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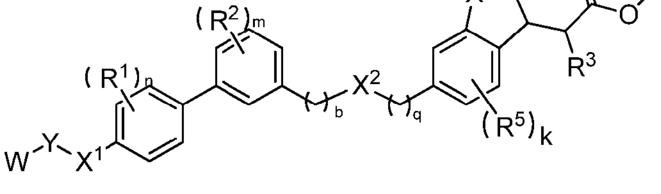
(54) Title: BIPHENYL COMPOUNDS AND USES THEREOF



(I)

(57) **Abstract**: The present invention relates to biphenyl compounds and uses thereof in medicine. Specifically, the present invention relates to a compound of Formula (I), or a stereoisomer, a geometric isomer, a tautomer, a mesomer, a racemate, an enantiomer, a diastereoisomer, an N-oxide, a hydrate, a solvate, a metabolite, a hydrolysate, a pharmaceutically acceptable salt or a prodrug thereof. The compound disclosed herein is used as a therapeutic agent particularly a GPR40 agonist for treating diabetes and metabolic disease in a patient.

BIPHENYL COMPOUNDS AND USES THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to Chinese Patent Application Serial No. 201310535024.2, filed with the State Intellectual Property Office of China on October 31, 2013; and Chinese Patent Application Serial No. 201410110018.7, filed with the State Intellectual Property Office of China on March 23, 2014, both of which are hereby incorporated by reference in their entireties and for all purposes as if specifically and fully set forth herein.

FIELD

[0002] The present invention relates to compounds with GPR40 activity modulation ability and uses thereof in the treatment of GPR40 related disorders. In addition the invention relates to compounds, pharmaceutical compositions containing the compounds and uses thereof in the treatment of certain GPR40-related deseases in a patient.

BACKGROUND

[0003] The production of insulin is central to the regulation of carbohydrate and lipid metabolism. Insulin imbalances lead to conditions such as type II diabetes mellitus, a serious metabolic disease that afflicts over 366 million people worldwide. Insulin is secreted from pancreatic β cells in response to elevated plasma glucose which is augmented by the presence of fatty acids. The recent recognition of the function of the G-protein coupled receptor 40 (GPR40) in modulating insulin secretion has provided insight into regulation of carbohydrate and lipid metabolism in vertebrates, and further provided targets for the development of therapeutic agents for disorders such as obesity, diabetes, cardiovascular disease and dyslipidemia.

[0004] GPR40 is a member of the gene superfamily of G-protein coupled receptors ("GPRs"). GPCRs are membrane proteins characterized as having seven putative transmembrane domains that respond to a variety of molecules by activating intra-cellular signaling pathways critical to a diversity of physiological functions. GPR40 was first identified as an orphan receptor (*i.e.*, a receptor without a known ligand) from a human genomic DNA fragment. Sawzdargo *et al.* (1997) *Biochem. Biophys. Res. Commun.* 239: 543-547. GPR40 is highly expressed in pancreatic β cells and insulin-secreting cell lines. GPR40 activation is linked to modulation of the G_q family of intracellular signaling proteins and concomitant induction of elevated calcium levels. It has been recognized that fatty acids serve as ligands for GPR40, and that fatty acids regulate insulin secretion through GPR40. Itoh *et al.* (2003) *Nature* 422: 173-176; Briscoe *et al.* (2003) *J. Biol. Chem.* 278: 1130311311; Kotarsky *et al.* (2003) *Biochem. Biophys. Res. Commun.* 301: 406-410.

[0005] Various documents have disclosed compounds reportedly having activity with respect to GPR40. For example, WO 2004/041266 and EP 1559422 disclose compounds that purportedly act as GPR40 receptor function regulators. WO 2005/086661 U.S. Patent Publication No. 2006/0004012, U.S. Patent Publication No. 2006/0270724, and U.S. Patent Publication No.2007/0066647 disclose compounds useful for modulating insulin levels in subjects and useful for treating type II diabetes.

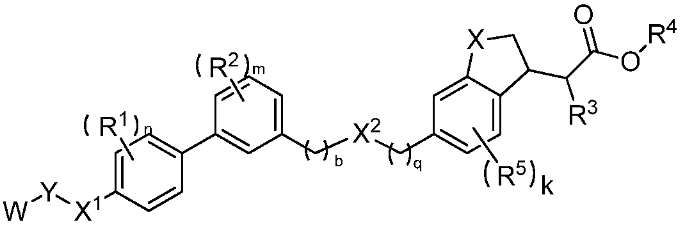
[0006] Although a number of compounds have been disclosed that reportedly modulate GPR40 activity, the prevalence of type II diabetes, obesity, hypertension, cardiovascular disease and dyslipidemia underscores the need for new therapies to effectively treat or prevent these conditions.

[0007] The present invention relates to novel substituted biphenyl compounds having modulation ability to GPR40. Such compounds are therefore potentially useful for the treatment or prophylaxis of diabetes and related conditions.

SUMMARY

[0008] Provided herein are compounds, pharmaceutical compositions and methods used for treating a condition or disorder such as diabetes, diabetic retinopathy, diabetic neuropathy, diabetic nephropathy, insulin resistance, hyperglycemia, hyperinsulinemia, elevated blood levels of fatty acids or glycerol, hyperlipidemia, obesity, hypertriglyceridemia, syndrome X, ketosis acidosis, glucose intolerance, hypercholesterolemia, dyslipidemia, metabolic syndrome, cardiovascular disease, renal disease, thrombotic disorders, nephropathy, sexual dysfunction, skin disease, indigestion, hypoglycemia, cancer, edema, diabetes complications, atherosclerosis or hypertension. The compounds or pharmaceutical compositions disclosed herein have the potent modulation ability to GPR40.

[0009] In one aspect, the present invention provides a compound having Formula (I) or a stereoisomer, a geometric isomer, a tautomer, a mesomer, a racemate, an enantiomer, a diastereoisomer, an *N*-oxide, a hydrate, a solvate, a metabolite, a hydrolysate, a pharmaceutically acceptable salt or a prodrug thereof:



(I)

wherein each of X and X^1 is independently O, NH, CH_2 or S;

X^2 is O, S or NH;

Y is alkylene or alkenylene, wherein one or more methylene groups of the alkylene or alkenylene are optionally independently replaced with NR^a, S, $S(=O)_2$ or S(=O), and wherein each of the alkylene and alkenylene is optionally independently substituted by one or more substituents independently selected from hydroxy, F, Cl, Br, I, cyano, amino, mercapto, nitro, oxo (=O), alkyl or hereoalkyl;

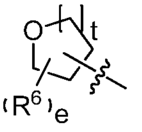
each R^1, R^2 and R^3 is independently H, F, Cl, Br, I, hydroxy, cyano, amino, mercapto, nitro, alkyl, heteroalkyl, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkoxy, alkylamino, cycloalkyl, heterocyclyl, aryl, heteroaryl or haloalkyl;

R^4 is H or alkyl;

each R^5 is independently H, F, Cl, Br, I, hydroxy, cyano, amino, mercapto, nitro, alkyl, alkoxy, alkylamino or heteroalkyl;

each of k, n, m, b and q is independently 0, 1, 2, 3 or 4;

W is adamantyl, bridged cyclyl, bridged heterocyclyl, spiro cyclyl, spiro heterocyclyl, fused cyclyl or fused heterocyclyl, wherein each of the damantyl, bridged cyclyl, bridged heterocyclyl, spiro cyclyl, spiro heterocyclyl, fused cyclyl and fused heterocyclyl is optionally independently substituted by one or more R^6 groups; or W is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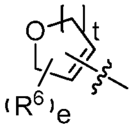
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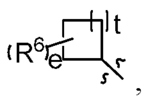
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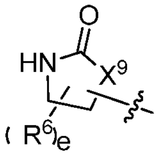
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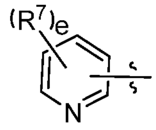
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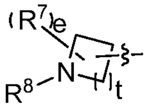
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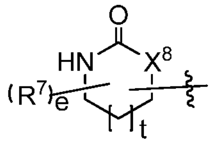
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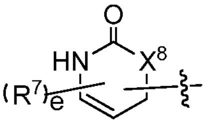
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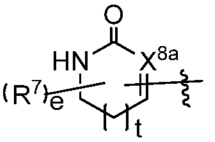
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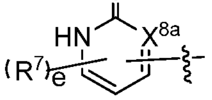
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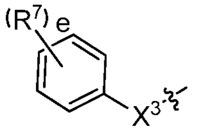
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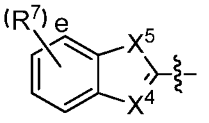
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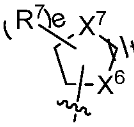
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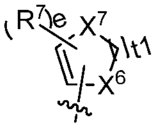
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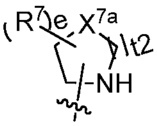
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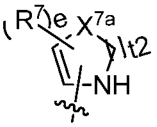
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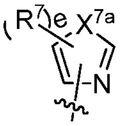
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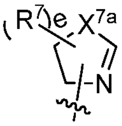
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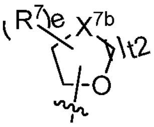
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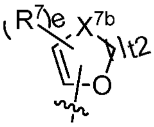
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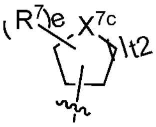
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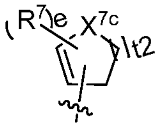
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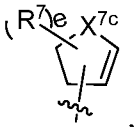
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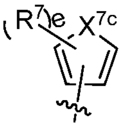
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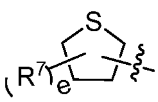
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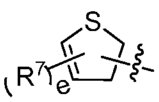
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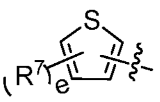
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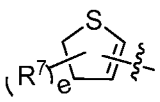
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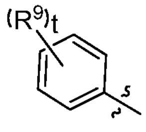
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wherein each R^6 is independently H, F, Cl, Br, I, hydroxy, cyano, amino, mercapto, nitro, oxo(=O), alkyl, heteroalkyl, haloalkyl, hydroxyalkyl, aminoalkyl, alkoxy, alkylamino, alkyl-S(=O)$_2$- or alkyl-S(=O)-;

each R^7 is independently H, F, Cl, Br, I, hydroxy, cyano, amino, mercapto, nitro, alkyl, heteroalkyl, haloalkyl, hydroxyalkyl, aminoalkyl, alkoxy, alkylamino, alkyl-S(=O)$_2$- or alkyl-S(=O)-;

R^8 is H, C_{2-10} alkyl, heteroalkyl, haloalkyl, hydroxyalkyl, aminoalkyl, alkyl-S(=O)$_2$- or alkyl-S(=O)-;

each R^9 is independently F, Cl, Br, I, hydroxy, cyano, amino, mercapto, nitro, alkyl, heteroalkyl, haloalkyl, hydroxyalkyl, aminoalkyl, alkoxy, alkylamino, alkyl-S(=O)$_2$- or alkyl-S(=O)-;

X^3 is NR^a, O, S, S(=O)$_2$ or S(=O);

each of X^4 and X^{8a} is independently CH or N;

each of X^5 and X^{7a} is independently CH_2 or NR^a;

each X^7 is independently CH_2, S, O or NR^a;

X^{7b} is CH_2, O or S;

X^{7c} is CH_2, O or NR^a;

each of X^6 and X^8 is independently CH_2, O or NH;

X^9 is O or NH;

each R^a is independently alkyl-$S(=O)_2$- or H;

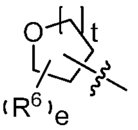
each e is independently 0, 1, 2, 3, 4, 5, 6, 7 or 8;

each t is independently 1, 2, 3, 4 or 5;

t1 is 3, 4 or 5; and

each t2 is independently 1 or 2.

