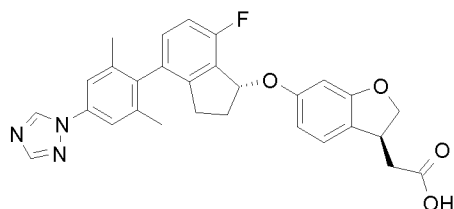
2-((S)-6-((R)-4-(2,6-Dimethyl-4-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



The title compound is prepared from methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-(1-methyl-
20 6-oxo-1,6-dihydropyridin-3-yl)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate following a procedure analogous to that described in example 10. LC (method 11): $t_R = 1.09$ min; Mass spectrum (ESI^+): $m/z = 540$ $[M+H]^+$.

25 **Example 126**

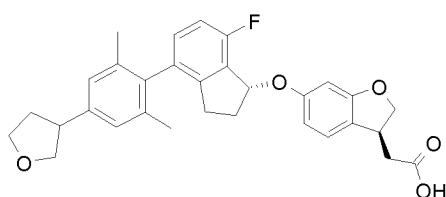
2-((S)-6-((R)-4-(2,6-Dimethyl-4-(1H-1,2,4-triazol-1-yl)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



The title compound is prepared from methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-(1H-1,2,4-triazol-1-yl)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate following a procedure analogous to that described in example 10. LC (method 7): $t_R = 1.06$ min; Mass spectrum (ESI^+): $m/z = 500$ $[M+H]^+$.

Example 127

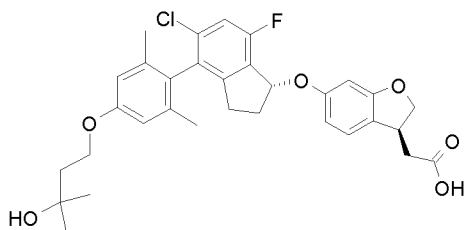
2-((3S)-6-((1R)-4-(2,6-Dimethyl-4-(tetrahydrofuran-3-yl)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



The title compound is prepared from 2-((S)-6-((R)-4-(4-(2,5-dihydrofuran-3-yl)-2,6-dimethylphenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid by hydrogenation in the presence of palladium (10 % on carbon) in ethyl acetate at room temperature. LC (method 9): $t_R = 1.17$ min; Mass spectrum (ESI^+): $m/z = 503$ $[M+H]^+$.

Example 128

2-((S)-6-((R)-5-Chloro-7-fluoro-4-(4-(3-hydroxy-3-methylbutoxy)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid

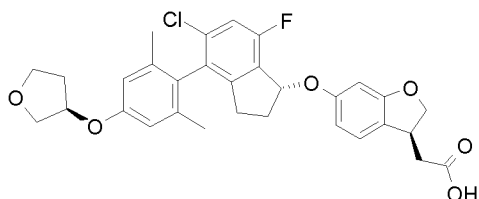


The title compound is prepared from methyl 2-((S)-6-((R)-5-chloro-7-fluoro-4-(4-(3-hydroxy-3-methylbutoxy)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-

dihydrobenzofuran-3-yl)acetate following a procedure analogous to that described in example 10. LC (method 9): $t_R = 1.17$ min; Mass spectrum (ESI^-): $m/z = 567$ $[M-H]^-$.

Example 129

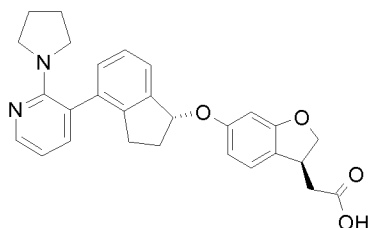
- 5 2-((S)-6-((R)-5-Chloro-4-(2,6-dimethyl-4-((R)-tetrahydrofuran-3-yloxy)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



- The title compound is prepared from methyl 2-((S)-6-((R)-5-chloro-4-(2,6-dimethyl-4-((R)-tetrahydrofuran-3-yloxy)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate following a procedure analogous to that described in example 10. LC (method 9): $t_R = 1.18$ min; Mass spectrum (ESI^-): $m/z = 551$ $[M-H]^-$.

Example 130

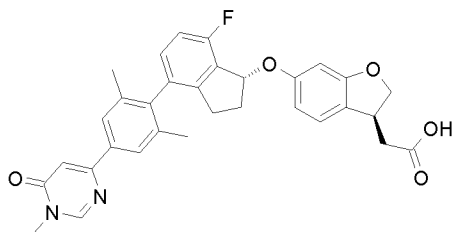
- 15 2-((3S)-6-((1R)-4-(2-(Pyrrolidin-1-yl)pyridin-3-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



- The title compound is prepared from methyl 2-((3S)-6-((1R)-4-(2-(pyrrolidin-1-yl)pyridin-3-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate following a procedure analogous to that described in example 10. LC (method 7): $t_R = 0.87$ min; Mass spectrum (ESI^+): $m/z = 457$ $[M+H]^+$.

Example 131

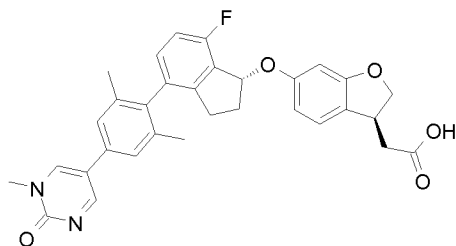
2-((S)-6-((R)-4-(2,6-Dimethyl-4-(1-methyl-6-oxo-1,6-dihydropyrimidin-4-yl)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



The title compound is prepared from methyl 2-((S)-6-((R)-5-cyano-4-(2,6-dimethyl-4-(1-methyl-2-oxo-1,2-dihydropyrimidin-4-yl)phenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate following a procedure analogous to that described in example 1. The mixture is stirred for 1 hour at 40°C. The product is purified by HPLC on reversed phase. LC (method 11): t_R = 1.09 min; Mass spectrum (ESI⁺): m/z = 541 [M+H]⁺.

Example 132

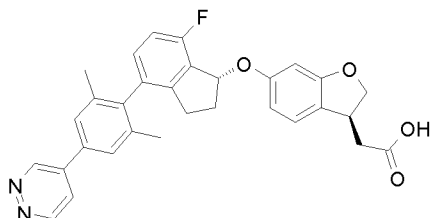
2-((S)-6-((R)-4-(2,6-Dimethyl-4-(1-methyl-2-oxo-1,2-dihydropyrimidin-5-yl)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



The title compound is prepared from methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-(1-methyl-2-oxo-1,2-dihydropyrimidin-5-yl)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate following a procedure analogous to that described in example 1. The mixture is stirred for 2 hours at 40°C. LC (method 15): t_R = 1.05 min; Mass spectrum (ESI⁺): m/z = 541 [M+H]⁺.

Example 133

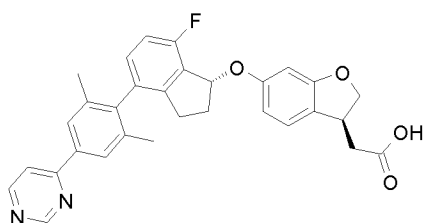
2-((S)-6-((R)-4-(2,6-Dimethyl-4-(pyridazin-4-yl)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



The title compound is prepared from methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-(pyridazin-4-yl)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate following a procedure analogous to that described in example 1. The mixture is stirred for 4 hours at 40°C. LC (method 15): t_R = 1.10 min;
5 Mass spectrum (ESI⁺): m/z = 511 [M+H]⁺.

Example 134

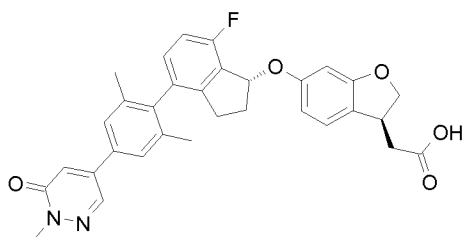
2-((S)-6-((R)-4-(2,6-Dimethyl-4-(pyrimidin-4-yl)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



10 The title compound is prepared from methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-(pyrimidin-4-yl)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate following a procedure analogous to that described in example 1. The mixture is stirred for 2 hours at 40°C. LC (method 15): t_R = 1.18 min;
15 Mass spectrum (ESI⁺): m/z = 511 [M+H]⁺.

Example 135

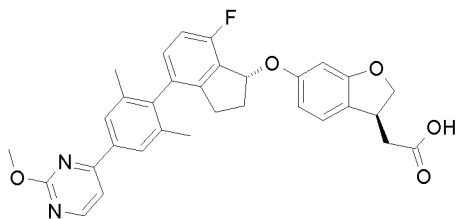
2-((S)-6-((R)-4-(2,6-Dimethyl-4-(1-methyl-6-oxo-1,6-dihydropyridazin-4-yl)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



20 The title compound is prepared from methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-(1-methyl-6-oxo-1,6-dihydropyridazin-4-yl)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate following a procedure analogous to that described in example 1. The mixture is stirred for 2 days at room temperature. LC (method 14): t_R
25 = 0.82 min; Mass spectrum (ESI⁺): m/z = 541 [M+H]⁺.

Example 136

Methyl 2-((S)-6-((R)-7-fluoro-4-(4-(2-methoxypyrimidin-4-yl)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate

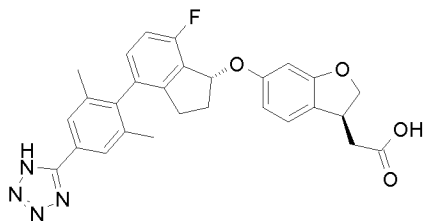


- 5 The title compound is prepared from methyl 2-((S)-6-((R)-7-fluoro-4-(4-(2-methoxypyrimidin-4-yl)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate following a procedure analogous to that described in example 1. The mixture is stirred for 4 hours at room temperature. LC (method 8): t_R = 0.60 min; Mass spectrum (ESI^+): m/z = 541 $[M+H]^+$.

10

Example 137

2-((S)-6-((R)-4-(2,6-Dimethyl-4-(1H-tetrazol-5-yl)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid

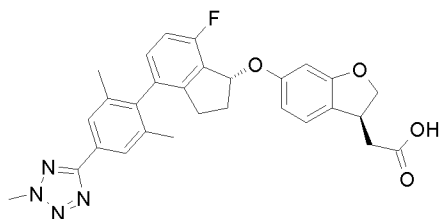


- 15 The title compound is prepared from methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-(1H-tetrazol-5-yl)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate following a procedure analogous to that described in example 1. The mixture is stirred for 2 hours at 40°C. The product is purified by HPLC on reversed phase. LC (method 11): t_R = 1.05 min; Mass spectrum (ESI^+): m/z = 501 $[M+H]^+$.

20

Example 138

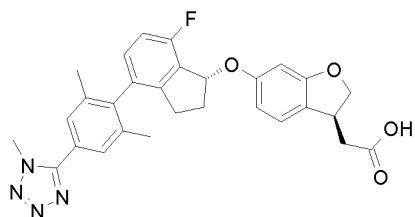
2-((S)-6-((R)-4-(2,6-Dimethyl-4-(2-methyl-2H-tetrazol-5-yl)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



The title compound is prepared from methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-(2-methyl-2H-tetrazol-5-yl)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate following a procedure analogous to that described in example 1. The mixture is stirred for 3 hours at 40°C. LC (method 11): t_R = 1.17 min; Mass spectrum (ESI⁺): m/z = 515 [M+H]⁺.

Example 139

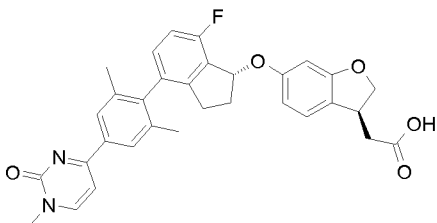
2-((S)-6-((R)-4-(2,6-Dimethyl-4-(1-methyl-1H-tetrazol-5-yl)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



The title compound is prepared from methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-(1-methyl-1H-tetrazol-5-yl)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate following a procedure analogous to that described in example 1. The mixture is stirred for 2 hours at 40°C. The product is purified by HPLC on reversed phase. LC (method 11): t_R = 1.10 min; Mass spectrum (ESI⁺): m/z = 515 [M+H]⁺.

Example 140

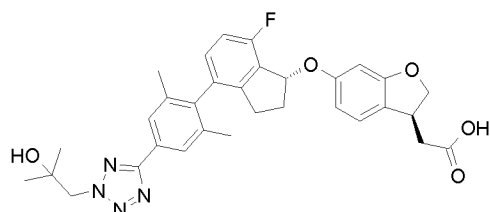
2-((S)-6-((R)-4-(2,6-Dimethyl-4-(1-methyl-2-oxo-1,2-dihydropyrimidin-4-yl)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



The title compound is prepared from methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-(1-methyl-2-oxo-1,2-dihydropyrimidin-4-yl)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate following a procedure analogous to that described in example 1. The mixture is stirred for 6 hours at room temperature. LC (method 11): t_R = 1.01 min; Mass spectrum (ESI⁺): m/z = 541 [M+H]⁺.

Example 141

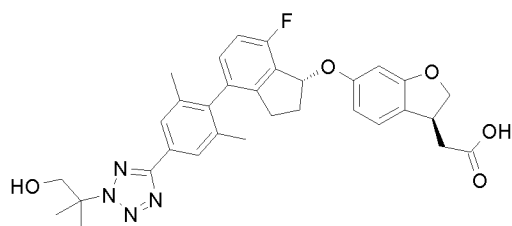
2-((S)-6-((R)-7-Fluoro-4-(4-(2-(2-hydroxy-2-methylpropyl)-2H-tetrazol-5-yl)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



The title compound is prepared from methyl 2-((S)-6-((R)-7-fluoro-4-(4-(2-(2-hydroxy-2-methylpropyl)-2H-tetrazol-5-yl)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate following a procedure analogous to that described in example 1. The mixture is stirred for 2 hours at 40°C. LC (method 11): t_R = 1.15 min; Mass spectrum (ESI⁺): m/z = 573 [M+H]⁺.

Example 142

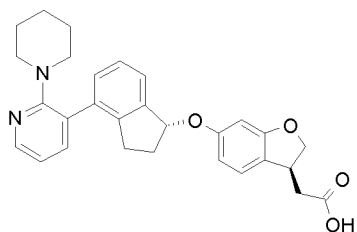
2-((S)-6-((R)-7-Fluoro-4-(4-(2-(1-hydroxy-2-methylpropan-2-yl)-2H-tetrazol-5-yl)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



The title compound is prepared from methyl 2-((S)-6-((R)-7-fluoro-4-(4-(2-(1-hydroxy-2-methylpropan-2-yl)-2H-tetrazol-5-yl)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate following a procedure analogous to that described in example 1. The mixture is stirred for 2 hours at 40°C. LC (method 11): t_R = 1.16 min; Mass spectrum (ESI⁺): m/z = 573 [M+H]⁺.

Example 143

2-((3S)-6-((1R)-4-(2-(Piperidin-1-yl)pyridin-3-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



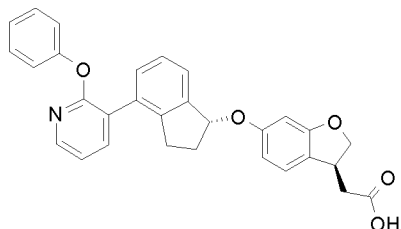
5

The title compound is prepared from methyl 2-((3S)-6-((1R)-4-(2-(piperidin-1-yl)pyridin-3-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate following a procedure analogous to that described in example 10. LC (method 7): t_R = 0.90 min; Mass spectrum (ESI⁺): m/z = 471 [M+H]⁺.

10

Example 144

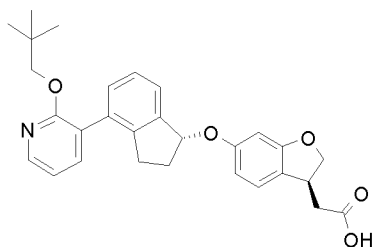
2-((3S)-6-((1R)-4-(2-Phenoxypyridin-3-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



15 The title compound is prepared from methyl 2-((3S)-6-((1R)-4-(2-phenoxypyridin-3-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate following a procedure analogous to that described in example 10. LC (method 7): t_R = 1.12 min; Mass spectrum (ESI⁺): m/z = 480 [M+H]⁺.

Example 145

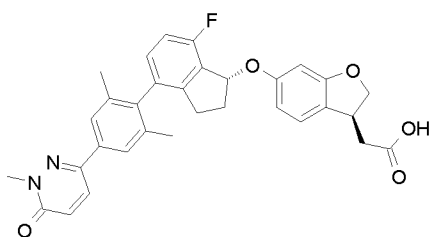
2-((3S)-6-((1R)-4-(2-(Neopentyloxy)pyridin-3-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



The title compound is prepared from methyl 2-((3S)-6-(((1R)-4-(2-(neopentyloxy)pyridin-3-yl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate following a procedure analogous to that described in example 1. The product is purified by HPLC on reversed phase. LC (method 15): t_R = 1.26 min; Mass spectrum (ESI⁺): m/z = 492 [M+H]⁺.

Example 146

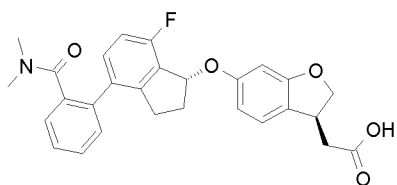
2-((S)-6-((R)-4-(2,6-Dimethyl-4-(1-methyl-6-oxo-1,6-dihydropyridazin-3-yl)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



The title compound is prepared from methyl 2-((S)-6-((R)-4-(2,6-dimethyl-4-(1-methyl-6-oxo-1,6-dihydropyridazin-3-yl)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate following a procedure analogous to that described in example 1. LC (method 7): t_R = 1.09 min; Mass spectrum (ESI⁺): m/z = 541 [M+H]⁺.

Example 147

2-((3S)-6-(((1R)-4-(2-(Dimethylcarbamoyl)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid

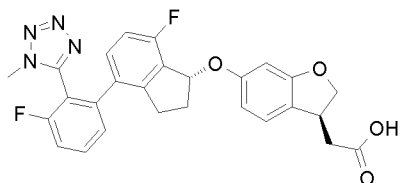


The title compound is prepared from methyl 2-((3S)-6-(((1R)-4-(2-(dimethylcarbamoyl)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate following a procedure analogous to that described in

example 1. The product is purified by HPLC on reversed phase. LC (method 9): t_R = 1.01 min; Mass spectrum (ESI⁺): m/z = 476 [M+H]⁺.

Example 148

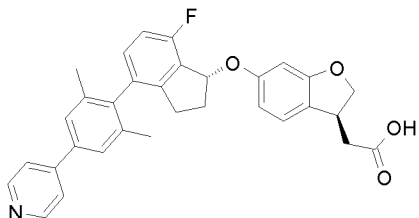
- 5 2-((3S)-6-((1R)-7-Fluoro-4-(3-fluoro-2-(1-methyl-1H-tetrazol-5-yl)phenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



- The title compound is prepared from methyl 2-((3S)-6-((1S)-7-fluoro-4-(3-fluoro-2-(1-methyl-1H-tetrazol-5-yl)phenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetate following a procedure analogous to that described in example 1. The product is purified by HPLC on reversed phase. LC (method 9): t_R = 1.01 min; Mass spectrum (ESI⁺): m/z = 505 [M+H]⁺.

Example 149

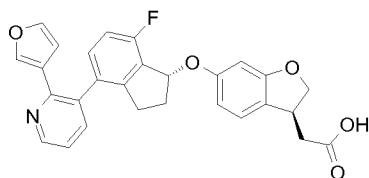
- 15 {{(S)-6-[(R)-4-(2,6-Dimethyl-4-pyridin-4-yl-phenyl)-7-fluoro-indan-1-yloxy]-2,3-dihydrobenzofuran-3-yl}-acetic acid



- The title compound is prepared from {{(S)-6-[(R)-4-(2,6-dimethyl-4-pyridin-4-yl-phenyl)-7-fluoro-indan-1-yloxy]-2,3-dihydrobenzofuran-3-yl}-acetic acid methyl ester following a procedure analogous to that described for Example 10; if the title compound does not precipitate from the aqueous solution, the crude title compound is purified by HPLC. LC (method 9): t_R = 0.98 min; Mass spectrum (ESI⁺): m/z = 510 [M+H]⁺.

Example 150

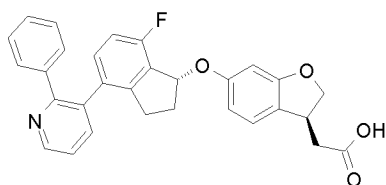
- 25 {{(S)-6-[(R)-7-Fluoro-4-(2-furan-3-yl-pyridin-3-yl)-indan-1-yloxy]-2,3-dihydrobenzofuran-3-yl}-acetic acid



The title compound is prepared from {(S)-6-[(R)-7-fluoro-4-(2-furan-3-yl-pyridin-3-yl)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester following a procedure analogous to that described for Example 10; if the title compound does not precipitate from the aqueous solution, the crude title compound is purified by HPLC. LC (method 9): t_R = 1.04 min; Mass spectrum (ESI⁺): m/z = 472 [M+H]⁺.

Example 151

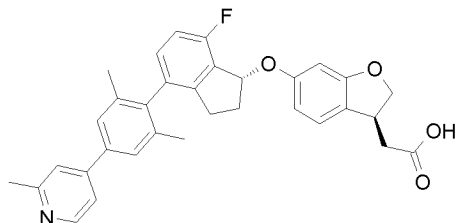
{(S)-6-[(R)-7-Fluoro-4-(2-phenyl-pyridin-3-yl)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid



The title compound is prepared from {(S)-6-[(R)-7-fluoro-4-(2-phenyl-pyridin-3-yl)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester following a procedure analogous to that described for Example 10; if the title compound does not precipitate from the aqueous solution, the crude title compound is purified by HPLC. LC (method 9): t_R = 1.04 min; Mass spectrum (ESI⁺): m/z = 482 [M+H]⁺.

Example 152

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



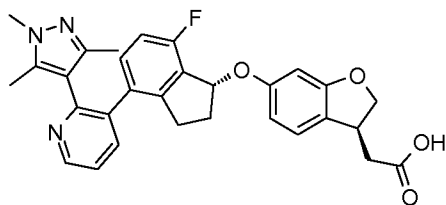
The methyl ester of the title compound is prepared from {(S)-6-[(R)-7-fluoro-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester and 4-(4-bromo-3,5-dimethyl-phenyl)-2-methyl-pyridine following a procedure analogous to that described in Step 5 of Intermediate 12.

Saponification of the methyl ester following a procedure analogous to that described for Example 10 gives the title compound; if the title compound does not precipitate from the aqueous solution, the crude title compound is purified by HPLC. LC (method 9): $t_R = 0.95$ min; Mass spectrum (ESI^+): $m/z = 524$ $[M+H]^+$.

5

Example 153

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

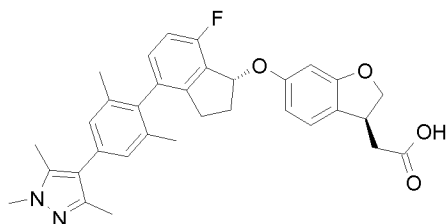


- 10 The methyl ester of the title compound is prepared from {(S)-6-[(R)-4-(2-bromo-pyridin-3-yl)-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester and 1,3,5-trimethyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-pyrazole following a procedure analogous to that described in Step 5 of Intermediate 12. Saponification of the methyl ester, {(S)-6-[(R)-7-fluoro- 4-[2-(1,3,5-trimethyl-1H-
- 15 pyrazol-4-yl)-pyridin-3-yl]-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester, following a procedure analogous to that described for Example 10 gives the title compound; if the title compound does not precipitate from the aqueous solution, the crude title compound is purified by HPLC. LC (method 9): $t_R = 0.88$ min; Mass spectrum (ESI^+): $m/z = 514$ $[M+H]^+$.

20

Example 154

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

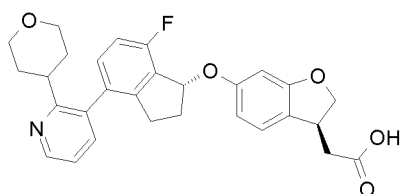


- 25 The title compound is prepared from {(S)-6-[(R)-7-fluoro-4-(2,6-dimethyl-4-(1,3,5-trimethyl-pyrazol-4-yl)-phenyl)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester following a procedure analogous to that described for Example 10; if the

title compound does not precipitate from the aqueous solution, the crude title compound is purified by HPLC. LC (method 9): $t_R = 1.13$ min; Mass spectrum (ESI⁺): $m/z = 541$ [M+H]⁺.

5 Example 155

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

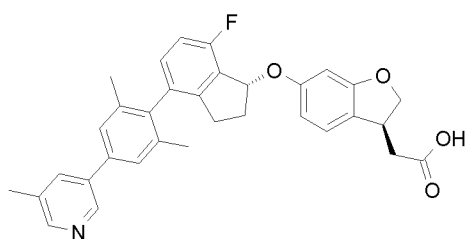


A mixture of {{(S)-6-[(R)-7-fluoro-4-(2-(3,6-dihydro-pyran-4-yl)-pyridin-3-yl)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid (30 mg), 10% palladium on carbon (10 mg) and methanol (3 mL) is shaken under hydrogen atmosphere (3 bar) at room temperature for 12 h. The mixture is filtered over Celite and the filtrate is concentrated to give the title compound. LC (method 9): $t_R = 0.96$ min; Mass spectrum (ESI⁺): $m/z = 490$ [M+H]⁺.

15

Example 156

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

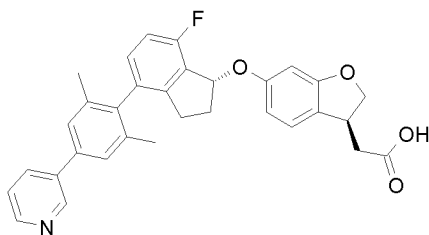


The title compound is prepared from {{(S)-6-[(R)-4-(2,6-dimethyl-4-(5-methyl-pyridin-3-yl)-phenyl)-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester following a procedure analogous to that described for Example 10; if the title compound does not precipitate from the aqueous solution, the crude title compound is purified by HPLC. LC (method 9): $t_R = 1.06$ min; Mass spectrum (ESI⁺): $m/z = 524$ [M+H]⁺.