[0010] In some embodiments, W is adamantyl, C_{5-12} bridged cyclyl, C_{5-12} bridged heterocyclyl, C_{5-12} spiro cyclyl, C_{5-12} spiro heterocyclyl, C_{4-12} fused cyclyl or C_{4-12} fused heterocyclyl, and wherein each of damantyl, C_{5-12} bridged cyclyl, C_{5-12} bridged heterocyclyl, C_{5-12} spiro cyclyl, C_{5-12} spiro heterocyclyl, C_{4-12} fused cyclyl and C_{4-12} fused heterocyclyl is optionally independently substituted by one or more R^6 groups; or W is



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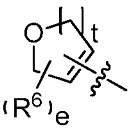

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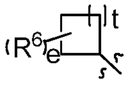

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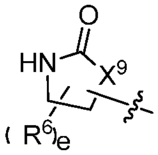

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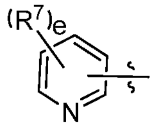

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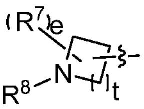

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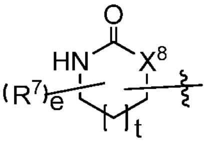

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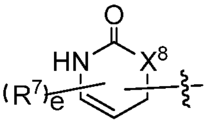

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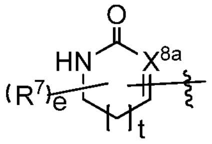

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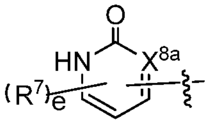

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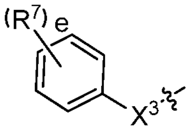

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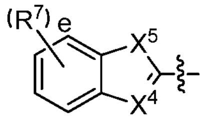

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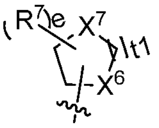

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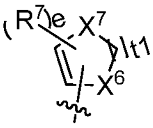

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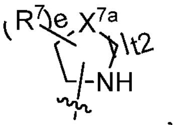

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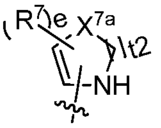

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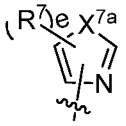

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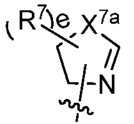

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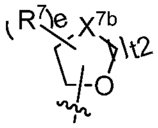

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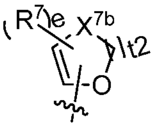

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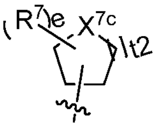

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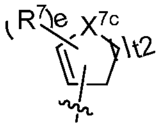

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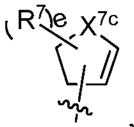

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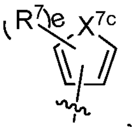

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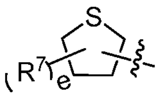

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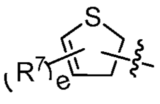

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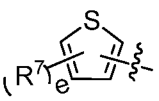

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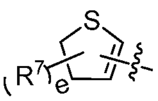

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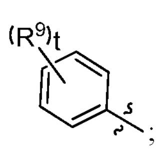


;

and wherein each R^6 is independently H, F, Cl, Br, I, hydroxy, cyano, amino, mercapto, nitro, oxo (=O), C_{1-6} alkyl, C_{2-6} heteroalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} aminoalkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{1-6} alkyl-$S(=O)_2$- or C_{1-6} alkyl-$S(=O)$-;

each R^7 is independently H, F, Cl, Br, I, hydroxy, cyano, amino, mercapto, nitro, C_{1-6} alkyl, C_{2-6} heteroalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} aminoalkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{1-6} alkyl-$S(=O)_2$- or C_{1-6} alkyl-$S(=O)$-;

R^8 is H, C_{2-6} alkyl, C_{2-6} heteroalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} aminoalkyl, C_{1-6} alkyl-S(=O)$_2$- or C_{1-6} alkyl-S(=O)-;

each R^9 is independently F, Cl, Br, I, hydroxy, cyano, amino, mercapto, nitro, C_{1-6} alkyl, C_{2-6} heteroalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} aminoalkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{1-6} alkyl-S(=O)$_2$- or C_{1-6} alkyl-S(=O)-; and

each R^a is independently C_{1-6} alkyl-S(=O)$_2$- or H.

[0011] In other embodiments, each R^6 is independently H, F, Cl, Br, I, hydroxy, cyano, amino, mercapto, nitro, oxo(=O), methyl, ethyl, propyl, isopropyl, butyl, trifluoromethyl, hydroxymethyl, aminomethyl, methoxy, ethoxy, methylamino, ethylamino, CH_3-S(=O)$_2$- or CH_3-S(=O)-;

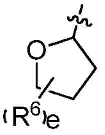
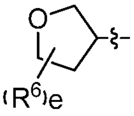
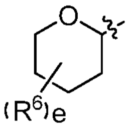
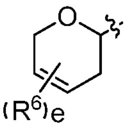
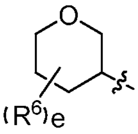
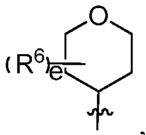
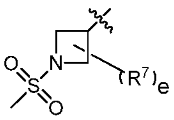
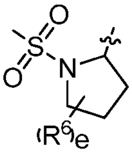
each R^7 is independently H, F, Cl, Br, I, hydroxy, cyano, amino, mercapto, nitro, methyl, ethyl, propyl, isopropyl, butyl, trifluoromethyl, hydroxymethyl, aminomethyl, methoxy, ethoxy, methylamino, ethylamino, CH_3-S(=O)$_2$- or CH_3-S(=O)-;

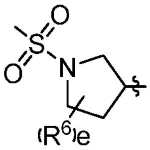
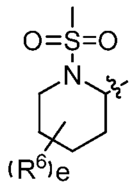
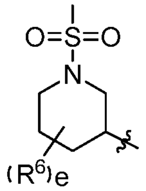
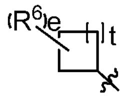
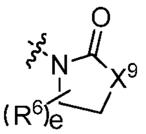
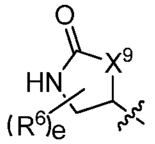
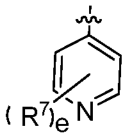
R^8 is H, ethyl, trifluoromethyl, hydroxymethyl, aminomethyl, CH_3-S(=O)$_2$- or CH_3-S(=O)-;

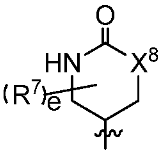
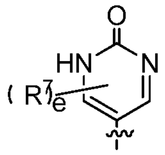
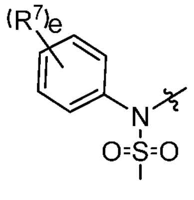
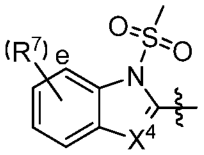
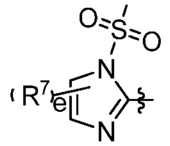
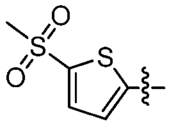
each R^9 is independently F, Cl, Br, I, hydroxy, cyano, amino, mercapto, nitro, methyl, ethyl, propyl, isopropyl, butyl, trifluoromethyl, hydroxymethyl, aminomethyl, methoxy, ethoxy, methylamino, ethylamino, CH_3-S(=O)$_2$- or CH_3-S(=O)-; and

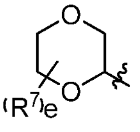
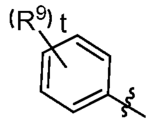
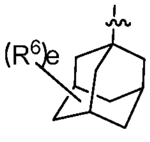
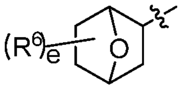
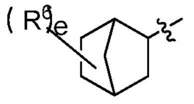
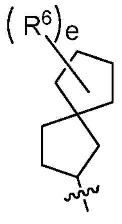
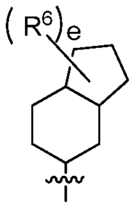
each R^a is independently CH_3-S(=O)$_2$- or H.

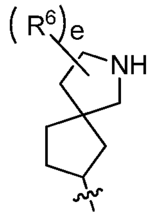
[0012] In some embodiments, W is

, , , , , , , ,

, , , , , , ,

, , , , , ,

, , , , , , ,



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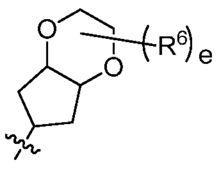

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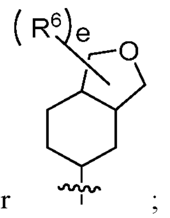

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wherein each R^6 is independently H, F, Cl, Br, I, hydroxy, cyano, amino, mercapto, nitro, oxo(=O), methyl, ethyl, propyl, isopropyl, butyl, trifluoromethyl, hydroxymethyl, aminomethyl, methoxy, ethoxy, methylamino, ethylamino, CH_3-S(=O)$_2$- or CH_3-S(=O)-;

each R^7 is independently H, F, Cl, Br, I, hydroxy, cyano, amino, mercapto, nitro, methyl, ethyl, propyl, isopropyl, butyl, trifluoromethyl, hydroxymethyl, aminomethyl, methoxy, ethoxy, methylamino, ethylamino, CH_3-S(=O)$_2$- or CH_3-S(=O)-; and

each R^9 is independently F, Cl, Br, I, hydroxy, cyano, amino, mercapto, nitro, methyl, ethyl, propyl, isopropyl, butyl, trifluoromethyl, hydroxymethyl, aminomethyl, methoxy, ethoxy, methylamino, ethylamino, CH_3-S(=O)$_2$- or CH_3-S(=O)-.

[0013] In some embodiments, Y is C_{2-6} alkylene or C_{2-6} alkenylene, and wherein one or more methylene groups of the C_{2-6} alkylene or C_{2-6} alkenylene are optionally replaced with NR^a, S, S(=O)$_2$ or S(=O), each of the C_{2-6} alkylene and C_{2-6} alkenylene is optionally independently substituted by one or more substituents independently selected from hydroxy, F, Cl, Br, I, cyano, amino, mercapto, nitro, oxo (=O), C_{1-6} alkyl or C_{2-6} hereoalkyl; and

R^a is CH_3-S(=O)$_2$- or H.

[0014] In some embodiments, each R^1, R^2 and R^3 is independently H, F, Cl, Br, I, hydroxy, cyano, amino, mercapto, nitro, C_{1-6} alkyl, C_{2-6} heteroalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} hydroxyalkyl, C_{1-6} aminoalkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{3-10} cycloalkyl, C_{2-10} heterocyclyl, C_{6-10} aryl, C_{1-9} heteroaryl or C_{1-6} haloalkyl;

R^4 is H or C_{1-6} alkyl; and

each R^5 independently is H, F, Cl, Br, I, hydroxy, cyano, amino, mercapto, nitro, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino or C_{2-6} heteroalkyl.

[0015] In some embodiments, each R^1, R^2 and R^3 is independently H, F, Cl, Br, I, hydroxy, cyano, amino, mercapto, nitro, methyl, ethyl, propyl, isopropyl, butyl, vinyl, ethynyl, hydroxymethyl, aminomethyl, methoxy, methylamino, cyclopropyl, tetrahydrofuranyl, phenyl, pyrrolyl or trifluoromethyl;

R^4 is H, methyl or ethyl; and

each R^5 is independently H, F, Cl, Br, I, hydroxy, cyano, amino, mercapto, nitro, methyl, ethyl, methoxy, ethoxy, isopropoxy, methylamino, ethylamino or propylamino.

[0016] In other aspect, provided herein is a pharmaceutical composition comprising the compound disclosed herein.

[0017] In some embodiments, the pharmaceutical composition further comprises at least one of pharmaceutically acceptable carriers, excipients, diluents, adjuvants and vehicles.