25

Example 157

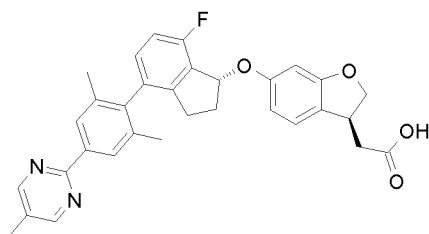
{{(S)-6-[(R)-4-(2,6-Dimethyl-4-pyridin-3-yl-phenyl)-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid



The title compound is prepared from {(S)-6-[(R)-4-(2,6-dimethyl-4-pyridin-3-yl-phenyl)-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester following a procedure analogous to that described for Example 10; if the title compound does not precipitate from the aqueous solution, the crude title compound is purified by HPLC. LC (method 9): $t_R = 1.06$ min; Mass spectrum (ESI⁺): $m/z = 510$ [M+H]⁺.

Example 158

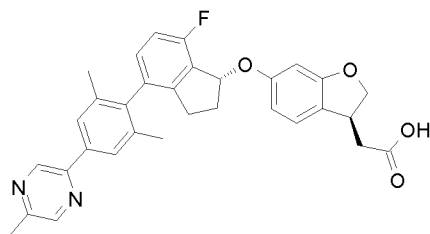
{{(S)-6-[(R)-4-(2,6-Dimethyl-4-(5-methyl-pyrimidin-2-yl)-phenyl)-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid



The title compound is prepared from {(S)-6-[(R)-4-(2,6-dimethyl-4-(5-methyl-pyrimidin-2-yl)-phenyl)-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester following a procedure analogous to that described for Example 10; if the title compound does not precipitate from the aqueous solution, the crude title compound is purified by HPLC. LC (method 7): $t_R = 1.19$ min; Mass spectrum (ESI⁻): $m/z = 523$ [M-H]⁻.

Example 159

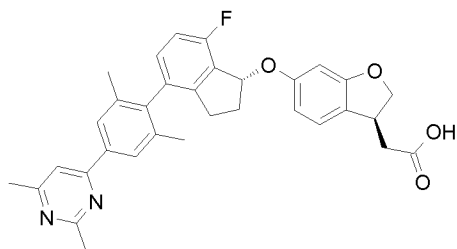
{{(S)-6-[(R)-4-(2,6-Dimethyl-4-(5-methyl-pyrazin-2-yl)-phenyl)-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid



The title compound is prepared from {(S)-6-[(R)-4-(2,6-dimethyl-4-(5-methyl-pyrazin-2-yl)-phenyl)-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester following a procedure analogous to that described for Example 10; if the title compound does not precipitate from the aqueous solution, the crude title compound is purified by HPLC. LC (method 7): $t_R = 1.05$ min; Mass spectrum (ESI^+): $m/z = 525$ $[M+H]^+$.

Example 160

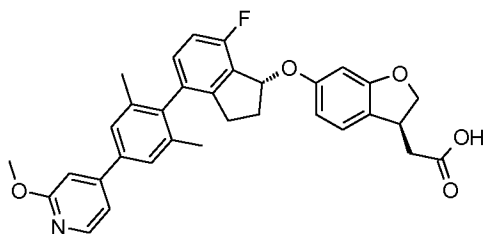
{(S)-6-[(R)-4-(2,6-Dimethyl-4-(2,6-dimethyl-pyrimidin-4-yl)-phenyl)-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid



The title compound is prepared from {(S)-6-[(R)-4-(2,6-dimethyl-4-(2,6-dimethyl-pyrimidin-4-yl)-phenyl)-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester following a procedure analogous to that described for Example 10; if the title compound does not precipitate from the aqueous solution, the crude title compound is purified by HPLC. LC (method 7): $t_R = 1.15$ min; Mass spectrum (ESI^-): $m/z = 537$ $[M-H]^-$.

Example 161

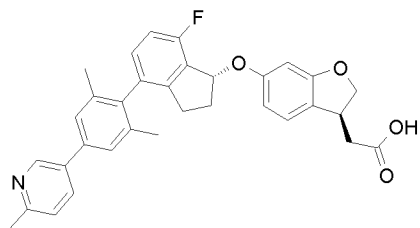
{(S)-6-[(R)-4-(2,6-Dimethyl-4-(2-methoxy-pyridin-4-yl)-phenyl)-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid



The title compound is prepared from {(S)-6-[(R)-4-(2,6-dimethyl-4-(2-methoxy-pyridin-4-yl)-phenyl)-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester following a procedure analogous to that described for Example 10; if the title compound does not precipitate from the aqueous solution, the crude title compound is purified by HPLC. LC (method 9): $t_R = 1.23$ min; Mass spectrum (ESI^+): $m/z = 540$ $[M+H]^+$.

Example 162

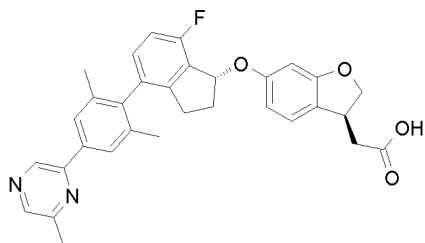
{(S)-6-[(R)-4-(2,6-Dimethyl-4-(6-methyl-pyridin-3-yl)-phenyl)-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid



The title compound is prepared from {(S)-6-[(R)-4-(2,6-dimethyl-4-(6-methyl-pyridin-3-yl)-phenyl)-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester following a procedure analogous to that described for Example 10; if the title compound does not precipitate from the aqueous solution, the crude title compound is purified by HPLC. LC (method 7): $t_R = 0.84$ min; Mass spectrum (ESI^+): $m/z = 524$ $[M+H]^+$.

Example 163

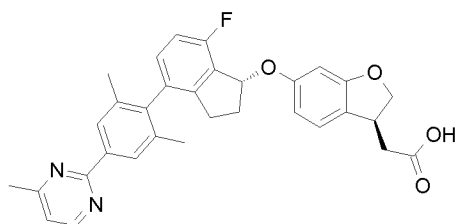
{(S)-6-[(R)-4-(2,6-Dimethyl-4-(6-methyl-pyrazin-2-yl)-phenyl)-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid



The title compound is prepared from {(S)-6-[(R)-4-(2,6-dimethyl-4-(6-methyl-pyrazin-2-yl)-phenyl)-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester following a procedure analogous to that described for Example 10; if the title compound does not precipitate from the aqueous solution, the crude title compound is purified by HPLC. LC (method 9): $t_R = 1.18$ min; Mass spectrum (ESI⁺): $m/z = 525$ [M+H]⁺.

Example 164

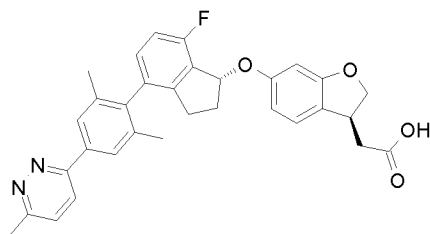
{(S)-6-[(R)-4-(2,6-Dimethyl-4-(4-methyl-pyrimidin-2-yl)-phenyl)-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid



The title compound is prepared from {(S)-6-[(R)-4-(2,6-dimethyl-4-(4-methyl-pyrimidin-2-yl)-phenyl)-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester following a procedure analogous to that described for Example 10; if the title compound does not precipitate from the aqueous solution, the crude title compound is purified by HPLC. LC (method 9): $t_R = 1.20$ min; Mass spectrum (ESI⁻): $m/z = 523$ [M-H]⁻.

Example 165

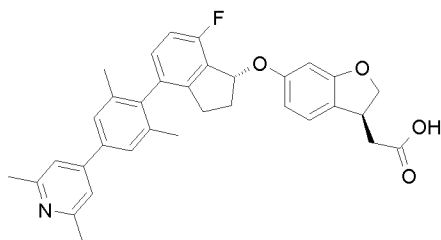
{(S)-6-[(R)-4-(2,6-Dimethyl-4-(6-methyl-pyridazin-3-yl)-phenyl)-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid



The title compound is prepared from {(S)-6-[(R)-4-(2,6-dimethyl-4-(6-methyl-pyridazin-3-yl)-phenyl)-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester following a procedure analogous to that described for Example 10;
 5 if the title compound does not precipitate from the aqueous solution, the crude title compound is purified by HPLC. LC (method 9): $t_R = 1.08$ min; Mass spectrum (ESI⁺): $m/z = 525$ [M+H]⁺.

Example 166

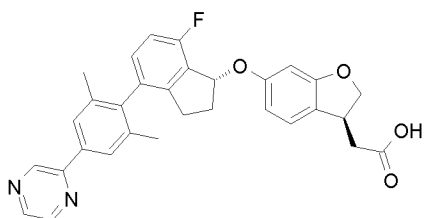
- 10 {(S)-6-[(R)-4-(2,6-Dimethyl-4-(2,6-dimethyl-pyridin-4-yl)-phenyl)-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid



The title compound is prepared from {(S)-6-[(R)-4-(2,6-dimethyl-4-(2,6-dimethyl-pyridin-4-yl)-phenyl)-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester following a procedure analogous to that described for Example 10; if the
 15 title compound does not precipitate from the aqueous solution, the crude title compound is purified by HPLC. LC (method 7): $t_R = 0.99$ min; Mass spectrum (ESI⁺): $m/z = 538$ [M+H]⁺.

- 20 **Example 167**

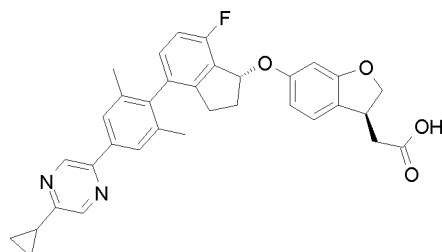
{(S)-6-[(R)-4-(2,6-Dimethyl-4-pyrazin-2-yl-phenyl)-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid



The title compound is prepared from {(S)-6-[(R)-4-(2,6-dimethyl-4-pyrazin-2-yl-phenyl)-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester following a procedure analogous to that described for Example 10; if the title compound does not precipitate from the aqueous solution, the crude title compound is purified by HPLC. LC (method 9): $t_R = 1.14$ min; Mass spectrum (ESI⁺): $m/z = 511$ [M+H]⁺.

Example 168

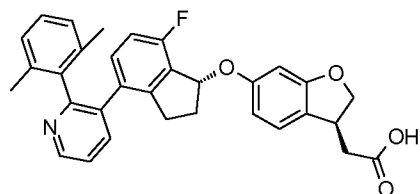
{(S)-6-[(R)-4-(2,6-Dimethyl-4-(5-cyclopropyl-pyrazin-2-yl)-phenyl)-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid



The title compound is prepared from {(S)-6-[(R)-4-(2,6-dimethyl-4-(5-cyclopropyl-pyrazin-2-yl)-phenyl)-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester following a procedure analogous to that described for Example 10; if the title compound does not precipitate from the aqueous solution, the crude title compound is purified by HPLC. LC (method 11): $t_R = 1.27$ min; Mass spectrum (ESI⁺): $m/z = 551$ [M+H]⁺.

Example 169

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

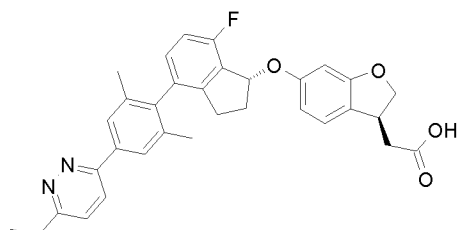


The title compound is prepared from {(S)-6-[(R)-4-(2-(2,6-dimethyl-phenyl)-pyridin-3-yl)-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester following a procedure analogous to that described for Example 10; if the title compound does not precipitate from the aqueous solution, the crude title compound

is purified by HPLC. LC (method 7): t_R = 0.80 min; Mass spectrum (ESI^+): m/z = 510 $[M+H]^+$.

Example 170

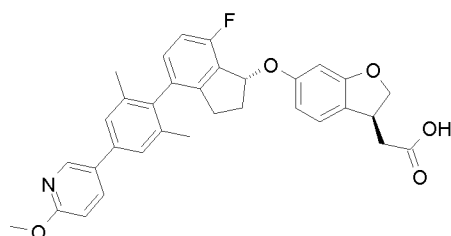
- 5 {{(S)-6-[(R)-4-(2,6-Dimethyl-4-(6-ethyl-pyridazin-3-yl)-phenyl)-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid



- The title compound is prepared from {{(S)-6-[(R)-4-(2,6-dimethyl-4-(6-ethyl-pyridazin-3-yl)-phenyl)-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester following a procedure analogous to that described for Example 10; if the title compound does not precipitate from the aqueous solution, the crude title compound is purified by HPLC. LC (method 11): t_R = 1.06 min; Mass spectrum (ESI^+): m/z = 539 $[M+H]^+$.

15 Example 171

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

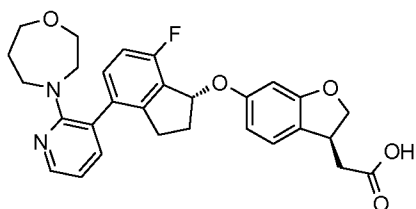


- The title compound is prepared from {{(S)-6-[(R)-4-(2,6-dimethyl-4-(6-methoxy-pyridin-3-yl)-phenyl)-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester following a procedure analogous to that described for Example 10; if the title compound does not precipitate from the aqueous solution, the crude title compound is purified by HPLC. LC (method 11): t_R = 1.24 min; Mass spectrum (ESI^+): m/z = 540 $[M+H]^+$.

25

Example 172

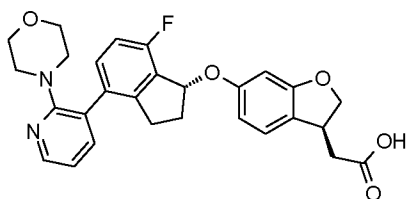
{{(S)-6-[(R)-7-Fluoro-4-(2-[1,4]oxazepan-4-yl-pyridin-3-yl)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid



The title compound is prepared from {(S)-6-[(R)-7-fluoro-4-(2-fluoro-pyridin-3-yl)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester and [1,4]oxazepane following a procedure analogous to that described for Example 173. LC (method 9): $t_R = 0.87$ min; Mass spectrum (ESI⁺): $m/z = 505$ [M+H]⁺.

Example 173

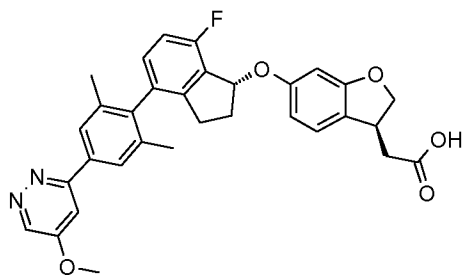
{{(S)-6-[(R)-7-Fluoro-4-(2-morpholin-4-yl-pyridin-3-yl)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid



A mixture of {(S)-6-[(R)-7-fluoro-4-(2-fluoro-pyridin-3-yl)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester (0.10 g), morpholine (0.10 g) and N-methyl-pyrrolidone (2 mL) is stirred at 180 °C for 48 h. After cooling to room temperature, 2 N aqueous NaOH solution (0.5 mL) is added, and the resulting mixture is stirred at 40 °C for 2 h. The mixture is neutralized with 1 N aqueous HCl solution and concentrated. The residue is chromatographed on reversed phase (HPLC; acetonitrile/water) to give the title compound. LC (method 7): $t_R = 0.89$ min; Mass spectrum (ESI⁺): $m/z = 491$ [M+H]⁺.

Example 174

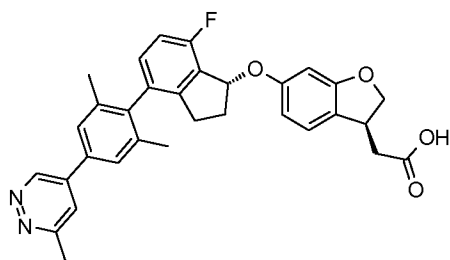
{{(S)-6-[(R)-4-(2,6-Dimethyl-4-(5-methoxy-pyridazin-3-yl)-phenyl)-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid



The title compound is prepared from {(S)-6-[(R)-4-(2,6-dimethyl-4-(5-methoxy-pyridazin-3-yl)-phenyl)-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester following a procedure analogous to that described for Example 10;
 5 if the title compound does not precipitate from the aqueous solution, the crude title compound is purified by HPLC. LC (method 11): t_R = 1.10 min; Mass spectrum (ESI⁺): m/z = 541 [M+H]⁺.

Example 175

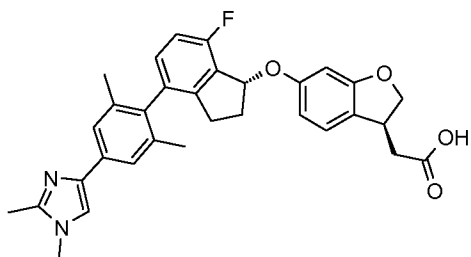
10 {(S)-6-[(R)-4-(2,6-Dimethyl-4-(6-methyl-pyridazin-4-yl)-phenyl)-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid



The title compound is prepared from {(S)-6-[(R)-4-(2,6-dimethyl-4-(6-methyl-pyridazin-4-yl)-phenyl)-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester following a procedure analogous to that described for Example 10.
 15 LC (method 11): t_R = 1.00 min; Mass spectrum (ESI⁺): m/z = 525 [M+H]⁺.

Example 176

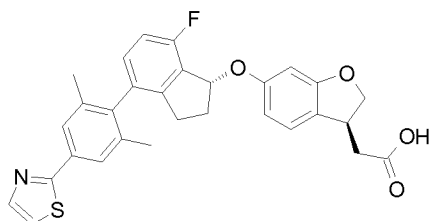
20 {(S)-6-[(R)-4-(2,6-Dimethyl-4-(1,2-dimethyl-imidazol-4-yl)-phenyl)-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid



The title compound is prepared from {(S)-6-[(R)-7-fluoro-4-(2,6-dimethyl-4-(1,2-dimethyl-imidazol-4-yl)-phenyl)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester following a procedure analogous to that described for Example 10; if the title compound does not precipitate from the aqueous solution, the crude title compound is purified by HPLC. LC (method 9): $t_R = 0.88$ min; Mass spectrum (ESI⁺): $m/z = 527$ [M+H]⁺.

Example 177

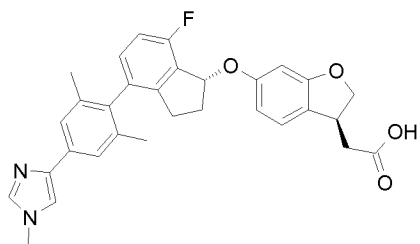
{(S)-6-[(R)-4-(2,6-Dimethyl-4-thiazol-2-yl-phenyl)-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid



The title compound is prepared from {(S)-6-[(R)-7-fluoro-4-(2,6-dimethyl-4-thiazol-2-yl-phenyl)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester following a procedure analogous to that described for Example 10; if the title compound does not precipitate from the aqueous solution, the crude title compound is purified by HPLC. LC (method 7): $t_R = 1.21$ min; Mass spectrum (ESI⁺): $m/z = 516$ [M+H]⁺.

Example 178

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

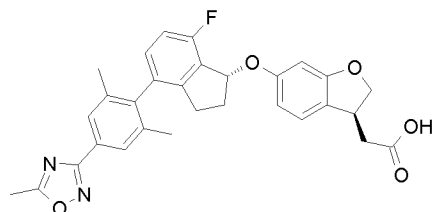


The title compound is prepared from {(S)-6-[(R)-7-fluoro-4-(2,6-dimethyl-4-(1-methyl-imidazol-4-yl)-phenyl)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester following a procedure analogous to that described for Example 10; if the title compound does not precipitate from the aqueous solution, the crude title compound

is purified by HPLC. LC (method 9): t_R = 0.89 min; Mass spectrum (ESI^+): m/z = 513 $[M+H]^+$.

Example 179

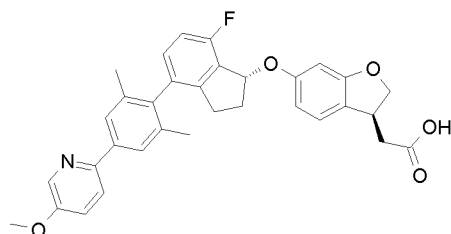
- 5 {{(S)-6-[(R)-4-(2,6-Dimethyl-4-(5-methyl-[1,2,4]oxadiazol-3-yl)-phenyl)-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid



- The title compound is prepared from {(S)-6-[(R)-7-fluoro-4-(2,6-dimethyl-4-(5-methyl-[1,2,4]oxadiazol-3-yl)-phenyl)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid
10 methyl ester following a procedure analogous to that described for Example 10; if the title compound does not precipitate from the aqueous solution, the crude title compound is purified by HPLC. LC (method 11): t_R = 1.20 min; Mass spectrum (ESI^+): m/z = 515 $[M+H]^+$.

- 15 **Example 180**

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

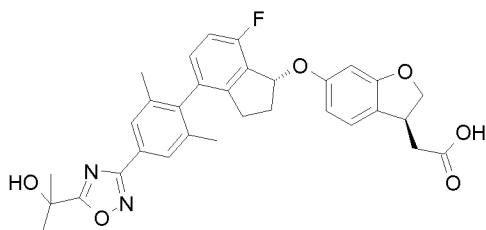


- The title compound is prepared from {(S)-6-[(R)-4-(2,6-dimethyl-4-(5-methoxy-pyridin-2-yl)-phenyl)-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl
20 ester following a procedure analogous to that described for Example 10; if the title compound does not precipitate from the aqueous solution, the crude title compound is purified by HPLC. LC (method 8): t_R = 0.79 min; Mass spectrum (ESI^+): m/z = 540 $[M+H]^+$.

25

Example 181

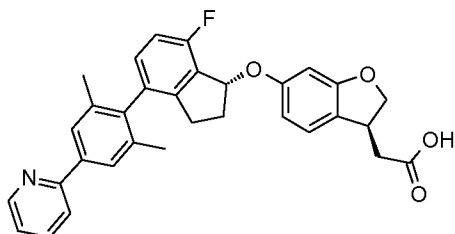
{{(S)-6-[(R)-4-(2,6-Dimethyl-4-(5-[2-hydroxy-prop-2-yl]-[1,2,4]oxadiazol-3-yl)-phenyl)-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid



The title compound is prepared from {{(S)-6-[(R)-7-fluoro-4-(2,6-dimethyl-4-(5-[2-hydroxy-prop-2-yl]-[1,2,4]oxadiazol-3-yl)-phenyl)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester following a procedure analogous to that described for Example 10; if the title compound does not precipitate from the aqueous solution, the crude title compound is purified by HPLC. LC (method 11): t_R = 1.16 min; Mass spectrum (ESI⁺): m/z = 559 [M+H]⁺.

Example 182

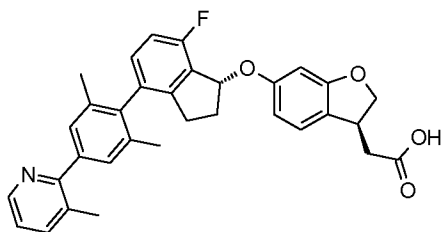
{{(S)-6-[(R)-4-(2,6-Dimethyl-4-pyridin-2-yl-phenyl)-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid



The title compound is prepared from {{(S)-6-[(R)-4-(2,6-dimethyl-4-pyridin-2-yl-phenyl)-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester following a procedure analogous to that described for Example 10; if the title compound does not precipitate from the aqueous solution, the crude title compound is purified by HPLC. LC (method 7): t_R = 0.99 min; Mass spectrum (ESI⁺): m/z = 510 [M+H]⁺.

Example 183

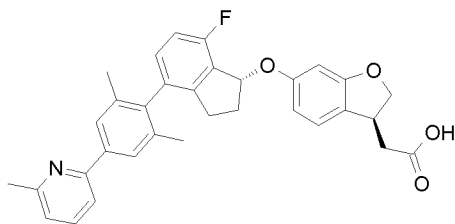
{{(S)-6-[(R)-4-(2,6-Dimethyl-4-(3-methyl-pyridin-2-yl)-phenyl)-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid



The title compound is prepared from {(S)-6-[(R)-4-(2,6-dimethyl-4-(3-methyl-pyridin-2-yl)-phenyl)-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester following a procedure analogous to that described for Example 10; if the title compound does not precipitate from the aqueous solution, the crude title compound is purified by HPLC. LC (method 7): t_R = 0.97 min; Mass spectrum (ESI⁺): m/z = 524 [M+H]⁺.

Example 184

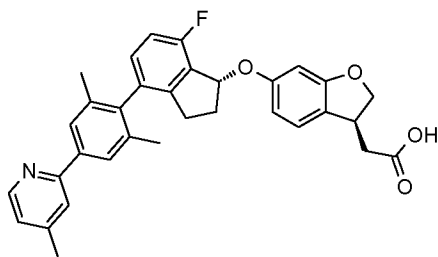
{(S)-6-[(R)-4-(2,6-Dimethyl-4-(6-methyl-pyridin-2-yl)-phenyl)-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid



The title compound is prepared from {(S)-6-[(R)-4-(2,6-dimethyl-4-(6-methyl-pyridin-2-yl)-phenyl)-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester following a procedure analogous to that described for Example 10; if the title compound does not precipitate from the aqueous solution, the crude title compound is purified by HPLC. LC (method 7): t_R = 0.99 min; Mass spectrum (ESI⁺): m/z = 524 [M+H]⁺.

Example 185

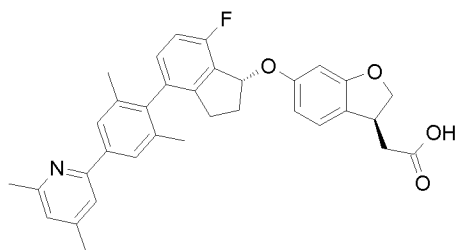
{(S)-6-[(R)-4-(2,6-Dimethyl-4-(4-methyl-pyridin-2-yl)-phenyl)-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid



The title compound is prepared from {(S)-6-[(R)-4-(2,6-dimethyl-4-(4-methyl-pyridin-2-yl)-phenyl)-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester following a procedure analogous to that described for Example 10; if the title compound does not precipitate from the aqueous solution, the crude title compound is purified by HPLC. LC (method 7): $t_R = 0.98$ min; Mass spectrum (ESI⁺): $m/z = 524$ [M+H]⁺.

Example 186

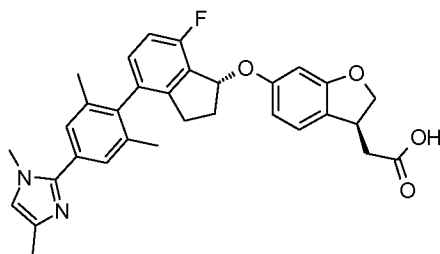
{(S)-6-[(R)-4-(2,6-Dimethyl-4-(4,6-dimethyl-pyridin-2-yl)-phenyl)-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid



The title compound is prepared from {(S)-6-[(R)-4-(2,6-dimethyl-4-(4,6-dimethyl-pyridin-2-yl)-phenyl)-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester following a procedure analogous to that described for Example 10; if the title compound does not precipitate from the aqueous solution, the crude title compound is purified by HPLC. LC (method 7): $t_R = 0.99$ min; Mass spectrum (ESI⁺): $m/z = 538$ [M+H]⁺.