[0018] In other embodiments, the pharmaceutical composition further comprises at least one of antidiabetic agents, antihyperglycemic agents, antiadipositas drugs, antihypertensive agents, antiplatelet agents, antiatherosclerotic drugs, lipid-lowering agents and anti-inflammatories.

[0019] In still other embodiments, the antidiabetic agent is at least one of SGLT-2 inhibitors, biguanides, sulfonylureas, glucosidase inhibitors, PPAR agonists, αP2 inhibitors, PPARα/γ dual agonists, dipeptidyl peptidase (DPP-IV) inhibitors, ndinedglinides, insulin, glucagon like peptide-1(GLP-1) inhibitors, PTP1B inhibitors, glycogen phosphorylase inhibitors and glucose-6-phosphatase inhibitors.

[0020] In yet other embodiments, the pharmaceutical composition further comprises at least one of GPR40 receptor agonists.

[0021] In other aspect, provided herein is use of the compound or the pharmaceutical composition disclosed herein in the manufacture of a medicament for preventing, treating, lessening or delaying diabetes, diabetic retinopathy, diabetic neuropathy, diabetic nephropathy, insulin resistance, hyperglycemia, hyperinsulinemia, elevated blood levels of fatty acids or glycerol, hyperlipidemia, obesity, hypertriglyceridemia, syndrome X, ketosis acidosis, glucose intolerance, hypercholesterolemia, dyslipidemia, metabolic syndrome, cardiovascular disease, renal disease, thrombotic disorders, nephropathy, sexual dysfunction, skin disease, indigestion, hypoglycemia, cancer, edema, diabetes complications, atherosclerosis or hypertension, or increasing high density lipoprotein level.

[0022] In other aspect, provided herein is use of the compound or the pharmaceutical composition disclosed herein in the manufacture of a medicament for exciting G-protein coupled receptor in a patient.

[0023] In some embodiments, the G-protein coupled receptor is GPR40 receptor.

[0024] In other aspect, provided herein is a method for preventing, treating, lessening or delaying diabetes, diabetic retinopathy, diabetic neuropathy, diabetic nephropathy, insulin resistance, hyperglycemia, hyperinsulinemia, elevated blood levels of fatty acids or glycerol, hyperlipidemia, obesity, hypertriglyceridemia, syndrome X, ketosis acidosis, glucose intolerance, hypercholesterolemia, dyslipidemia, metabolic syndrome, cardiovascular disease, renal disease, thrombotic disorders, nephropathy, sexual dysfunction, skin disease, indigestion, hypoglycemia, cancer, edema, diabetes complications, atherosclerosis or hypertension, or increasing high density lipoprotein level, comprising administering to a subject in need thereof a therapeutically effective amount of the compound or the pharmaceutical composition disclosed herein.

[0025] In other aspect, provided herein is a method for exciting G-protein coupled receptor, comprising administering to a subject a therapeutically effective amount of the compound or the pharmaceutical composition disclosed herein.

[0026] In some embodiments, the G-protein coupled receptor is GPR40 receptor.

[0027] In other aspect, provided herein is a compound or the pharmaceutical composition disclosed herein for use in preventing, treating, lessening or delaying diabetes, diabetic retinopathy, diabetic neuropathy, diabetic nephropathy, insulin resistance, hyperglycemia, hyperinsulinemia, elevated blood levels of fatty acids or glycerol, hyperlipidemia, obesity, hypertriglyceridemia, syndrome X, ketosis acidosis, glucose intolerance, hypercholesterolemia, dyslipidemia, metabolic syndrome, cardiovascular disease, renal disease, thrombotic disorders, nephropathy, sexual dysfunction, skin disease, indigestion, hypoglycemia, cancer, edema, diabetes complications, atherosclerosis or hypertension, or increasing high density lipoprotein level.

[0028] In some embodiments, the compound or the pharmaceutical composition disclosed herein for use in exciting G-protein coupled receptor.

[0029] In some embodiments, the G-protein coupled receptor is GPR40 receptor.

[0030] In other aspect, provided herein are methods ahout preparation, isolation and purification of the compound of Formula (I).

[0031] The foregoing merely summarizes certain aspects disclosed herein and is not intended to be limiting in nature. These aspects and other aspects and embodiments are described more fully below

DETAILED DESCRIPTION

DEFINITIONS AND GENERAL TERMINOLOGY

[0032] Reference will now be maded in detail to certain embodiments disclosed herein, examples of which are illustrated in the accompanying structures and formulas. The invention is intended to cover all alternatives, modifications, and equivalents that may be included within the scope disclosed herein as defined by the claims. One skilled in the art will recognize many methods and materials similar or equivalent to those described herein, which could be used in the practice disclosed herein. Described herein is in no way limited to the methods and materials. In the event that one or more of the incorporated literature, patents, and similar materials differ from or contradict this application, including but not limited to defined terms, term usage, described techniques, or the like, this application controls.

[0033] As used herein, the following definitions shall be applied unless otherwise indicated. For purposes disclosed herein, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, and *the Handbook of Chemistry and Physics*, 75th Ed. 1994. Additionally, general principles of organic chemistry are described in Sorrell et al., "*Organic Chemistry*", University Science Books, Sausalito: 1999, and Smith et al., "*March's Advanced Organic Chemistry*", John Wiley & Sons, New York: 2007, all of which are incorporated herein by reference in their entireties.

[0034] As described herein, compounds optionally are substituted with one or more substituents, such as those illustrated above, or as exemplified by particular classes, subclasses, and species disclosed herein. It will be appreciated that the phrase "optionally substituted" is used interchangeably with the phrase "substituted or unsubstituted". In general, the term "substituted" whether preceded by the term "optionally" or not, refers to the replacement of one or more hydrogen radicals in a given structure with the radical of a specified substituent. Unless otherwise indicated, an optionally substituted group may have a substituent at each substitutable position of the group. When more than one position in a given structure can be substituted with more than one substituent selected from a specified group, the substituent may be either the same or different at each position. Wherein the substituents described herein include, but are not limited to, deuterium, hydroxy, amino, halo, cyano, aryl, heteroaryl, alkoxy, alkylamino, alkylthio, alkyl, alkenyl, alkynyl, heterocyclyl, mercapto, nitro, aryloxy, heteroaryloxy, oxo (=O), carboxy, hydroxy-substituted alkoxy, hydroxy-substituted alkyl-C(=O)-, alkyl-C(=O)-, alkyl-S(=O)-, alkyl-$S(=O)_2$-, hydroxy-substituted alkyl-S(=O)-, hydroxy-substituted alkyl-$S(=O)_2$-, carboxyalkoxy, and the like.

[0035] Unless otherwise stated, the term "alkyl" refers to a saturated linear or branched chain monovalent hydrocarbon radical of one to twenty carbon atoms, or one to ten carbon atoms, or one to eight carbon atoms, or one to six carbon atoms, or one to four carbon atoms, or one to three carbon atoms, wherein the alkyl radical may be optionally substituted independently with one or more substituents described below. The examples of alkyl group include, but are not limited to, methyl (Me, $-CH_3$), ethyl (Et, $-CH_2CH_3$), *n*-propyl (*n*-Pr, $-CH_2CH_2CH_3$), *i*-propyl (*i*-Pr, $-CH(CH_3)_2$), *n*-butyl (*n*-Bu, $-CH_2CH_2CH_2CH_3$), *i*-butyl (*i*-Bu, $-CH_2CH(CH_3)_2$), *s*-butyl (*s*-Bu, $-CH(CH_3)CH_2CH_3$), *t*-butyl (*t*-Bu, $-C(CH_3)_3$), *n*-pentyl,($-CH_2CH_2CH_2CH_2CH_3$), 2-pentyl ($-CH(CH_3)CH_2CH_2CH_3$), 3-pentyl ($-CH(CH_2CH_3)_2$), 2-methyl-2-butyl ($-C(CH_3)_2CH_2CH_3$), 3-methyl-2-butyl ($-CH(CH_3)CH(CH_3)_2$), 3-methyl-l-butyl ($-CH_2CH_2CH(CH_3)_2$), 2-methyl-l-butyl ($-CH_2CH(CH_3)CH_2CH_3$), *n*-hexyl ($-CH_2CH_2CH_2CH_2CH_2CH_3$), 2-hexyl ($-CH(CH_3)CH_2CH_2CH_2CH_3$), 3-hexyl ($-CH(CH_2CH_3)(CH_2CH_2CH_3)$), 2-methyl-2-pentyl ($-C(CH_3)_2CH_2CH_2CH_3$), 3-methyl-2-pentyl ($-CH(CH_3)CH(CH_3)CH_2CH_3$), 4-methyl-2-pentyl ($-CH(CH_3)CH_2CH(CH_3)_2$), 3-methyl-3-pentyl ($-C(CH_3)(CH_2CH_3)_2$), 2-methyl-3-pentyl ($-CH(CH_2CH_3)CH(CH_3)_2$), 2,3-dimethyl-2-butyl ($-C(CH_3)_2CH(CH_3)_2$), 3,3-dimethyl-2-butyl ($-CH(CH_3)C(CH_3)_3$ and *n*-heptyl, *n*-octyl, and the like. The prefix "alk-" refers to inclusive of both straight chain and branched saturated carbon chain. The term "alkylene" refers to a saturated divalent hydrocarbon group derived from a straight or branched chain saturated hydrocarbon by the removal of two hydrogen atoms, and is exemplified by methylene, ethylene, isopropylene, and the like

[0036] The term "heteroalkyl" refers to hydrocarbon chain, inserted with one or more heteroatoms. Unless otherwise specified, heteroalkyl groups contain 1-10 carbon atoms. In other embodiments, the heteroalkyl group contains 1-8 carbon atoms. In still other embodiments, the heteroalkyl group contains 1-6 carbon atoms, and in yet other embodiments, the heteroalkyl group contains 1-4 carbon atoms. In other embodiments, the heteroalkyl group contains 1-3 carbon atoms. Some non-limiting examples of the heteroalkyl group include CH_3OCH_2-, $CH_3CH_2OCH_2$-, CH_3SCH_2-, $(CH_3)_2NCH_2$-, $(CH_3)_2CH_2OCH_2$-, $CH_3OCH_2CH_2$- and $CH_3CH_2OCH_2CH_2$-, and the like.

[0037] The term "alkenyl" refers to a linear or branched chain monovalent hydrocarbon radical of two to twelve carbon atoms, or two to eight carbon atoms, or two to six carbon atoms, or two to four carbon atoms, with at least one site of unsaturation, *i.e.*, a carbon-carbon, sp^2 double bond, wherein the alkenyl radical may be optionally substituted independently with one or more substituents described herein, and includes radicals having "cis" and "trans" orientations, or alternatively, "*E*" and "*Z*" orientations. Some non-limiting examples of the alkenyl group include ethenyl or vinyl (-CH=CH_2) and allyl (-CH_2CH=CH_2), and the like.

[0038] The term "alkynyl" refers to a linear or branched chain monovalent hydrocarbon radical of two to twelve carbon atoms, or two to eight carbon atoms, or two to six carbon atoms, or two to four carbon atoms, with at least one site of unsaturation, *i.e.*, a carbon-carbon, sp triple bond, wherein the alkynyl radical may be optionally substituted independently with one or more substituents described herein. Some non-limiting examples of the alkynyl group include ethynyl (-C≡CH) and propynyl (propargyl, -CH_2C≡CH), and the like.