Example 187

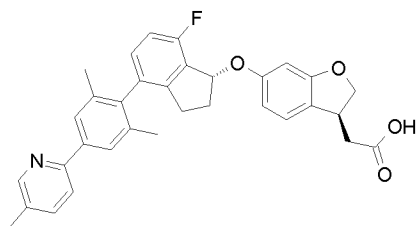
{(S)-6-[(R)-4-(2,6-Dimethyl-4-(1,4-dimethyl-imidazol-2-yl)-phenyl)-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid



The title compound is prepared from {(S)-6-[(R)-7-fluoro-4-(2,6-dimethyl-4-(1,4-dimethyl-imidazol-2-yl)-phenyl)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester following a procedure analogous to that described for Example 10; if the title compound does not precipitate from the aqueous solution, the crude title compound is purified by HPLC. LC (method 7): t_R = 0.95 min; Mass spectrum (ESI⁺): m/z = 527 [M+H]⁺.

Example 188

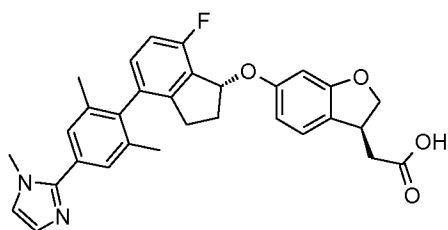
10 {(S)-6-[(R)-4-(2,6-Dimethyl-4-(5-methyl-pyridin-2-yl)-phenyl)-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid



The title compound is prepared from {(S)-6-[(R)-4-(2,6-dimethyl-4-(5-methyl-pyridin-2-yl)-phenyl)-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester following a procedure analogous to that described for Example 10; if the title compound does not precipitate from the aqueous solution, the crude title compound is purified by HPLC. LC (method 7): t_R = 0.99 min; Mass spectrum (ESI⁺): m/z = 524 [M+H]⁺.

20 Example 189

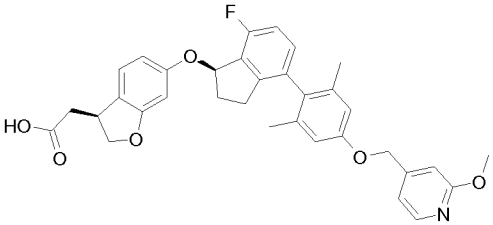
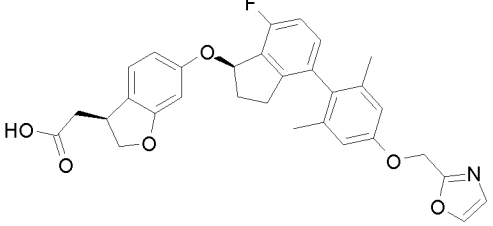
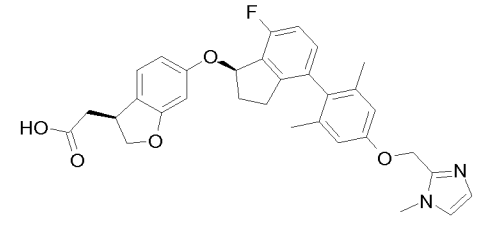
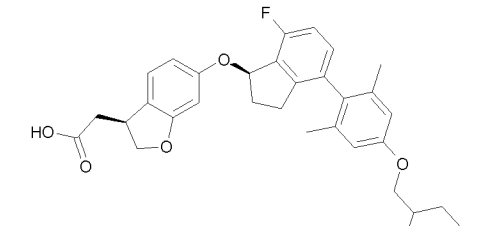
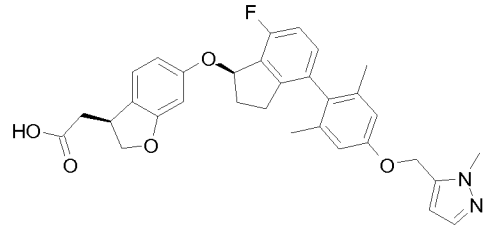
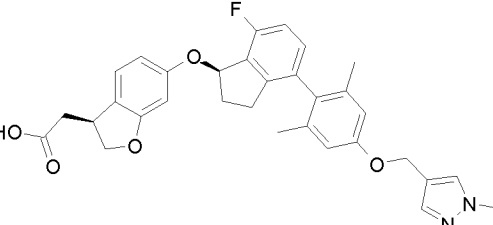
{(S)-6-[(R)-4-(2,6-Dimethyl-4-(1-methyl-imidazol-2-yl)-phenyl)-7-fluoro-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid

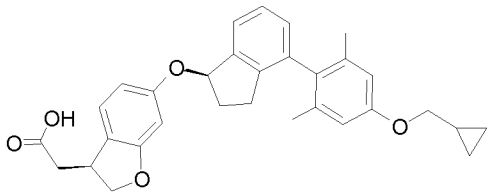
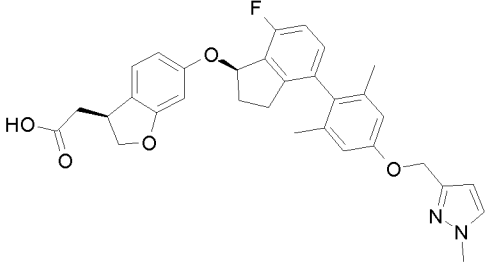
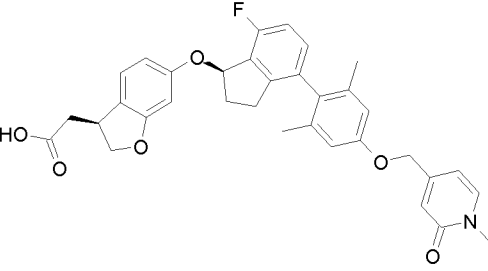
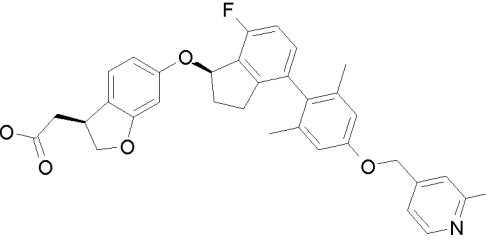
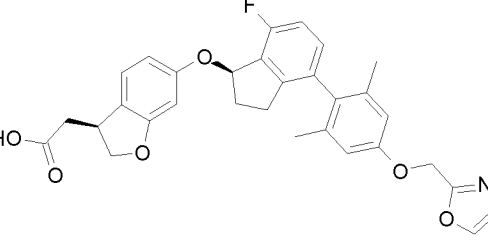
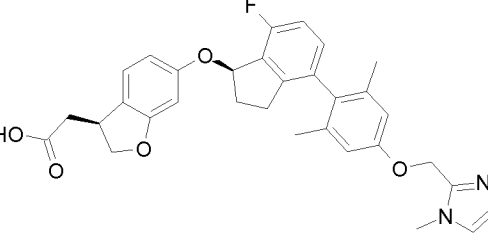


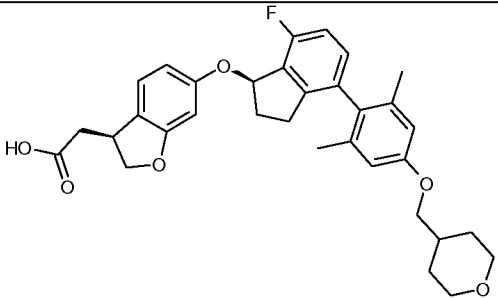
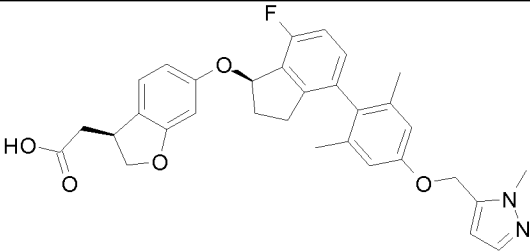
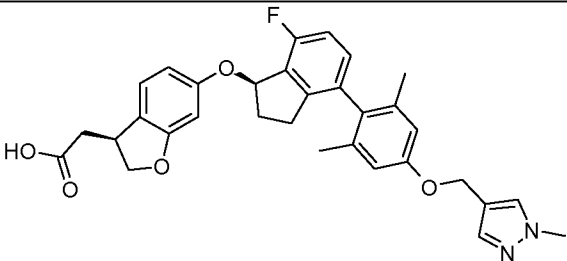
The title compound is prepared from {(S)-6-[(R)-7-fluoro-4-(2,6-dimethyl-4-(1-methylimidazol-2-yl)-phenyl)-indan-1-yloxy]-2,3-dihydro-benzofuran-3-yl}-acetic acid methyl ester following a procedure analogous to that described for Example 10; if the title compound does not precipitate from the aqueous solution, the crude title compound is purified by HPLC. LC (method 7): t_R = 0.94 min; Mass spectrum (ESI⁺): m/z = 513 [M+H]⁺.

Saponification of the esters in the following table is performed in analogy to example 71

Example No	Structure	Name
190		2-((S)-6-((R)-4-(4-(cyclopropylmethoxy)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid
191		2-((S)-6-((R)-4-(2,6-dimethyl-4-((1-methyl-1H-pyrazol-3-yl)methoxy)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid
192		2-((S)-6-((R)-4-(2,6-dimethyl-4-((1-methyl-2-oxo-1,2-dihydropyridin-4-yl)methoxy)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid

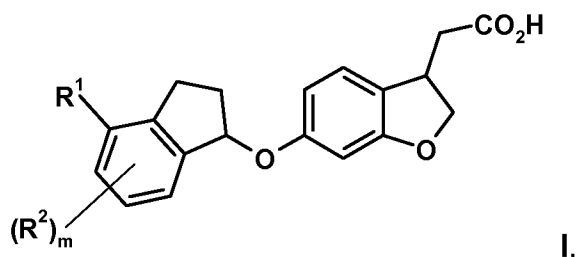
193		2-((S)-6-((R)-7-fluoro-4-(4-((2-methoxypyridin-4-yl)methoxy)-2,6-dimethylphenyl)-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid
194		2-((S)-6-((R)-4-(2,6-dimethyl-4-(oxazol-2-ylmethoxy)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid
195		2-((S)-6-((R)-4-(2,6-dimethyl-4-((1-methyl-1H-imidazol-2-yl)methoxy)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid
196		2-((S)-6-((R)-4-(2,6-dimethyl-4-((tetrahydro-2H-pyran-4-yl)methoxy)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid
197		2-((S)-6-((R)-4-(2,6-dimethyl-4-((1-methyl-1H-pyrazol-5-yl)methoxy)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid
198		2-((S)-6-((R)-4-(2,6-dimethyl-4-((1-methyl-1H-pyrazol-4-yl)methoxy)phenyl)-7-fluoro-2,3-dihydro-1H-inden-1-yloxy)-2,3-dihydrobenzofuran-3-yl)acetic acid

Example No	Structure	t _R [Min]	LC method No	(ESI ⁺): m/z
190		0.9	24	484,9 [M+H] ⁺ .
191		0.69	14	543 [M+H] ⁺ .
192		0.66	14	570 [M+H] ⁺ .
193		0.74	14	570 [M+H] ⁺ .
194		0.68	14	530 [M+H] ⁺ .
195		0.66	14	543 [M+H] ⁺ .

196		0.74	14	547 [M+H] ⁺ .
197		1.04	11	543 [M+H] ⁺ .
198		1.87	23	543 [M+H] ⁺ .