[0039] The term "alkylene" refers to a saturated divalent hydrocarbon group derived from a straight or branched-chain saturated hydrocarbon by the removal of two hydrogen atoms. The alkylene group is optionally substituted with one or more substituents. The substituents include, but are not limited to, deuterium, hydroxy, amino, halo, cyano, aryl, heteroaryl, alkoxy, alkyl, alkenyl, alkynyl, heterocyclyl, mercapto, nitro, or aryloxy. Some non-limiting examples of the alkylene group include methylene (-CH_2-), ethylene (-CH_2-CH_2-), isopropylidene (-CH_2-CH(CH_3)-), ethylidene, 2-methoxy-1,1-propylidene and 2-hydroxy-1,1-propylidene, 2-methyl-2-hydroxy-1,1-propylidene, and the like.

[0040] The term "alkenylene" refers to an unsaturated divalent hydrocarbon group derived from a straight or branched-chain unsaturated hydrocarbon alkene by the removal of two hydrogen atoms. The alkenylene group is optionally substituted with one or more substituents. The substituents include, but are not limited to, deuterium, hydroxy, amino, halo, cyano, aryl, heteroaryl, alkoxy, alkyl, alkenyl, alkynyl, heterocyclyl, mercapto, nitro, or aryloxy. Some non-limiting examples of the alkenylene group include ethenylene (-CH=CH-), isopropenylene (-C(CH_3)=CH-), 3-methoxy-1,1-propenylidene and 2-methyl-1,1-butenylidene, and the like.

[0041] The term "hydroxyalkyl" refers to an alkyl group substituted with one or more hydroxy groups, wherein the alkyl group is as defined herein. Some non-limiting examples of the hydroxyalkyl group include hydroxyethyl, 2-hydroxypropyl and hydroxymethyl, and the like.

[0042] The term "aminoalkyl" refers to an alkyl group substituted with one or more amino groups, wherein the alkyl group is as defined herein. Some non-limiting examples of the aminoalkyl group include aminomethyl, 2-aminoethyl and 2-amino isopropyl, and the like.

[0043] The term "alkoxy" refers to an alkyl group, as previously defined, attached to the principal carbon chain through an oxygen ("alkoxy") atom. Some non-limiting examples of the alkoxy group include methoxy, ethoxy, propoxy, butoxy, and the like. And the alkoxy defined above may be substituted or unsubstituted, wherein the substituent may be, but is not limited to, deuterium, hydroxy, amino, halo, cyano, alkoxy, alkyl, alkenyl, alkynyl, mercapto and nitro, and the like.

[0044] The term "alkylamino" refers to an alkyl group, as previously defined, attached to the principal carbon chain through a nitrogen atom. Some non-limiting examples of the alkylamino group include methylamino, ethylamino, propylamino, butylamino, and the like. And the alkylamino defined above may be substituted or unsubstituted, wherein the substituent may be, but is not limited to, deuterium, hydroxy, amino, halo, cyano, alkoxy, alkyl, alkenyl, alkynyl, mercapto and nitro, and the like.

[0045] The term "cycloaliphatic", "carbocycle", "carbocyclyl", or "cycloalkyl" refers to a monovalent or multivalent non-aromatic, saturated or partially unsaturated ring exclusive of heteroatoms, having 3 to 12 carbon atoms as a monocyclic ring or 7 to 12 carbon atoms as a bicyclic ring. Bicyclic carbocycles having 7 to 12 atoms can be arranged, for example, as a bicyclo [4,5], [5,5], [5,6] or [6,6] system, and bicyclic carbocycles having 9 or 10 ring atoms can be arranged as a bicyclo [5,6] or [6,6] system. Some non-limiting examples of the cycloaliphatic group include cycloalkyl, cycloalkenyl, and cycloalkynyl. Further examples of the cycloaliphatic group include cyclopropyl, cyclobutyl, cyclopentyl, 1-cyclopentyl-l-enyl, l-cyclopentyl-2-enyl, l-cyclopentyl-3-enyl, cyclohexyl, 1-cyclohexyl-l-enyl, l-cyclohexyl-2-enyl, l-cyclohexyl-3-enyl, cyclohexadienyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, cycloundecyl, cyclododecyl, and the like. The term "cycloaliphatic", "carbocycle", "carbocyclyl", or "cycloalkyl" may be substituted or unsubstituted, wherein the substitutent may be, but is not limited to, hydroxy, amino, halo, cyano, aryl, heteroaryl, alkoxy, alkylamino, alkyl, alkenyl, alkynyl, heterocyclyl, mercapto, nitro, aryloxy, hydroxy-substituted alkoxy, hydroxy-substituted alkyl-C(=O)-, alkyl-C(=O)-, alkyl-S(=O)-, alkyl-S(=O)$_2$-, hydroxy-substituted alkyl-S(=O)-, hydroxy-substituted alkyl-S(=O)$_2$-, carboxy alkoxy, and the like.

[0046] The term "heterocycle", "heterocyclyl", "heterocycloaliphatic", or "heterocyclic" as used interchangeably herein refers to a monocyclic, bicyclic, or tricyclic ring system in which one or more ring members are an independently selected heteroatom and that is completely saturated or that contains one or more units of unsaturation, but not aromatic having a single point or multipoint of attachment to the rest of the molecule. One or more ring atoms are optionally substituted independently with one or more substituents described herein. In some embodiments, the "heterocycle", "heterocyclyl", "heterocycloaliphatic" or "heterocyclic" group is a monocycle having 3 to 7 ring members (*e.g.*, 1 to 6 carbon atoms and 1 to 3 heteroatoms selected from N, O, P or S, wherein the S or P is optionally substituted with one or more oxo to provide the group SO or SO$_2$, PO or PO$_2$, with the proviso that when the ring is a 3-membered ring, there is only one heteroatom) or a bicycle having 7 to 10 ring members (*e.g.*, 4 to 9 carbon atoms and 1 to 3 heteroatoms selected from N, O, P or S, wherein the S or P is optionally substituted with one or more oxo to provide the group SO or SO$_2$, PO or PO$_2$).

[0047] The heterocyclyl may be a carbon radical or heteroatom radical. "Heterocyclyl" also includes radicals where heterocycle radicals are fused with a saturated, partially unsaturated ring, or heterocyclic ring. Some non-limiting examples of heterocyclic rings include pyrrolidinyl, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothienyl, tetrahydropyranyl, dihydropyranyl, tetrahydrothiopyranyl, piperidyl, morpholinyl, thiomorpholinyl, thioxanyl, thiazolidinyl, oxazolidinyl, piperazinyl, homopiperazinyl, azetidinyl, oxetanyl, thietanyl, homopiperidinyl, epoxypropyl (oxiranyl), azepanyl, oxepanyl, thiepanyl, 4-methoxy-piperidin-1-yl, 1,2,3,6-tetrahydropyridine-1-yl, oxazepinyl, diazepinyl, thiazepinyl, pyrrolidin-1-yl, 2-pyrrolinyl, 3-pyrrolinyl, 2*H*-indolinyl, 2*H*-pyranyl, 4*H*-pyranyl, dioxolan-2-yl, 1,3-dioxopenyl, pyrazolinyl, dithianyl, ditholanyl, dihydrothienyl, pyrazolidinylimidazolinyl, imidazolidinyl, 1,2,3,4-tetrahydroisoquinolinyl, 1,2,6-dithiazinyl, 1,1-dioxo-2-yl, 4-hydroxy-1,4-azaphosphine-4-oxide-1-yl, 2-hydroxy-1-(piperazin-1-yl)- ethanone-4-yl, 2-hydroxy-1-(5,6-dihydro-1,2,4-triazin-1(4*H*)-yl)ethanone-4-yl, 5,6-dihydro-4*H*-1,2,4- oxadiazine-4-yl, 2-hydroxy-1-(5,6-diludine-1(2*H*)-yl)ethanone-4-yl, 3-azabicyclo[3,1,0]hexyl, 3-azabicyclo[4,1,0]heptyl, azabicyclo[2,2,2]hexyl, 2-methyl-5,6,7,8–tetrahydro- [1,2,4]triazole[1,5-*c*] pyrimidine-6-yl, 4,5,6,7-teterhydro-isoxazolo[4,3-*c*] pyrimidine-5-yl, 3*H*-indoxyl-2-oxo-5- azabicyclo[2,2,1]heptane-5-yl, 2-oxo-5-azabicyclo[2,2,2]octane-5-yl, quinolizinyl and *N*-pyridyl urea. Some non-limiting examples of a heterocyclic ring include 1,1-dioxo-thiomorpholinyl and heterocyclic group wherein 2 carbon atoms on the ring are substituted with oxo (=O) moieties are pyrimidindionyl. The heterocyclic groups herein may be substituted or unsubstituted, wherein the substituent may be, but is not limited to, oxo (=O), hydroxy, amino, halo, cyano, heteroaryl, alkoxy, alkylamino, alkyl, alkenyl, alkynyl, heterocyclyl, mercapto, nitro, aryloxy, hydroxy-substituted alkoxy, hydroxy-substituted alkyl-C(=O)-, alkyl-C(=O)-, alkyl-S(=O)-, alkyl-S(=O)$_2$-, hydroxy-substituted alkyl-S(=O)-, hydroxy-substituted alkyl-S(=O)$_2$-, carboxy alkoxy, and the like.

[0048] The term "heteroatom" refers to one or more of oxygen, sulfur, nitrogen, phosphorus and silicon, including any oxidized form of nitrogen, sulfur, or phosphorus; the quaternized form of any basic nitrogen; or a substitutable nitrogen of a heterocyclic ring, for example, N (as in 3,4-dihydro-2*H*-pyrrolyl), NH (as in pyrrolidinyl) or NR (as in *N*-substituted pyrrolidinyl).

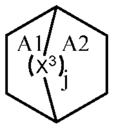
[0049] The term "aryl" used alone or as part of a larger moiety as in "aralkyl", "arylalkoxy" or "aryloxyalkyl" refers to monocyclic, bicyclic, and tricyclic carbocyclic ring systems having a total of six to fourteen ring members, wherein at least one ring in the system is aromatic, wherein each ring in the system contains 3 to 7 ring members and that has a single point or multipoint of attachment to the rest of the molecule. The term "aryl" may be used interchangeably with the term "aryl ring". Some non-limiting examples of aryl rings include phenyl, naphthyl, and anthryl. The aryl may be substituted or unsubstituted, wherein the substituents include, but are not limited to, hydroxy, amino, halo, cyano, aryl, heteroaryl, alkoxy, alkylamino, alkyl, alkenyl, alkynyl, heterocyclyl, mercapto, nitro, aryloxy, hydroxy-substituted alkoxy, hydroxy-substituted alkyl-C(=O)-, alkyl-C(=O)-, alkyl-S(=O)-, alkyl-S(=O)$_2$-, hydroxy-substituted alkyl-S(=O)-, hydroxy-substituted alkyl-S(=O)$_2$-, carboxy alkoxy, and the like.

[0050] The term "heteroaryl" used alone or as part of a larger moiety as in "heteroarylalkyl" or "heteroarylalkoxy" refers to monocyclic, bicyclic, and tricyclic ring systems having a total of five to fourteen ring members, wherein at least one ring in the system is aromatic, and at least one ring in the system is inclusive of one or more heteroatoms, wherein each ring in the system contains 3 to 7 ring members and that has a single point of attachment to the rest of the molecule. The term "heteroaryl" may be used interchangeably with the term "heteroaryl ring" or "heteroaromatic compound". The heteroaryl defined herein may be substituted or unsubstituted, wherein the substituents include, but are not limited to, hydroxy, amino, halo, cyano, aryl, heteroaryl, alkoxy, alkylamino, alkyl, alkenyl, alkynyl, heterocyclyl, mercapto, nitro, aryloxy, hydroxy-substituted alkoxy, hydroxy-substituted alkyl-C(=O)-, alkyl-C(=O)-, alkyl-S(=O)-, alkyl-S(=O)$_2$-, hydroxy-substituted alkyl-S(=O)-, hydroxy-substituted alkyl-S(=O)$_2$- and carboxy alkoxy, and the like.

[0051] Some non-limiting examples of the suitable heteroaryl ring include the following monocycles: 2-furanyl, 3-furanyl, N-imidazolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, 4-methylisoxazolyl-5-yl, *N*-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidinyl, 4-pyrimidinyl, pyrimidine-5-yl, pyridazinyl (*e.g.*, 3-pyridazinyl), 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, tetrazolyl (*e.g.*, 5-tetrazolyl), triazolyl (*e.g.*, 2-triazolyl and 5-triazolyl), 2-thienyl, 3-thienyl, pyrazolyl (*e.g.*, 2-pyrazolyl), isothiazolyl, 1,2,3-oxadiazolyl, 1,2,5-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,3-triazolyl, 1,2,3-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazol-2-yl, pyrazinyl, pyrazine-2-yl, 1,3,5-triazinyl, benzo[*d*]thiazol-2-yl, imidazo[1,5-*a*]pyridin-6-yl, and the following bicycles: benzimidazolyl, benzofuryl, benzothiophenyl, indolyl (*e.g.*, 2-indolyl), purinyl, quinolinyl (*e.g.*, 2-quinolinyl, 3-quinolinyl, 4-quinolinyl), and isoquinolinyl (*e.g.*, 1-isoquinolinyl, 3-isoquinolinyl, or 4-isoquinolinyl).

[0052] The term "haloalkyl" refers to an alkyl group substituted with one or more of the same or different halogen atoms, wherein the alkyl group is as defined herein. Some non-limiting examples of the haloalkyl group include trifluoromethyl, trifluoroethyl, chloromethyl, fluoromethyl and and the like.

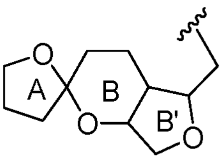
[0053] The term "bridged cycle" or "bridged cyclyl" refer to unsaturated or saturated bridged ring system that is not aromatic. For example, as depicted below (Formula (a1)), ring A1 and ring A2 share a bond that is an alkyl or heteroalkyl chain, wherein j is 1, 2, 3 or 4. Such a system may contain isolated or conjugated unsaturation, but not aromatic or heteroaromatic rings in its core structure (but may have aromatic substitution thereon). Each cyclic ring in a bridged bicyclyl can be either a carbocyclic or a heteroalicyclic. Some non-limiting examples of the bridged ring system include bicyclo[2.2.1]heptyl, 7-azabicyclo[2.2.1]heptyl,2-azabicyclo[2.2.1]hepty, and the like. The bridged bicyclyl defined herein may be substituted or unsubstituted, wherein the substituents include, but are not limited to, deuterium, oxo (=O), hydroxy, amino, halo, cyano, aryl, heteroaryl, alkoxy, alkylamino, alkyl, alkenyl, alkynyl, heterocyclyl, mercapto, nitro, aryloxy, hydroxy-substituted alkoxy, hydroxy-substituted alkyl-C(=O)-, alkyl-C(=O)-, alkyl-S(=O)-, alkyl-S(=O)$_2$-, hydroxy-substituted alkyl-S(=O)-, hydroxy-substituted alkyl-S(=O)$_2$-, carboxy alkoxy, and the like.



(a1)

[0054] The term "bridged heterocyclyl" refers to unsaturated or saturated bridged cyclic system that is not aromatic. Such a system may contain isolated or conjugated unsaturation, but not aromatic or heteroaromatic rings in its core structure (but may have aromatic substitution thereon). And at least one ring in the system is inclusive of one or more heteroatoms, wherein each ring in the system contains 3 to 7 ring members, *e.g.*, 1 to 6 carbon atoms and 1 to 3 heteroatoms selected from N, O, P or S, wherein the S or P is optionally substituted with one or more oxo to provide the group SO or SO_2, PO or PO_2. Some non-limiting examples of bridged heterobicyclic ring system include 2-azabicyclo[2.2.1]heptane, and the like. The bridged heterobicyclyl defined herein may be substituted or unsubstituted, wherein the substituents include, but are not limited to, deuterium, oxo (=O), hydroxy, amino, halo, cyano, aryl, heteroaryl, alkoxy, alkylamino, alkyl, alkenyl, alkynyl, heterocyclyl, mercapto, nitro, aryloxy, hydroxy-substituted alkoxy, hydroxy-substituted alkyl-C(=O)-, alkyl-C(=O)-, alkyl-S(=O)-, alkyl-$S(=O)_2$-, hydroxy-substituted alkyl-S(=O)-, hydroxy-substituted alkyl-$S(=O)_2$- and carboxy alkoxy, and the like.

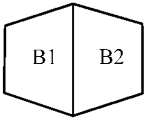
[0055] The term "spirocyclyl", "spirocyclic", "spiro bicyclyl" or "spiro bicyclic" refers to a ring originating from a particular annular carbon of another ring. For example, as depicted below (Formula (a2)), ring A and ring B share a carbon atom between the two saturated ring system, which terms as a "spirocyclyl" or "spiro bicyclyl". Each cyclic ring in the spirocyclyl or spiro bicyclyl can be either a carbocyclic or a heteroalicyclic. Some non-limiting examples of such radical include 2,7-diaza-spiro[4.4]non-2-yl, 7-oxo-2-azaspiro[4.5]dec-2-yl, 4-azaspiro[2.4]hept-5-yl, 4-oxaspiro[2.4]hept-5-yl, 5-azaspiro[2.4]hept-5-yl, spiro[2.4]heptyl, spiro[4.4]nonyl, 7-hydroxy-5-azaspiro[2.4]hept-5-yl, and the like. The spirocyclyl or spiro bicyclyl may be substituted or unsubstituted, wherein the substituents include, but are not limited to, oxo (=O), hydroxy, amino, halo, cyano, aryl, heteroaryl, alkoxy, alkylamino, alkyl, alkenyl, alkynyl, heterocyclyl, mercapto, nitro, aryloxy, hydroxy-substituted alkoxy, hydroxy-substituted alkyl-C(=O)-, alkyl-C(=O)-, alkyl-S(=O)-, alkyl-$S(=O)_2$-, hydroxy-substituted alkyl-S(=O)-, hydroxy-substituted alkyl-$S(=O)_2$- and carboxy alkoxy, and the like.



(a2)

[0056] The term "spiro heterocyclyl" refers to a ring originating from a particular annular carbon of another ring. For example, as depicted above, ring A and ring B share a carbon atom between the two saturated ring system, which terms as a "spirocyclyl". And at least one ring in the system is inclusive of one or more heteroatoms, wherein each ring in the system contains 3 to 7 ring members, *e.g.*, 1 to 6 carbon atoms and 1 to 3 heteroatoms selected from N, O, P or S, wherein the S or P is optionally substituted with one or more oxo to provide the group SO or SO_2, PO or PO_2. Some non-limiting examples of such radicals include 4-azaspiro[2,4]hept-5-yl, 4-oxaspiro[2,4]hept-5-yl, 5-azaspiro[2,4]hept-5-yl, 7-hydroxy-5-azaspiro[2,4]hept-5-yl, 5-azaspiro[2,4]hept-6-yl, 1,4-dioxo-7-azaspiro[4,4]non-8-yl, and the like. The spiro heterobicyclyl defined herein may be substituted or unsubstituted, wherein the substituents include, but are not limited to, oxo (=O), hydroxy, amino, halo, cyano, aryl, heteroaryl, alkoxy, alkylamino, alkyl, alkenyl, alkynyl, heterocyclyl, mercapto, nitro, aryloxy, hydroxy-substituted alkoxy, hydroxy-substituted alkyl-C(=O)-, alkyl-C(=O)-, alkyl-S(=O)-, alkyl-S(=O)$_2$-, hydroxy-substituted alkyl-S(=O)-, hydroxy-substituted alkyl-S(=O)$_2$-, carboxy alkoxy, and the like.

[0057] The term "fused bicyclic", "fused cyclic", "fused bicyclyl" or "fused cyclyl" refers to unsaturated or saturated fused cyclic system that is not aromatic. For example, as depicted below (Formula (b1)), ring B1 and ring B2 share a bond Such a system may contain isolated or conjugated unsaturation, but not aromatic or heteroaromatic rings in its core structure (but may have aromatic substitution thereon). Each cyclic ring in a fused bicyclyl can be either a carbocyclic or a heteroalicyclic. Some non-limiting examples of the fused bicyclic ring system include hexahydro-furo[3,2-*b*]furan, 2,3,3a,4,7,7*a*-hexahydro-1*H*-indene, 7-azabicyclo[2.3.0]heptane, fused bicyclo[3.3.0]octane, fused bicyclo[3.1.0]hexane, and 1,2,3,4,4*a*,5,8,8*a*-octahydro-naphthalene. The fused bicyclyl defined herein may be substituted or unsubstituted, wherein the substituents include, but are not limited to, deuterium, oxo (=O), hydroxy, amino, halo, cyano, aryl, heteroaryl, alkoxy, alkylamino, alkyl, alkenyl, alkynyl, heterocyclyl, mercapto, nitro, aryloxy, hydroxy-substituted alkoxy, hydroxy-substituted alkyl-C(=O)-, alkyl-C(=O)-, alkyl-S(=O)-, alkyl-S(=O)$_2$-, hydroxy-substituted alkyl-S(=O)-, hydroxy-substituted alkyl-S(=O)$_2$-, carboxy alkoxy, and the like.



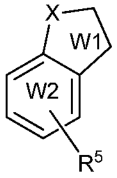
(b1)

[0058] The term "fused heterobicyclyl" refers to unsaturated or saturated fused cyclic system that is not aromatic. Such a system may contain isolated or conjugated unsaturation, but not aromatic or heteroaromatic rings in its core structure (but may have aromatic substitution thereon). And at least one ring in the system is inclusive of one or more heteroatoms, wherein each ring in the system contains 3 to 7 ring members, *e.g.*, 1 to 6 carbon atoms and 1 to 3 heteroatoms selected from N, O, P or S, wherein the S or P is optionally substituted with one or more oxo to provide the group SO or SO$_2$, PO or PO$_2$. Some non-limiting examples of fused heterobicyclic ring system include hexahydro-furo[3,2-*b*]furan, 6-azabicyclo[3.2.0]heptane, 2-azabicyclo[3.1.0]heptane, 3-azabicyclo[3.1.0]heptane, and the like. The fused heterobicyclyl defined herein may be substituted or unsubstituted, wherein the substituents include, but are not limited to, deuterium, oxo (=O), hydroxy, amino, halo, cyano, aryl, heteroaryl, alkoxy, alkylamino, alkyl, alkenyl, alkynyl, heterocyclyl, mercapto, nitro, aryloxy, hydroxy-substituted alkoxy, hydroxy-substituted alkyl-C(=O)-, alkyl-C(=O)-, alkyl-S(=O)-, alkyl-S(=O)$_2$-, hydroxy-substituted alkyl-S(=O)-, hydroxy-substituted alkyl-S(=O)$_2$- and carboxy alkoxy, and the like.

[0059] The term "oxo" refers to a group be substituted by =O at any substitutable position.

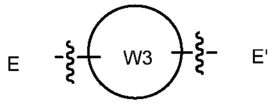
[0060] The term "halogen" refers to Fluoro (F), Chloro (Cl), Bromo (Br), or Iodo (I).

[0061] As described herein, a bond drawn from a substituent to the center of one ring within a ring system (as shown below (a)) represents substitution of the substituent R^5 at any substitutable position on the rings to which it is attached. For example, Figure (a) represents possible substitution in any of the positions on the W1 and W2 ring.