Claims

1. A compound of formula (I)



5 wherein

R^1 is selected from the group R^1 -G1 consisting of a phenyl ring, a tetrazolyl ring, and a 5- or 6-membered heteroaromatic ring which contains 1, 2, or 3 heteroatoms independently of each other selected from =N-, -NH-, -O- and -S-;

10 wherein optionally a second ring is annulated to said phenyl or heteroaromatic ring,

wherein said second ring is 5- or 6-membered, unsaturated or aromatic and may contain 1, 2, or 3 heteroatoms independently of each other selected from =N-, -NH-, -O- and -S- with the proviso that only up to two of the heteroatoms are O and S and no O-O, S-S, and S-O bond is formed, and wherein in said second ring independently of the presence of heteroatoms 1 or 2 CH_2 groups may be replaced by -C(=O)-, -S(=O)- or -S(=O)₂-, and

15 wherein said phenyl ring, tetrazolyl ring, heteroaromatic ring, annulated phenyl ring, and annulated heteroaromatic ring are substituted with one group R^3 ; and

20 wherein each of the phenyl ring, tetrazolyl ring, heteroaromatic ring, annulated phenyl ring, and annulated heteroaromatic ring is optionally additionally substituted with 1 to 4 groups independently selected from R^4 ; and

25 wherein in said heteroaromatic ring and/or said second ring the H-atom in one or more NH groups, if present, is replaced by R^N or R^3 ;

R^2 is selected from the group R^2 -G1 consisting of F, Cl, Br, I, C_{1-4} -alkyl, C_{3-6} -cycloalkyl, NC-, $H_2N-C(=O)-$, C_{1-4} -alkyl- $NR^N-C(=O)-$, $HO-C(=O)-$, C_{1-4} -alkyl-O-C(=O)-, C_{1-4} -alkyloxy, and C_{1-4} -alkyl-S(=O)₂-,

wherein any alkyl and cycloalkyl group or sub-group within the groups mentioned is optionally substituted with one or more F atoms, and wherein multiple R² may be identical or different, if m is 2 or 3;

5 R³ is selected from the group R³-G1 consisting of

C₁₋₆-alkyl, C₂₋₆-alkenyl, C₂₋₆-alkinyl, C₃₋₆-cycloalkyl-, C₁₋₄-alkyl-NH-, (C₁₋₄-alkyl)₂N-, C₁₋₆-alkyl-O-, C₃₋₆-cycloalkyl-O-, C₁₋₄-alkyl-S-, C₁₋₄-alkyl-S(=O)-, and C₁₋₄-alkyl-S(=O)₂,

wherein each alkyl and cycloalkyl group and each alkyl and cycloalkyl sub-group
10 within the groups mentioned is substituted with 1 to 3 groups independently selected from R⁵ and optionally substituted with 1 or more F atoms;

or from C₁₋₄-alkyl-C(=O)-, heterocyclyl-C(=O)-, HNR^N-C(=O)-, C₁₋₄-alkyl-NR^N-C(=O)-, C₃₋₆-cycloalkyl-NR^N-C(=O)-, heterocyclyl-NR^N-C(=O)-, phenyl-NR^N-C(=O)-, heteroaryl-NR^N-C(=O)-, HO₂C-, C₁₋₄-alkyl-O-C(=O)-, C₃₋₆-cycloalkyl-O-C(=O)-, heterocyclyl-O-C(=O)-, -NHR^N, C₁₋₄-alkyl-C(=O)NR^N-, C₃₋₆-cycloalkyl-C(=O)NR^N-, heterocyclyl-C(=O)NR^N-, phenyl-C(=O)NR^N-, heteroaryl-C(=O)NR^N-, C₁₋₄-alkyl-S(=O)₂NR^N-, C₃₋₆-cycloalkyl-S(=O)₂NR^N-, heterocyclyl-S(=O)₂NR^N-, phenyl-S(=O)₂NR^N-, heteroaryl-S(=O)₂NR^N-, heterocyclyl-O-, phenyl-O-,
15 heteroaryl-O-, C₃₋₆-cycloalkyl-S-, heterocyclyl-S-, phenyl-S-, heteroaryl-S-, C₃₋₆-cycloalkyl-S(=O)-, heterocyclyl-S(=O)-, phenyl-S(=O)-, heteroaryl-S(=O)-, C₃₋₆-cycloalkyl-S(=O)₂-, heterocyclyl-S(=O)₂-, phenyl-S(=O)₂-, heteroaryl-S(=O)₂-, HNR^N-S(=O)₂-, C₁₋₄-alkyl-NR^N-S(=O)₂-, heterocyclyl, phenyl, and heteroaryl,

wherein each alkyl, cycloalkyl, and heterocyclyl group or sub-group within the
20 groups mentioned is optionally substituted with 1 to 3 groups independently selected from R⁵ and optionally substituted with 1 or more F atoms; and
wherein each phenyl and heteroaryl group is optionally substituted with 1 to 5 substituents independently selected from R⁶;

wherein heterocyclyl is selected from

30 a cyclobutyl group wherein 1 CH₂ group is replaced by -NH- or -O-,
a saturated or partially unsaturated C₅₋₇-cycloalkyl group wherein 1 CH₂ group is replaced by -C(=O)-, -NH-, -O-, -S(=O)- or -S(=O)₂- and/or 1 CH group by N;

a saturated or partially unsaturated C₅₋₇-cycloalkyl group wherein 1 CH₂ group is replaced by -NH- or -O-, a second CH₂ group is replaced by -NH-, -C(=O)-, -S(=O)- or -S(=O)₂- and/or 1 CH group is replaced by N; and

a saturated or partially unsaturated C₅₋₇-cycloalkyl group wherein 2 CH₂ groups are replaced by -NH- or 1 CH₂ group by -NH- and the other by -O- and a third CH₂ group is replaced by -C(=O)-, -S(=O)- or -S(=O)₂- and/or 1 CH group by N;

wherein heteroaryl is selected from

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

wherein in heteroaryl and heterocyclyl rings with one or more NH groups each of them is replaced by NR^N or NR⁵;

with the proviso that R³ in total cannot be C₁₋₄-alkyl-, C₁₋₄-alkyl-O-C₁₋₄-alkyl, HO-C₁₋₄-alkyl, C₃₋₄-alkenyl, C₃₋₄-alkinyl, H₂N-, C₁₋₄-alkyl-NH-, (C₁₋₄-alkyl)₂N-, C₁₋₄-alkyl-O-, C₁₋₄-alkyl-S-, C₁₋₄-alkyl-S(=O)-, and C₁₋₄-alkyl-S(=O)₂;

R⁴ is selected from the group R⁴-G1 consisting of F, Cl, Br, I, CN, -OH, C₁₋₄-alkyl, C₃₋₆-cycloalkyl-, HO-C₁₋₄-alkyl, C₁₋₄-alkyl-O-C₁₋₄-alkyl, -NR^NH, C₁₋₄-alkyl-NR^N-, C₁₋₄-alkyl-O-, C₃₋₆-cycloalkyl-O-, C₁₋₄-alkyl-O-C₁₋₄-alkyl-O-, C₁₋₄-alkyl-S-, C₁₋₄-alkyl-S(=O)-, and C₁₋₄-alkyl-S(=O)₂-,

wherein any alkyl and cycloalkyl group or sub-group within the groups mentioned is optionally substituted with 1 or more F atoms;

R⁵ is selected from the group R⁵-G1 consisting of Cl, Br, I, C₁₋₄-alkyl-, CN, C₃₋₆-cycloalkyl-, heterocyclyl-C(=O)-, H₂N-C(=O)-, C₁₋₄-alkyl-NR^N-C(=O)-, C₃₋₆-cycloalkyl-NR^N-C(=O)-, heterocyclyl-NR^N-C(=O)-, phenyl-NR^N-C(=O)-, heteroaryl-NR^N-C(=O)-, HO-C(=O)-, C₁₋₄-alkyl-O-C(=O)-, -NHR^N, C₁₋₄-alkyl-NR^N-, C₁₋₄-alkyl-C(=O)NR^N-, C₃₋₆-cycloalkyl-C(=O)NR^N-, heterocyclyl-C(=O)NR^N-, phenyl-C(=O)NR^N-, heteroaryl-C(=O)NR^N-, C₁₋₄-alkyl-S(=O)₂NR^N-, C₃₋₆-cycloalkyl-S(=O)₂NR^N-, heterocyclyl-S(=O)₂NR^N-, phenyl-S(=O)₂NR^N-, heteroaryl-S(=O)₂NR^N-, -OH, C₁₋₄-alkyl-O-, C₁₋₄-alkyl-O-C₁₋₄-alkyl-O-, C₃₋₆-cycloalkyl-O-,

heterocyclyl-O-, phenyl-O-, heteroaryl-O-, C₁₋₄-alkyl-S-, C₃₋₆-cycloalkyl-S-, heterocyclyl-S-, phenyl-S-, heteroaryl-S-, C₁₋₄-alkyl-S(=O)-, C₃₋₆-cycloalkyl-S(=O)-, heterocyclyl-S(=O)-, phenyl-S(=O)-, heteroaryl-S(=O)-, C₁₋₄-alkyl-S(=O)₂-, C₃₋₆-cycloalkyl-S(=O)₂-, heterocyclyl-S(=O)₂-, phenyl-S(=O)₂-, heteroaryl-S(=O)₂-,
 5 H₂N-S(=O)₂-, C₁₋₄-alkyl-NR^N-S(=O)₂-, heterocyclyl, phenyl, and heteroaryl,
 wherein any alkyl, cycloalkyl and heterocyclyl group or sub-group within the groups mentioned is optionally substituted with 1 or more F atoms and optionally substituted with 1 or 2 groups independently selected from H₃C-, HO-, H₃C-O-, and -CN;

10 wherein heterocyclyl is selected from

a cyclobutyl group wherein 1 CH₂ group is replaced by -NR^N- or -O-,
 a saturated or partially unsaturated C₅₋₇-cycloalkyl group wherein 1 CH₂ group is replaced by -C(=O)-, -NR^N-, -O-, -S(=O)- or -S(=O)₂- and/or 1 CH group by N;

15 a saturated or partially unsaturated C₅₋₇-cycloalkyl group wherein 1 CH₂ group is replaced by -NR^N- or -O-, a second CH₂ group is replaced by -NR^N-, -C(=O)-, -S(=O)- or -S(=O)₂- and/or 1 CH group is replaced by N; and

a saturated or partially unsaturated C₅₋₇-cycloalkyl group wherein 2 CH₂ groups are replaced by -NR^N- or 1 CH₂ group by -NR^N- and the other by -O-,
 20 and a third CH₂ group is replaced by -C(=O)-, -S(=O)- or -S(=O)₂- and/or 1 CH group by N;

and wherein heteroaryl is selected from

a tetrazolyl ring, and a 5- or 6-membered heteroaromatic ring which contains 1, 2, or 3 heteroatoms independently of each other selected from =N-, -NH-, -O-, and -S-, wherein in heteroaromatic groups containing a -HC=N- unit this group is optionally replaced by -NR^N-C(=O)-, and wherein in heteroaromatic rings with one or more NH groups each of them is replaced by NR^N, and each heteroaryl group is optionally substituted with 1 to 3 substituents independently selected from F, Cl, -CH₃, -CN, and -O-CH₃;

30 R⁶ is selected from the group R⁶-G1 consisting of F, Cl, Br, I, CN, C₁₋₄-alkyl, C₃₋₆-cycloalkyl-, HO-C₁₋₄-alkyl-, C₁₋₄-alkyl-O-C₁₋₄-alkyl-, R^NHN-, C₁₋₄-alkyl-O-, -S(=O)-C₁₋₄-alkyl, and S(=O)₂-C₁₋₄-alkyl,

wherein any alkyl and cycloalkyl group or sub-group within the groups mentioned is optionally substituted with one or more F atoms;

R^N is independently of each other selected from the group R^N -G1 consisting of H, C₁₋₄-alkyl, C₁₋₄-alkyl-C(=O)-, C₁₋₄-alkyl-NH-C(=O)-, C₁₋₄-alkyl-N(C₁₋₄-alkyl)-C(=O)-, C₁₋₄-alkyl-O-C(=O)-, and C₁₋₄-alkyl-S(=O)₂-; and

m is 0, 1, 2, or 3;

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.

2. A compound according to claim 1, wherein

R^1 is selected from the group R^1 -G2 consisting of a phenyl ring, a tetrazolyl ring, a 5-membered heteroaromatic ring which contains 2 or 3 heteroatoms independently of each other selected from =N-, -NH-, -O- and -S- with the proviso that not more than one heteroatom is -O- or -S-, and a 6-membered heteroaromatic ring which contains 1 or 2 =N- atoms;

wherein optionally a second ring is annulated to said phenyl ring and 5- and 6-membered heteroaromatic rings, wherein said second ring is 5- or 6-membered, unsaturated or aromatic and may contain 1 or 2 heteroatoms independently of each other selected from =N-, -NH-, -O- and -S- with the proviso that no O-O, S-S, and S-O bond is formed, and wherein in said second ring independently of the presence of heteroatoms 1 or 2 -CH₂- groups may be replaced by -C(=O)- or -S(=O)₂-, and

wherein in said heteroaromatic ring and/or said second ring the H-atom in one or more NH groups, if present, is replaced by R^N or R^3 , and

wherein each of said phenyl ring, tetrazolyl ring, heteroaromatic rings, annulated phenyl ring, and annulated heteroaromatic rings is substituted with one group R^3 and optionally additionally substituted with 1 or 2 substituents independently selected from R^4 .