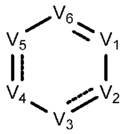
(a)

[0062] As described herein, two attaching points either E or E’, within a ring system (as shown in Figure (b)), attach to the rest of the molecule, *e.g.*, E and E’ may be used interchangeably with each other.

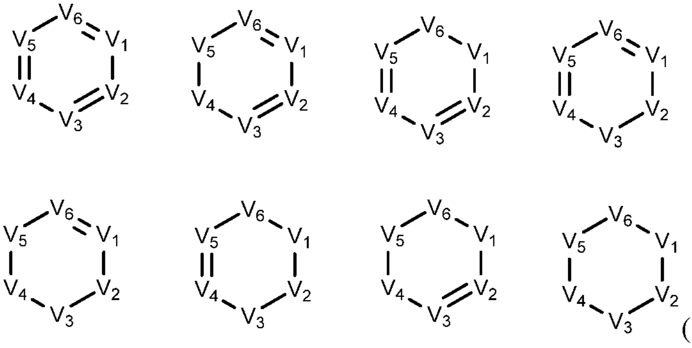


(b)

[0063] As described herein, a dotted line drawn together with a bond within a ring system (as shown in Figure (c)) represents either a double bond or a single bond. For example, structure in Figure (c) represents any structures selected from Figure (d).

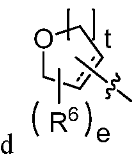
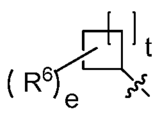


(c)



(d)

[0064] Unless otherwise stated, structures depicted herein are also meant to include all isomeric (*e.g.*, enantiomeric, diastereomeric, and geometric (or conformational)) forms of the structure; for example, the *R* and *S* configurations for each asymmetric center, (*Z*) and (*E*) double bond isomers, and (*Z*) and (*E*) conformational isomers. Therefore, single stereochemical isomers as well as enantiomeric, diastereomeric, or geometric (or conformational) mixtures of the present compounds are within the scope disclosed herein.

[0065] Furthermore, unless otherwise stated, the phrase "each…is independently" is used interchangeably with the phrase "each (of)…and…is independently". It should be broadly understood that the specific options expressed by the same symbol are independently of each other in different radicals; or the specific options expressed by the same symbol are independently of each other in same radicals. For example, R^6 of the structure and  and , whose specific options are independent of each other; meanwhile, multiple R^6 of the same structure, whose specific options are independent of each other.

[0066] The term "prodrug" refers to a compound that is transformed *in vivo* into a compound of Formula (I). Such a transformation can be affected, for example, by hydrolysis in blood or enzymatic transformation of the prodrug form to the parent form in blood or tissue. Prodrugs of the compounds disclosed herein may be, for example, esters. Esters that may be utilized as prodrugs in the present invention are phenyl esters, aliphatic (C_1-C_{24}) esters, acyloxymethyl esters, carbonates, carbamates, and amino acid esters. For example, a compound disclosed herein that contains an OH group may be acylated at this position in its prodrug form. Other prodrug forms include phosphates, such as, for example those phosphates resulting from the phosphonation of an OH group on the parent compound. A thorough discussion of prodrugs is provided in T. Higuchi *et al.*, *Pro-drugs as Novel Delivery Systems*, Vol. 14, A.C.S. Symposium Series; Roche, *et al.* ed., *Bioreversible Carriers in Drug Design*, American Pharmaceutical Association and Pergamon Press, 1987; Rautio *et al.*, Prodrugs: Design and Clinical Applications, *Nat. Rev. Drug Discovery*, 2008, 7, 255-270, and Hecker *et al*, Prodrugs of Phosphates and Phosphonates, *J. Med. Chem.*, 2008, 51, 2328-2345, all of which are incorporated herein by reference.

[0067] Unless otherwise stated, all tautomeric forms of the compounds disclosed herein are within the scope of the invention. Additionally, unless otherwise stated, structures depicted herein are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms.

[0068] A "metabolite" is a product produced through metabolism in the body of a specified compound or salt thereof. The metabolites of a compound may be identified using routine techniques known in the art and their activities determined using tests such as those described herein. Such products may result for example from the oxidation, reduction, hydrolysis, amidation, deamidation, esterification, deesterification, enzyme cleavage, and the like, of the administered compound. Accordingly, the invention includes metabolites of compounds disclosed herein, including compounds produced by a process comprising contacting a compound disclosed herein with a mammal for a period of time sufficient to yield a metabolic product thereof.

[0069] Stereochemical definitions and conventions used herein generally follow Parker *et al.*, McGraw-Hill Dictionary of Chemical Terms (1984) McGraw-Hill Book Company, New York and Eliel *et al.*, "*Stereochemistry of Organic Compounds*", John Wiley & Sons, Inc., New York, 1994. The compounds disclosed herein may contain asymmetric or chiral centers, and therefore exist in different stereoisomeric forms. It is intended that all stereoisomeric forms of the compounds disclosed herein, including but not limited to, diastereomers, enantiomers and atropisomers, as well as mixtures thereof such as racemic mixtures, form part of the present invention. Many organic compounds exist in optically active forms, *i.e.*, they have the ability to rotate the plane of plane-polarized light. In describing an optically active compound, the prefixes D and L, or *R* and *S*, are used to denote the absolute configuration of the molecule about its chiral center(s). The prefixes d and l or (+) and (-) are employed to designate the sign of rotation of plane-polarized light by the compound, with (-) or l meaning that the compound is levorotatory. A compound prefixed with (+) or d is dextrorotatory. For a given chemical structure, these stereoisomers are identical except that they are mirror images of one another. A specific stereoisomer may also be referred to as an enantiomer, and a mixture of such isomers is often called an enantiomeric mixture. A 50:50 mixture of enantiomers is referred to as a racemic mixture or a racemate, which may occur where there has been no stereoselection or stereospecificity in a chemical reaction or process. The term "racemic mixture" or "racemate" refers to an equimolar mixture of two enantiomeric species, devoid of optical activity.

[0070] The term "tautomer" or "tautomeric form" refers to structural isomers of different energies which are interconvertible via a low energy barrier. Some non-limiting examples of proton tautomers (also known as prototropic tautomers) include interconversions via migration of a proton, such as keto-enol and imine-enamine isomerizations. Valence tautomers include interconversions by reorganization of some of the bonding electrons.

[0071] A "pharmaceutically acceptable salts" refers to organic or inorganic salts of a compound disclosed herein. The pharmaceutically acceptable salts are well known in the art. For example, Berge *et al.*, describe pharmaceutically acceptable salts in detail in *J. Pharmacol Sci*, 1977, 66: 1-19, which is incorporated herein by reference. Some non-limiting examples of the pharmaceutically salts include salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, laurylsulfate, malate, sodium malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, stearate, thiocyanate, *p*-toluenesulfonate, undecanoate and valerate salts, and the like. Salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium and $N^+(C_{1-4}\text{ alkyl})_4$ salts. This invention also envisions the quaternization of any basic nitrogen-containing groups of the compounds disclosed herein. Water or oilsoluble or dispersable products may be obtained by such quaternization. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, C_{1-8} sulfonate or aryl sulfonate.

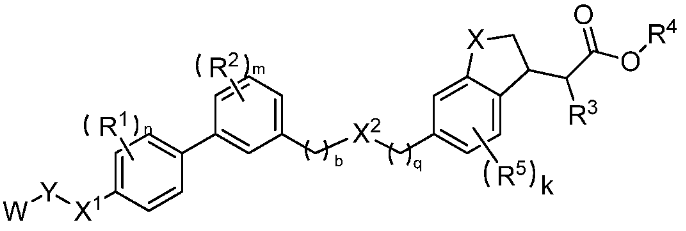
[0072] A "solvate" refers to an association or complex of one or more solvent molecules and a compound disclosed herein. Some non-limiting examples of the solvents that form solvates include water, isopropanol, ethanol, methanol, dimethylsulfoxide, ethyl acetate, acetic acid and ethanolamine. The term "hydrate" refers to the complex where the solvent molecule is water.

[0073] The term "protecting group" or "Pg" refers to a substituent that is commonly employed to block or protect a particular functionality while reacting with other functional groups on the compound. For example, an "amino-protecting group" is a substituent attached to an amino group that blocks or protects the amino functionality in the compound. Some non-limiting examples of suitable amino-protecting groups include acetyl, trifluoroacetyl, t-butoxycarbonyl (BOC), benzyloxycarbonyl (CBZ) and 9-fluorenylmethylenoxycarbonyl (Fmoc). Similarly, a "hydroxy-protecting group" refers to a substituent of a hydroxy group that blocks or protects the hydroxy functionality. Some non-limiting examples of suitable hydroxy-protecting groups include acetyl and silyl. A "carboxy-protecting group"" refers to a substituent of the carboxy group that blocks or protects the carboxy functionality. Some non-limiting examples of common carboxy-protecting groups include $-CH_2CH_2SO_2Ph$, cyanoethyl, 2-(trimethylsilyl)ethyl, 2-(trimethylsilyl) ethoxymethyl, 2-(*p*-toluenesulfonyl)ethyl, 2-(*p*-nitrophenylsulfonyl)ethyl, 2-(diphenyl phosphino)-ethyl, nitroethyl, and the like. For a general description of protecting groups and their use, see Greene et al., *Protective Groups in Organic Synthesis,* John Wiley & Sons, New York, 1991 and Kocienski et al., *Protecting Groups*, Thieme, Stuttgart, 2005.

DESCRIPTION OF COMPOUNDS OF THE INVENTION

[0074] Provided herein are biphenyl compounds, pharmaceutical compositions and pharmaceutical formulations thereof which are useful in modulating GPR40 receptor.

[0075] In one aspect, the present invention provides a compound having Formula (I) or a stereoisomer, a geometric isomer, a tautomer, a mesomer, a racemate, an enantiomer, a diastereoisomer, an *N*-oxide, a hydrate, a solvate, a metabolite, a hydrolysate, a pharmaceutically acceptable salt or a prodrug thereof:



(I)

wherein each of X and X^1 is independently O, NH, CH_2 or S;

X^2 is O, S or NH;

Y is alkylene or alkenylene, wherein one or more methylene groups of the alkylene or alkenylene are optionally independently replaced with NR^a, S, $S(=O)_2$ or S(=O), and wherein each of the alkylene and alkenylene is optionally independently substituted by one or more substituents independently selected from hydroxy, F, Cl, Br, I, cyano, amino, mercapto, nitro, oxo (=O), alkyl or hereoalkyl;

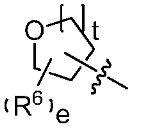
each R^1, R^2 and R^3 is independently H, F, Cl, Br, I, hydroxy, cyano, amino, mercapto, nitro, alkyl, heteroalkyl, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkoxy, alkylamino, cycloalkyl, heterocyclyl, aryl, heteroaryl or haloalkyl;

R^4 is H or alkyl;

each R^5 is independently H, F, Cl, Br, I, hydroxy, cyano, amino, mercapto, nitro, alkyl, alkoxy, alkylamino or heteroalkyl;

each of k, n, m, b and q is independently 0, 1, 2, 3 or 4;

W is adamantyl, bridged cyclyl, bridged heterocyclyl, spiro cyclyl, spiro heterocyclyl, fused cyclyl or fused heterocyclyl, wherein each of the damantyl, bridged cyclyl, bridged heterocyclyl, spiro cyclyl, spiro heterocyclyl, fused cyclyl and fused heterocyclyl is optionally independently substituted by one or more R^6 groups; or W is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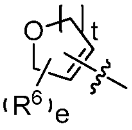
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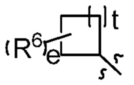
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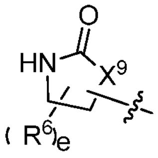
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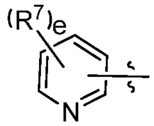
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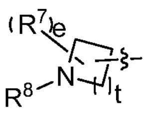
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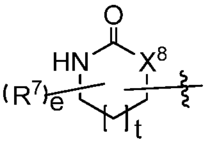
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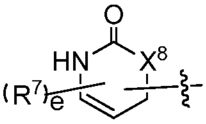
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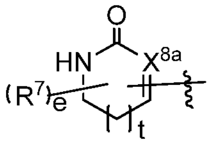
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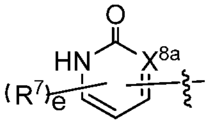
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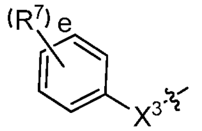
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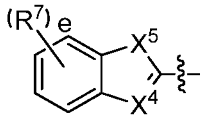
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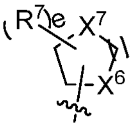
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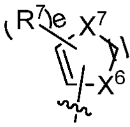
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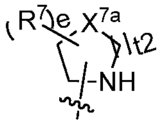
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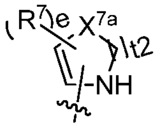
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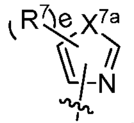
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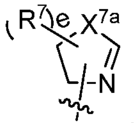
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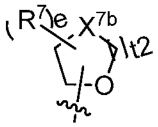
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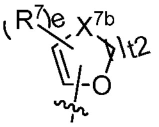
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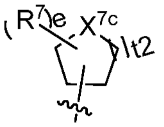
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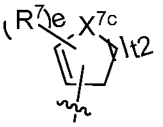
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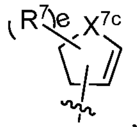
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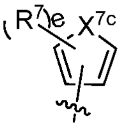
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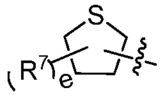
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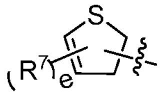
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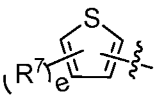
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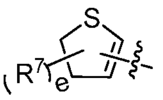
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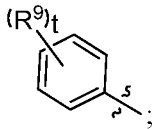
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wherein each R^6 is independently H, F, Cl, Br, I, hydroxy, cyano, amino, mercapto, nitro, oxo(=O), alkyl, heteroalkyl, haloalkyl, hydroxyalkyl, aminoalkyl, alkoxy, alkylamino, alkyl-S(=O)$_2$- or alkyl-S(=O)-;

each R^7 is independently H, F, Cl, Br, I, hydroxy, cyano, amino, mercapto, nitro, alkyl, heteroalkyl, haloalkyl, hydroxyalkyl, aminoalkyl, alkoxy, alkylamino, alkyl-S(=O)$_2$- or alkyl-S(=O)-;

R^8 is H, C_{2-10} alkyl, heteroalkyl, haloalkyl, hydroxyalkyl, aminoalkyl, alkyl-S(=O)$_2$- or alkyl-S(=O)-;

each R^9 is independently F, Cl, Br, I, hydroxy, cyano, amino, mercapto, nitro, alkyl, heteroalkyl, haloalkyl, hydroxyalkyl, aminoalkyl, alkoxy, alkylamino, alkyl-S(=O)$_2$- or alkyl-S(=O)-;

X^3 is NR^a, O, S, S(=O)$_2$ or S(=O);

each of X^4 and X^{8a} is independently CH or N;

each of X^5 and X^{7a} is independently CH_2 or NR^a;

each X^7 is independently CH_2, S, O or NR^a;

X^{7b} is CH_2, O or S;

X^{7c} is CH_2, O or NR^a;

each of X^6 and X^8 is independently CH_2, O or NH;

X^9 is O or NH;

each R^a is independently alkyl-$S(=O)_2$- or H;

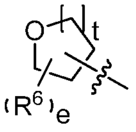
each e is independently 0, 1, 2, 3, 4, 5, 6, 7 or 8;

each t is independently 1, 2, 3, 4 or 5;

t1 is 3, 4 or 5; and

each t2 is independently 1 or 2.

[0076] In some embodiments, W is adamantyl, C_{5-12} bridged cyclyl, C_{5-12} bridged heterocyclyl, C_{5-12} spiro cyclyl, C_{5-12} spiro heterocyclyl, C_{4-12} fused cyclyl or C_{4-12} fused heterocyclyl, and wherein each of damantyl, C_{5-12} bridged cyclyl, C_{5-12} bridged heterocyclyl, C_{5-12} spiro cyclyl, C_{5-12} spiro heterocyclyl, C_{4-12} fused cyclyl and C_{4-12} fused heterocyclyl is optionally independently substituted by one or more R^6 groups; or W is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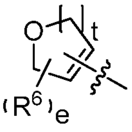
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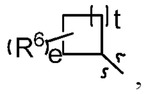
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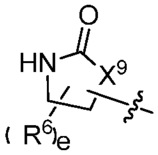
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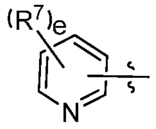
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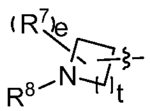
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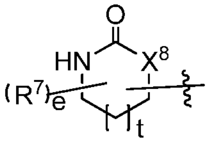
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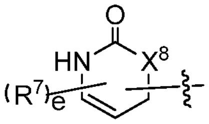
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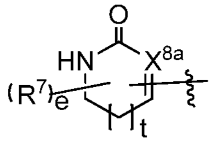
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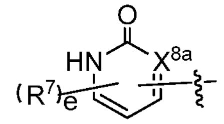
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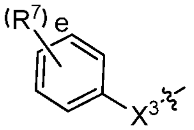
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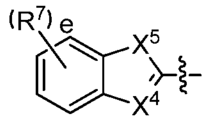
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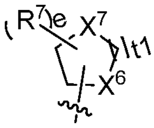
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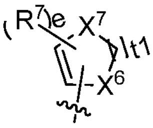
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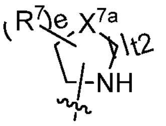
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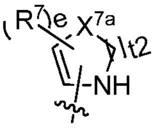
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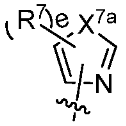
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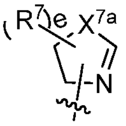
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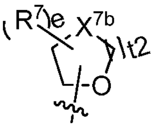
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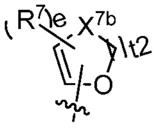
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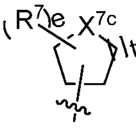
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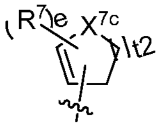
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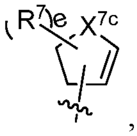
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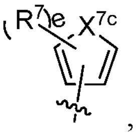
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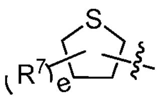
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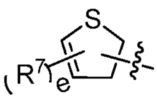
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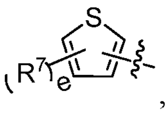
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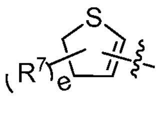
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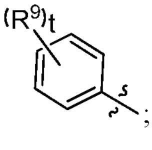
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and wherein each R^6 is independently H, F, Cl, Br, I, hydroxy, cyano, amino, mercapto, nitro, oxo (=O), C_{1-6} alkyl, C_{2-6} heteroalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} aminoalkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{1-6} alkyl-$S(=O)_2$- or C_{1-6} alkyl-$S(=O)$-;

each R^7 is independently H, F, Cl, Br, I, hydroxy, cyano, amino, mercapto, nitro, C_{1-6} alkyl, C_{2-6} heteroalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} aminoalkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{1-6} alkyl-$S(=O)_2$- or C_{1-6} alkyl-$S(=O)$-;

R^8 is H, C_{2-6} alkyl, C_{2-6} heteroalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} aminoalkyl, C_{1-6} alkyl-S(=O)$_2$- or C_{1-6} alkyl-S(=O)-;

each R^9 is independently F, Cl, Br, I, hydroxy, cyano, amino, mercapto, nitro, C_{1-6} alkyl, C_{2-6} heteroalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} aminoalkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{1-6} alkyl-S(=O)$_2$- or C_{1-6} alkyl-S(=O)-; and

each R^a is independently C_{1-6} alkyl-S(=O)$_2$- or H.

[0077] In other embodiments, each R^6 is independently H, F, Cl, Br, I, hydroxy, cyano, amino, mercapto, nitro, oxo(=O), methyl, ethyl, propyl, isopropyl, butyl, trifluoromethyl, hydroxymethyl, aminomethyl, methoxy, ethoxy, methylamino, ethylamino, CH_3-S(=O)$_2$- or CH_3-S(=O)-;

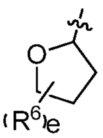
each R^7 is independently H, F, Cl, Br, I, hydroxy, cyano, amino, mercapto, nitro, methyl, ethyl, propyl, isopropyl, butyl, trifluoromethyl, hydroxymethyl, aminomethyl, methoxy, ethoxy, methylamino, ethylamino, CH_3-S(=O)$_2$- or CH_3-S(=O)-;

R^8 is H, ethyl, trifluoromethyl, hydroxymethyl, aminomethyl, CH_3-S(=O)$_2$- or CH_3-S(=O)-;

each R^9 is independently F, Cl, Br, I, hydroxy, cyano, amino, mercapto, nitro, methyl, ethyl, propyl, isopropyl, butyl, trifluoromethyl, hydroxymethyl, aminomethyl, methoxy, ethoxy, methylamino, ethylamino, CH_3-S(=O)$_2$- or CH_3-S(=O)-; and

each R^a is independently CH_3-S(=O)$_2$- or H.

[0078] In some embodiments, W is



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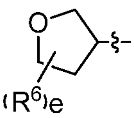

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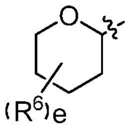

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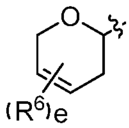

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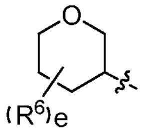

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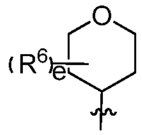

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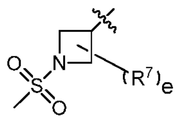

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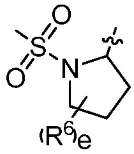

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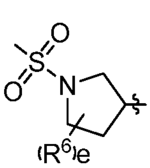

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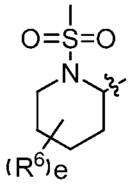

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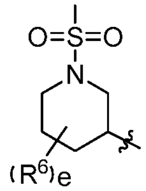

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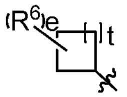

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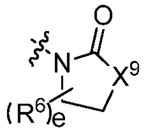

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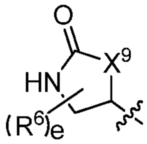

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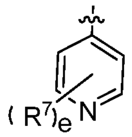

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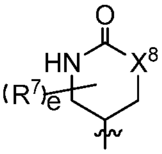

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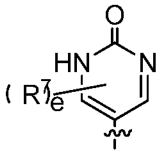

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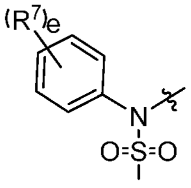

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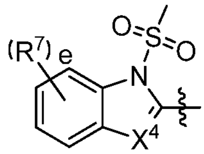

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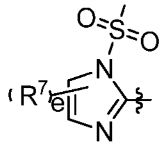

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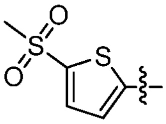

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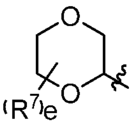

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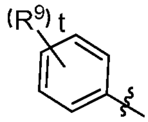

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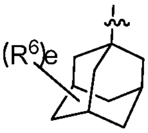