R² is selected from the group R²-G2 consisting of

F, Cl, Br, H₃C-, H₂FC-, F₃C-, cyclopropyl, NC-, F₂HC-O-, F₃C-O-, and H₃C-S(=O)₂-,

R³ is selected from the group R³-G2 consisting of

- 5 C₁₋₄-alkyl, C₃₋₆-cycloalkyl-, C₁₋₄-alkyl-O-, C₃₋₆-cycloalkyl-O-, C₁₋₄-alkyl-S(=O)-, and C₁₋₄-alkyl-S(=O)₂-,

wherein each alkyl and cycloalkyl group and each alkyl and cycloalkyl sub-group within the groups mentioned is substituted with 1 to 3 groups independently selected from R⁵ and optionally substituted with 1 or more F atoms;

10

or from C₁₋₄-alkyl-C(=O)-, heterocyclyl-C(=O)-, HNR^N-C(=O)-, C₁₋₄-alkyl-NR^N-C(=O)-, C₃₋₆-cycloalkyl-NR^N-C(=O)-, heterocyclyl-NR^N-C(=O)-, phenyl-NR^N-C(=O)-, heteroaryl-NR^N-C(=O)-, C₁₋₄-alkyl-C(=O)NR^N-, C₃₋₆-cycloalkyl-C(=O)NR^N-, heterocyclyl-C(=O)NR^N-, phenyl-C(=O)NR^N-, heteroaryl-C(=O)NR^N-, C₁₋₄-alkyl-S(=O)₂NR^N-, C₃₋₆-cycloalkyl-S(=O)₂NR^N-, heterocyclyl-S(=O)₂NR^N-, phenyl-S(=O)₂NR^N-, heteroaryl-S(=O)₂NR^N-, heterocyclyl-O-, phenyl-O-, heteroaryl-O-, C₃₋₆-cycloalkyl-S(=O)-, heterocyclyl-S(=O)-, phenyl-S(=O)-, heteroaryl-S(=O)-, C₃₋₆-cycloalkyl-S(=O)₂-, heterocyclyl-S(=O)₂-, phenyl-S(=O)₂-, heteroaryl-S(=O)₂-, HNR^N-S(=O)₂-, C₁₋₄-alkyl-NR^N-S(=O)₂-, heterocyclyl, phenyl, and heteroaryl,

15

- 20 wherein each alkyl, cycloalkyl, and heterocyclyl group or sub-group within the groups mentioned is optionally substituted with 1 to 3 groups independently selected from R⁵ and optionally substituted with 1 or more F atoms; and

wherein each phenyl and heteroaryl group is optionally substituted with 1 to 3 substituents independently selected from R⁶;

25

wherein heterocyclyl is selected from

a cyclobutyl group wherein 1 CH₂ group is replaced by -NH- or -O-,

a saturated or mono-unsaturated C₅₋₆-cycloalkyl group wherein 1 CH₂ group is replaced by -C(=O)-, -NH-, -O-, -S(=O)- or -S(=O)₂- and/or 1 CH group by N;

a saturated or mono-unsaturated C₅₋₆-cycloalkyl group wherein 1 CH₂ group is replaced by -NH- or -O-, a second CH₂ group is replaced by -NH-, -C(=O)-, -S(=O)- or -S(=O)₂- and/or 1 CH group is replaced by N; and

30

a saturated or mono-unsaturated C₅₋₆-cycloalkyl group wherein 2 CH₂ groups are replaced by -NH- or 1 CH₂ group by -NH- and the other by -O- and a third CH₂ group is replaced by -C(=O)-, -S(=O)- or -S(=O)₂- and/or 1 CH group by N;

wherein heteroaryl is selected from

a tetrazolyl ring, a pyridin-2-onyl ring, a 5-membered heteroaromatic ring which contains 1, 2, or 3 heteroatoms independently of each other selected from =N-, -NH-, O, and S, and a 6-membered heteroaromatic ring which contains 1 or 2 =N- atom,

and wherein in heteroaryl and heterocyclyl rings with one ore more NH groups each of them is replaced by NR^{N} or NR^5 ,

with the proviso that R^3 in total cannot be C_{1-4} -alkyl-, C_{1-4} -alkyl-O- C_{1-4} -alkyl, HO- C_{1-4} -alkyl, C_{1-4} -alkyl-O-, C_{1-4} -alkyl-S(=O)-, and C_{1-4} -alkyl-S(=O)₂,

R^4 is selected from the group R^4 -G2 consisting of F, Cl, Br, CN, C_{1-3} -alkyl, C_{3-4} -cycloalkyl-, H O- C_{1-3} -alkyl, C_{1-3} -alkyl-O- C_{1-3} -alkyl, $-\text{NR}^{\text{N}}\text{H}$, C_{1-4} -alkyl-O-, C_{3-5} -cycloalkyl-O-, $\text{H}_3\text{C-S(=O)-}$, $\text{H}_3\text{C-S(=O)}_2$ -, wherein any alkyl and cycloalkyl group is optionally substituted with 1 or more F atoms,

R^5 is selected from the group R^5 -G2 consisting of Cl, C_{1-4} -alkyl-, -CN, C_{3-6} -cycloalkyl-, heterocyclyl-C(=O)-, $\text{H}_2\text{N-C(=O)-}$, C_{1-4} -alkyl- NR^{N} -C(=O)-, C_{3-6} -cycloalkyl- NR^{N} -C(=O)-, heterocyclyl- NR^{N} -C(=O)-, heteroaryl- NR^{N} -C(=O)-, $-\text{NH}_2$, C_{1-4} -alkyl- NR^{N} -, C_{1-4} -alkyl-C(=O) NR^{N} -, C_{3-6} -cycloalkyl-C(=O) NR^{N} -, heterocyclyl-C(=O) NR^{N} -, heteroaryl-C(=O) NR^{N} -, C_{1-4} -alkyl-S(=O)₂ NR^{N} -, -OH, C_{1-4} -alkyl-O-, C_{1-4} -alkyl-O- C_{1-4} -alkyl-O-, C_{3-6} -cycloalkyl-O-, heterocyclyl-O-, phenyl-O-, heteroaryl-O-, C_{1-4} -alkyl-S(=O)-, C_{3-6} -cycloalkyl-S(=O)-, C_{1-4} -alkyl-S(=O)₂-, C_{3-6} -cycloalkyl-S(=O)₂-, heterocyclyl, and heteroaryl,

wherein any alkyl, cycloalkyl, and heterocyclyl group or sub-group within the groups mentioned is optionally substituted with 1 or more F atoms and optionally substituted with 1 or 2 groups independently selected from $\text{H}_3\text{C-}$, HO-, $\text{H}_3\text{C-O-}$, and -CN,

wherein heterocyclyl is selected from

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

a saturated or partially unsaturated C_{5-6} -cycloalkyl group wherein 1 CH_2 group is replaced by -C(=O)-, $-\text{NR}^{\text{N}}$ -, -O-, -S(=O)- or -S(=O)₂- and/or 1 CH group by N;

a saturated or partially unsaturated C₅₋₆-cycloalkyl group wherein 1 CH₂ group is replaced by -NR^N-, or -O-, a second CH₂ group is replaced by -NR^N-, -C(=O)-, -S(=O)- or -S(=O)₂- and/or 1 CH group is replaced by N; and

a saturated or partially unsaturated C₅₋₆-cycloalkyl group wherein 2 CH₂ group are replaced by -NR^N- or 1 CH₂ group by -NR^N- and the other by -O-, and a third CH₂ group is replaced by -C(=O)-, -S(=O)- or -S(=O)₂- and/or 1 CH group by N;

and wherein heteroaryl is selected from a tetrazolyl ring, a pyridin-2-onyl ring, a 5-membered heteroaromatic ring which contains 1, 2, or 3 heteroatoms independently of each other selected from =N-, -NH-, -O-, and -S-, and a 6-membered heteroaromatic ring which contains 1 or 2 =N- atoms, and wherein in heteroaromatic rings with one or more NH groups each of them is replaced by NR^N, and each heteroaryl group is optionally substituted with 1 to 3 substituents independently selected from F, Cl, -CH₃, -CN, and -O-CH₃,

R⁶ is selected from the group R⁶-G2 consisting of F, Cl, -CN, C₁₋₃-alkyl, cyclopropyl, HO-C₁₋₃-alkyl-, H₃C-O-C₁₋₃-alkyl-, H₃C-O-, -S(=O)CH₃, and -S(=O)₂-CH₃, wherein any alkyl and cycloalkyl group or sub-group within the groups mentioned is optionally substituted with one or more F atoms,

R^N is selected from the group R^N-G2 consisting of H, C₁₋₃-alkyl, H₃C-C(=O)-, and C₁₋₃-alkyl-S(=O)₂-,

m is 0, 1, or 2,

or a salt thereof.

3. A compound according to claim 2, wherein

R¹ is selected from the group R¹-G2a consisting of a phenyl ring, a tetrazolyl ring, a 5-membered heteroaromatic ring which contains 2 or 3 heteroatoms independently of each other selected from =N-, -NH-, -O- and -S-, and a 6-membered heteroaromatic ring which contains 1 or 2 =N- atoms;

wherein in said 5-membered heteroaromatic ring the H-atom in one or more NH groups is replaced with R^N or R³, and

wherein each of said phenyl ring, tetrazolyl ring, and heteroaromatic rings is substituted with one group R^3 and optionally additionally substituted with 1 or 2 substituents independently selected from R^4 ,

5 and m is 1 or 2,

or a salt thereof.

4. A compound according to claim 2, wherein

10

R^1 is selected from the group R^1 -G2b consisting of a phenyl ring, a 5-membered heteroaromatic ring which contains 2 or 3 heteroatoms independently of each other selected from =N-, -NH-, -O- and -S-, and a 6-membered heteroaromatic ring which contains 1 or 2 =N- atoms, wherein a second 5- or 6-membered, unsaturated or aromatic ring is annulated to said phenyl ring and 5- and 6-membered heteroaromatic rings, which may contain 1 or 2 heteroatoms independently of each other selected from =N-, -NH-, -O- and -S- with the proviso that no O-O, S-S, and S-O bond is formed, and wherein in said second ring 1 or 2 $-CH_2-$ groups may be replaced by $-C(=O)-$ or $-S(=O)_2-$, and

15

20 wherein in said heteroaromatic rings and said second rings the H-atom in one or more NH groups, if present, is replaced by R^N or R^3 , and

wherein each annulated phenyl ring and annulated heteroaromatic ring is substituted with one group R^3 and optionally additionally substituted with 1 or 2 substituents independently selected from R^4 .

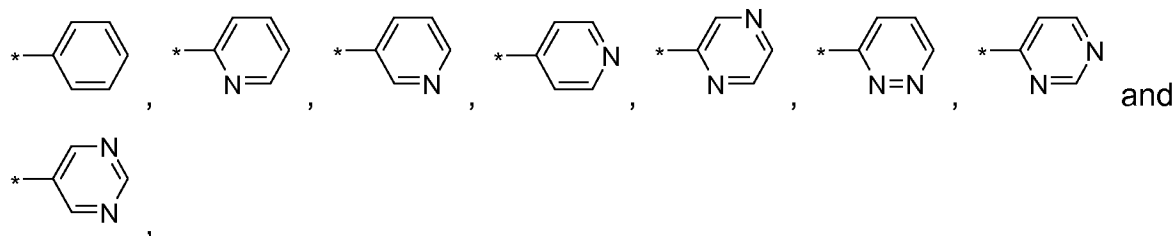
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and m is 1 or 2,

or a salt thereof.

30 5. A compound according to claim 1, wherein

R^1 is selected from the group consisting of



wherein each group is substituted with one group R^3 and optionally additionally substituted with 1 or 2 groups independently selected from R^4 ;

5

R^2 is selected from the group consisting of F, Cl, Br, H_2FC- , F_3C- , $NC-$, and F_3C-O- ;

R^3 is selected from the group consisting of C_{1-4} -alkyl, C_{3-6} -cycloalkyl-, C_{1-4} -alkyl-O-, and C_{3-6} -cycloalkyl-O-,

10 wherein each alkyl and cycloalkyl group and each alkyl and cycloalkyl sub-group within the groups mentioned is substituted with 1 to 3 groups independently selected from R^5 and optionally substituted with 1 or more F atoms;

or from $H_3C-C(=O)-$, heterocyclyl- $C(=O)-$, $H_2N-C(=O)-$, C_{1-3} -alkyl- $NR^N-C(=O)-$, C_{1-4} -alkyl- $C(=O)NR^N-$, C_{3-6} -cycloalkyl- $C(=O)NR^N-$, heterocyclyl- $C(=O)NR^N-$, C_{1-4} -alkyl-
 15 $S(=O)_2NR^N-$, heterocyclyl-O-, phenyl-O-, heteroaryl-O-, heterocyclyl- $S(=O)_2-$, $H_2N-S(=O)_2-$, heterocyclyl, phenyl, and heteroaryl,

wherein each alkyl, cycloalkyl, and heterocyclyl group or sub-group within the groups mentioned is optionally substituted with 1 or 2 groups independently selected from R^5 and optionally substituted with 1 or more F atoms; and

20 wherein each phenyl and heteroaryl group is optionally substituted with 1 to 3 substituents independently selected from R^6 ;

wherein heterocyclyl is selected from

a cyclobutyl group wherein 1 CH_2 group is replaced by -NH- or -O-;

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

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

wherein heteroaryl is selected from a pyridin-2-onyl ring, a 5-membered
 30 heteroaromatic ring which contains 1, 2, or 3 heteroatoms independently of each

other selected from =N-, -NH-, O, and S, and a 6-membered heteroaromatic ring which contains 1 or 2 =N- atoms,
and wherein in heteroaryl and heterocyclyl rings with one or more NH groups each of them is replaced by NR^N or NR⁵;

5

with the proviso that R³ in total cannot be C₁₋₄-alkyl-, C₁₋₄-alkyl-O-C₁₋₄-alkyl, HO-C₁₋₄-alkyl, and C₁₋₄-alkyl-O-;

10

R⁴ is selected from the group consisting of F, Cl, CN, -CH₃, -CF₃, isopropyl, cyclopropyl, H₃C-O-CH₂-, H₃C-O-, and F₃C-O-;

15

R⁵ is selected from the group consisting of C₁₋₄-alkyl-, -CN, C₃₋₆-cycloalkyl-, heterocyclyl-C(=O)-, H₂N-C(=O)-, C₁₋₄-alkyl-NR^N-C(=O)-, C₁₋₄-alkyl-NR^N-, C₁₋₄-alkyl-C(=O)NR^N-, C₁₋₄-alkyl-S(=O)₂NR^N-, -OH, C₁₋₄-alkyl-O-, C₁₋₄-alkyl-O-C₁₋₄-alkyl-O-, C₃₋₆-cycloalkyl-O-, heterocyclyl-O-, C₁₋₄-alkyl-S(=O)-, C₁₋₄-alkyl-S(=O)₂-, heterocyclyl, and heteroaryl,

20

wherein any alkyl, cycloalkyl, and heterocyclyl group or sub-group within the groups mentioned is optionally substituted with 1 or more F atoms and optionally substituted with 1 or 2 groups independently selected from H₃C-, H₃C-O-, and -CN,

wherein heterocyclyl is selected from

a cyclobutyl group wherein 1 CH₂ group is replaced by -NR^N- or -O-;

a saturated or partially unsaturated C₅₋₆-cycloalkyl group wherein 1 CH₂ group is replaced by -C(=O)-, -NR^N-, -O-, -S(=O)- or -S(=O)₂- and/or 1 CH group by N;

25

a saturated or partially unsaturated C₅₋₆-cycloalkyl group wherein 1 CH₂ group is replaced by -NR^N-, or -O-, a second CH₂ group is replaced by -NR^N-, -C(=O)-, -S(=O)- or -S(=O)₂- and/or 1 CH group is replaced by N; and

a saturated or partially unsaturated C₅₋₆-cycloalkyl group wherein 2 CH₂ group are replaced by -NR^N- or 1 CH₂ group by -NR^N- and the other by -O-, and a third

30

CH₂ group is replaced by -C(=O)-, -S(=O)- or -S(=O)₂- and/or 1 CH group by N;

and wherein heteroaryl is selected from a pyridin-2-onyl ring, a 5-membered heteroaromatic ring which contains 1 or 2 heteroatoms independently of each other selected from =N-, -NH-, -O-, and -S-, and a 6-membered heteroaromatic ring which contains 1 or 2 =N- atoms, and wherein in heteroaromatic rings with

one or more NH groups each of them is replaced by NR^{N} , and each heteroaryl group is optionally substituted with 1 or 2 substituents independently selected from F, Cl, $-\text{CH}_3$, $-\text{CN}$, and $-\text{O}-\text{CH}_3$;

- 5 R^6 is selected from the group consisting of F, Cl, $-\text{CN}$, $-\text{CH}_3$, $-\text{CF}_3$, $-\text{OCH}_3$, $-\text{OCF}_3$, $-\text{S}(=\text{O})\text{CH}_3$, and $-\text{S}(=\text{O})_2\text{CH}_3$;

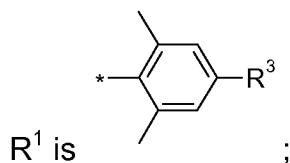
R^{N} is selected from the group consisting of H, $\text{H}_3\text{C}-$, $\text{H}_3\text{C}-\text{C}(=\text{O})-$, and C_{1-3} -alkyl- $\text{S}(=\text{O})_2-$; and

10

m is 1 or 2,

or a salt thereof.

- 15 6. A compound according to claim 1, wherein



R^2 is selected from the group consisting of F, Cl, and $\text{NC}-$;

- 20 R^3 is selected from the group consisting of C_{1-4} -alkyl, C_{3-6} -cycloalkyl-, C_{1-4} -alkyl- $\text{O}-$, and C_{3-6} -cycloalkyl- $\text{O}-$,

wherein each alkyl and cycloalkyl group and each alkyl and cycloalkyl sub-group within the groups mentioned is substituted with 1 group selected from R^5 and optionally substituted with 1 or 2 $\text{H}_3\text{C}-$ group;

- 25 or from $\text{H}_3\text{C}-\text{C}(=\text{O})-$, heterocyclyl- $\text{C}(=\text{O})-$, $\text{H}_2\text{N}-\text{C}(=\text{O})-$, $\text{H}_3\text{C}-\text{NR}^{\text{N}}-\text{C}(=\text{O})-$, heterocyclyl- $\text{O}-$, heteroaryl- $\text{O}-$, $\text{H}_2\text{N}-\text{S}(=\text{O})_2-$, heterocyclyl, phenyl, and heteroaryl, wherein each heterocyclyl group or sub-group within the groups mentioned is optionally substituted with 1 or 2 groups independently selected from R^5 and optionally substituted with 1 or more F atoms; and

- 30 wherein each phenyl and heteroaryl group is optionally substituted with 1 or 2 substituents independently selected from R^6 ;

wherein heterocyclyl is selected from

a cyclobutyl group wherein 1 CH₂ group is replaced by -NH- or -O-;

a saturated or mono-unsaturated C₅₋₆-cycloalkyl group wherein 1 CH₂ group is replaced by -C(=O)-, -NH-, -O- or -S(=O)₂- and/or 1 CH group by N;

5 a saturated or mono-unsaturated C₅₋₆-cycloalkyl group wherein 1 CH₂ group is replaced by -NH- or -O-, a second CH₂ group is replaced by -NH-, -C(=O)- or -S(=O)₂- and/or 1 CH group is replaced by N; and

wherein heteroaryl is selected from a 5-membered heteroaromatic ring which contains 1 or 2 heteroatoms independently of each other selected from =N-, -NH-,
10 , -O-, and -S-, and a 6-membered heteroaromatic ring which contains 1 or 2 =N-atoms, and wherein in heteroaryl and heterocyclyl rings with one ore more NH group each of them is replaced with NR^N or NR⁵;

with the proviso that R³ in total cannot be C₁₋₄-alkyl-, C₁₋₄-alkyl-O-C₁₋₄-alkyl, HO-C₁₋₄-alkyl, and C₁₋₄-alkyl-O-;

R⁵ is selected from the group consisting of C₁₋₄-alkyl-, -CN, C₃₋₆-cycloalkyl-, heterocyclyl-C(=O)-, H₂N-C(=O)-, C₁₋₄-alkyl-NR^N-C(=O)-, C₁₋₄-alkyl-NR^N-, C₁₋₄-alkyl-C(=O)NR^N-, C₁₋₄-alkyl-S(=O)₂NR^N-, -OH, C₁₋₄-alkyl-O-, C₁₋₄-alkyl-O-C₁₋₄-alkyl-O-, C₃₋₆-
20 cycloalkyl-O-, heterocyclyl-O-, C₁₋₄-alkyl-S(=O)-, C₁₋₄-alkyl-S(=O)₂-, heterocyclyl, and heteroaryl,

wherein any alkyl, cycloalkyl, and heterocyclyl group or sub-group within the groups mentioned is optionally substituted with 1 or more F atoms and optionally substituted with 1 or 2 groups independently selected from H₃C-, H₃C-O-, and
25 -CN,

wherein heterocyclyl is selected from

a cyclobutyl group wherein 1 CH₂ group is replaced by -NR^N- or -O-;

a saturated or partially unsaturated C₅₋₆-cycloalkyl group wherein 1 CH₂ group is replaced by -C(=O)-, -NR^N-, -O-, -S(=O)- or -S(=O)₂- and/or 1 CH group by N;

30 a saturated or partially unsaturated C₅₋₆-cycloalkyl group wherein 1 CH₂ group is replaced by -NR^N-, or -O-, a second CH₂ group is replaced by -NR^N-, -C(=O)-, -S(=O)- or -S(=O)₂- and/or 1 CH group is replaced by N; and

a saturated or partially unsaturated C₅₋₆-cycloalkyl group wherein 2 CH₂ group are replaced by -NR^N- or 1 CH₂ group by -NR^N- and the other by -O-, and a third CH₂ group is replaced by -C(=O)-, -S(=O)- or -S(=O)₂- and/or 1 CH group by N; and wherein heteroaryl is selected from a pyridin-2-onyl ring, a 5-membered
5 heteroaromatic ring which contains 1 or 2 heteroatoms independently of each other selected from =N-, -NH-, -O-, and -S-, and a 6-membered heteroaromatic ring which contains 1 or 2 =N- atoms, and wherein in heteroaromatic rings with one ore more NH group each of them is replaced by NR^N, and each heteroaryl group is optionally substituted with 1 or 2 substituents independently selected
10 from F, Cl, -CH₃, -CN, and -O-CH₃;

R⁶ is selected from the group consisting of F, -CH₃, CN, and -OCH₃;

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

m is 1 or 2;

or a salt thereof.

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

8. A pharmaceutical composition comprising one or more compounds according
25 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.

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

5 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, 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
10 the disease, including insulin resistance, obesity, cardiovascular disease and dyslipidemia.

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
15 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 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
20 high blood pressure, heart failure and/or atherosclerosis

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2013/056313

A. CLASSIFICATION OF SUBJECT MATTER INV. C07D307/80 A61K31/343 A61P3/10 C07D405/12 C07D405/14 C07D407/12 C07D409/12 C07D413/12 C07D413/14 C07D417/12 ADD.		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) C07D		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) EPO-Internal, CHEM ABS Data, WPI Data, BEILSTEIN Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 1 630 152 A1 (TAKEDA PHARMACEUTICAL [JP]) 1 March 2006 (2006-03-01) the whole document; in particular, pages 85-86, the examples 70 and 72 -----	1-13
Y	WO 2008/001931 A2 (TAKEDA PHARMACEUTICAL [JP]; YASUMA TSUNEO [JP]; NEGORO NOBUYUKI [JP];) 3 January 2008 (2008-01-03) the whole document -----	1-13
Y	EP 1 559 422 A1 (TAKEDA PHARMACEUTICAL [JP]) 3 August 2005 (2005-08-03) cited in the application the whole document; in particular, claims 10 and 13, and the examples 8 and 53 ----- -/-	1-13
☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.		
* Special categories of cited documents : "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family		
Date of the actual completion of the international search 13 June 2013		Date of mailing of the international search report 25/06/2013
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016		Authorized officer Fink, Dieter

INTERNATIONAL SEARCH REPORT

International application No

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2010/143733 A1 (TAKEDA PHARMACEUTICAL [JP]; NEGORO NOBUYUKI [JP]; TERA0 YOSHITO [JP];) 16 December 2010 (2010-12-16) the whole document; in particular, pages 434-437, the examples 224-227 -----	1-13
Y	NEGORO, NOBUYUKI ET AL: "Identification of Fused-Ring Alkanoic Acids with Improved Pharmacokinetic Profiles that Act as G Protein-Coupled Receptor 40/Free Fatty Acid Receptor 1 Agonists", JOURNAL OF MEDICINAL CHEMISTRY, CODEN: JMCMAR; ISSN: 0022-2623, vol. 55, no. 4, 16 January 2012 (2012-01-16), pages 1538-1552, XP002696495, the whole document; in particular, pages 1546, table 3, the compounds 73 and 53 -----	1-13
Y	MIKAMI, SATOSHI ET AL: "Discovery of Phenylpropanoic Acid Derivatives Containing Polar Functionalities as Potent and Orally Bioavailable G Protein-Coupled Receptor 40 Agonists for the Treatment of Type 2 Diabetes", JOURNAL OF MEDICINAL CHEMISTRY, CODEN: JMCMAR; ISSN: 0022-2623, vol. 55, no. 8, 19 March 2012 (2012-03-19), pages 3756-3776, XP002696496, the whole document; in particular, pages 3761-3764, the tables 1, 2, and 4 -----	1-13
X,P	WO 2012/072691 A1 (BOEHRINGER INGELHEIM INT [DE]; HIMMELSBACH FRANK [DE]; BAKKER REMKO [D]) 7 June 2012 (2012-06-07) the whole document -----	1-13

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2013/056313

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 1630152	A1	01-03-2006	CA 2527691 A1 09-12-2004
		EP 1630152 A1 01-03-2006	
		US 2006258722 A1 16-11-2006	
		WO 2004106276 A1 09-12-2004	
WO 2008001931	A2	03-01-2008	AR 061644 A1 10-09-2008
		AT 543815 T 15-02-2012	
		AU 2007265966 A1 03-01-2008	
		BR PI0713378 A2 03-04-2012	
		CA 2656003 A1 03-01-2008	
		CN 101616913 A 30-12-2009	
		CN 102731451 A 17-10-2012	
		CN 103070854 A 01-05-2013	
		CN 103083307 A 08-05-2013	
		CO 6160234 A2 20-05-2010	
		CR 10564 A 18-06-2012	
		DK 2041123 T3 07-05-2012	
		EP 2041123 A2 01-04-2009	
		EP 2248812 A2 10-11-2010	
		EP 2431367 A2 21-03-2012	
		ES 2379661 T3 30-04-2012	
		GE P20115359 B 26-12-2011	
		HK 1131126 A1 02-11-2012	
		HR P20120333 T1 31-05-2012	
		JP 4401428 B2 20-01-2010	
		JP 4917634 B2 18-04-2012	
		JP 2009280595 A 03-12-2009	
		JP 2009542580 A 03-12-2009	
		JP 2012062320 A 29-03-2012	
		KR 20090027743 A 17-03-2009	
		MA 30537 B1 01-06-2009	
		NZ 574038 A 22-12-2011	
		PE 09932008 A1 06-10-2008	
		PT 2041123 E 09-04-2012	
		RS 52307 B 31-12-2012	
		RU 2009102515 A 10-08-2010	
		SI 2041123 T1 31-05-2012	
		TW 200811125 A 01-03-2008	
		US 2010004312 A1 07-01-2010	
		US 2010197761 A1 05-08-2010	
		US 2012046338 A1 23-02-2012	
		WO 2008001931 A2 03-01-2008	
		ZA 200900154 A 31-03-2010	
EP 1559422	A1	03-08-2005	AU 2003277576 A1 07-06-2004
			CA 2505322 A1 21-05-2004
			EP 1559422 A1 03-08-2005
			EP 2385032 A1 09-11-2011
			US 2009012093 A1 08-01-2009
			WO 2004041266 A1 21-05-2004
WO 2010143733	A1	16-12-2010	EP 2440541 A1 18-04-2012
			JP 2012529422 A 22-11-2012
			US 2012172351 A1 05-07-2012
			WO 2010143733 A1 16-12-2010
WO 2012072691	A1	07-06-2012	AR 084050 A1 17-04-2013
			US 2012302566 A1 29-11-2012

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2013/056313

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
		UY 33758 A	29-06-2012
		W0 2012072691 A1	07-06-2012