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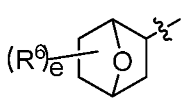

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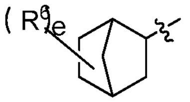

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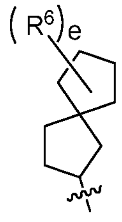

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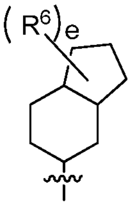

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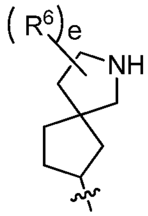
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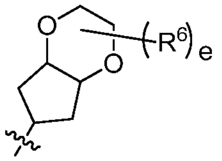
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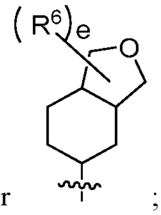
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wherein each R^6 is independently H, F, Cl, Br, I, hydroxy, cyano, amino, mercapto, nitro, oxo(=O), methyl, ethyl, propyl, isopropyl, butyl, trifluoromethyl, hydroxymethyl, aminomethyl, methoxy, ethoxy, methylamino, ethylamino, CH_3-S(=O)$_2$- or CH_3-S(=O)-;

each R^7 is independently H, F, Cl, Br, I, hydroxy, cyano, amino, mercapto, nitro, methyl, ethyl, propyl, isopropyl, butyl, trifluoromethyl, hydroxymethyl, aminomethyl, methoxy, ethoxy, methylamino, ethylamino, CH_3-S(=O)$_2$- or CH_3-S(=O)-; and

each R^9 is independently F, Cl, Br, I, hydroxy, cyano, amino, mercapto, nitro, methyl, ethyl, propyl, isopropyl, butyl, trifluoromethyl, hydroxymethyl, aminomethyl, methoxy, ethoxy, methylamino, ethylamino, CH_3-S(=O)$_2$- or CH_3-S(=O)-.

[0079] In some embodiments, Y is C_{2-6} alkylene or C_{2-6} alkenylene, and wherein one or more methylene groups of the C_{2-6} alkylene or C_{2-6} alkenylene are optionally replaced with NR^a, S, S(=O)$_2$ or S(=O), each of the C_{2-6} alkylene and C_{2-6} alkenylene is optionally independently substituted by one or more substituents independently selected from hydroxy, F, Cl, Br, I, cyano, amino, mercapto, nitro, oxo (=O), C_{1-6} alkyl or C_{2-6} hereoalkyl; and

R^a is CH_3-S(=O)$_2$- or H.

[0080] In some embodiments, each R^1, R^2 and R^3 is independently H, F, Cl, Br, I, hydroxy, cyano, amino, mercapto, nitro, C_{1-6} alkyl, C_{2-6} heteroalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} hydroxyalkyl, C_{1-6} aminoalkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{3-10} cycloalkyl, C_{2-10} heterocyclyl, C_{6-10} aryl, C_{1-9} heteroaryl or C_{1-6} haloalkyl;

R^4 is H or C_{1-6} alkyl; and

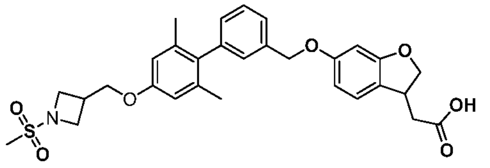
each R^5 is indenpendeH, F, Cl, Br, I, hydroxy, cyano, amino, mercapto, nitro, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino or C_{2-6} heteroalkyl.

[0081] In some embodiments, each R^1, R^2 and R^3 is independently H, F, Cl, Br, I, hydroxy, cyano, amino, mercapto, nitro, methyl, ethyl, propyl, isopropyl, butyl, vinyl, ethynyl, hydroxymethyl, aminomethyl, methoxy, methylamino, cyclopropyl, tetrahydrofuranyl, phenyl, pyrrolyl or trifluoromethyl;

R^4 is H, methyl or ethyl; and

each R^5 is indenpendently H, F, Cl, Br, I, hydroxy, cyano, amino, mercapto, nitro, methyl, ethyl, methoxy, ethoxy, isopropoxy, methylamino, ethylamino or propylamino.

[0082] In some embodiments, provided herein is a compound having one of the following structures: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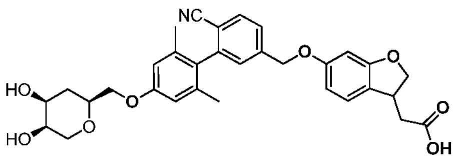
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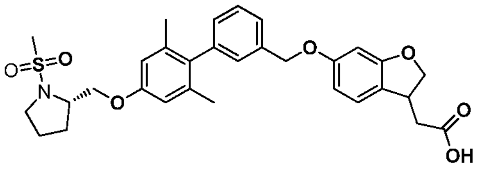
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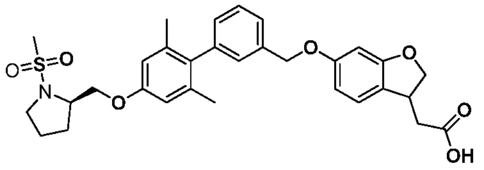
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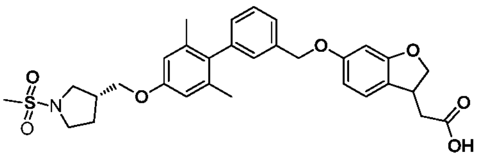
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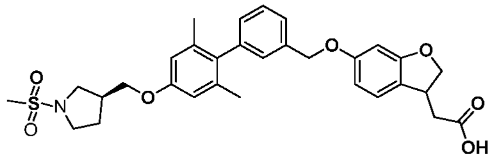
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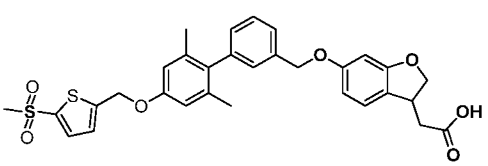
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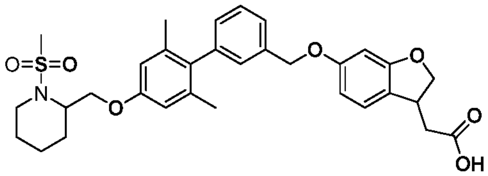
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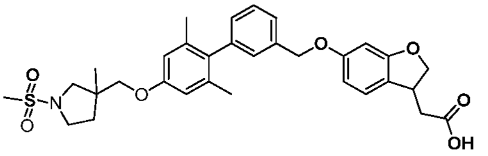
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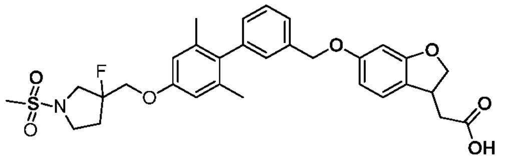
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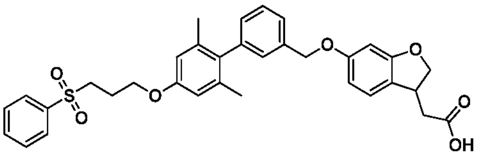
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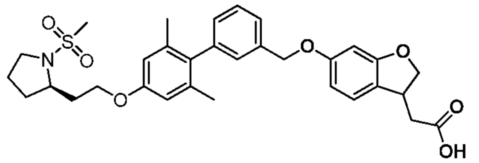
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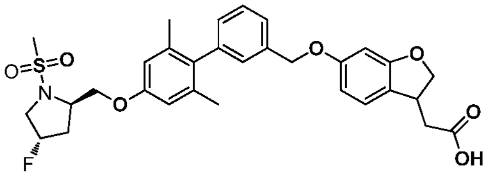
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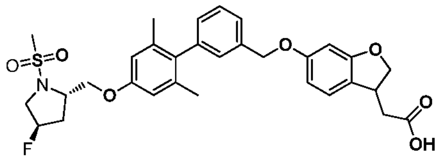
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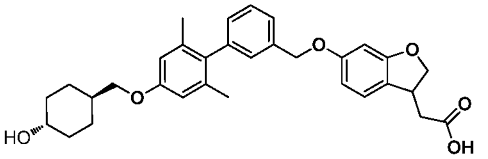
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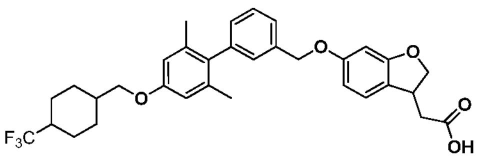
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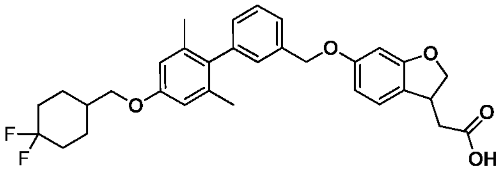
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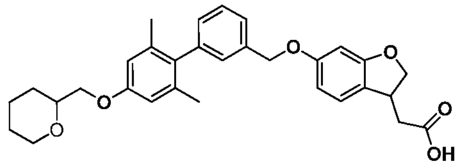
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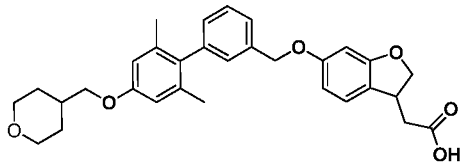
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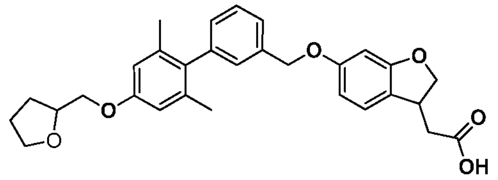
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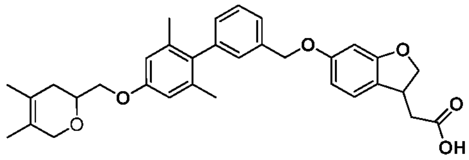
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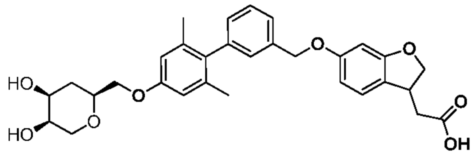
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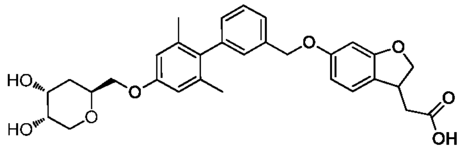
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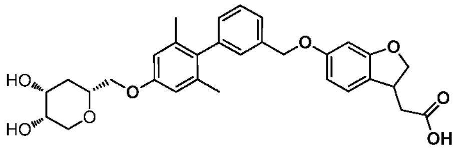
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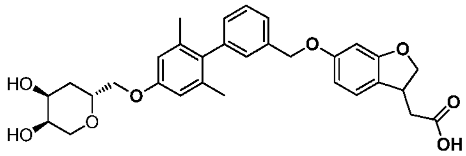
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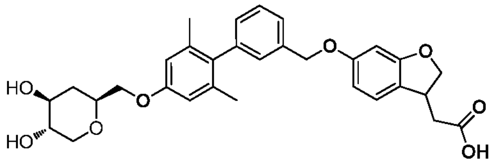
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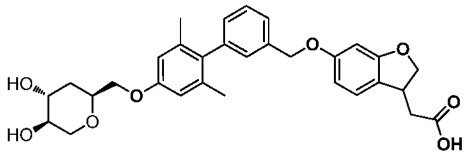
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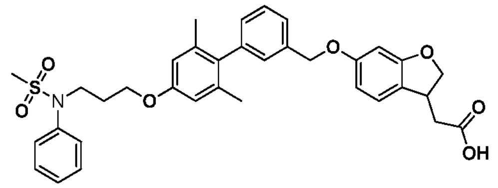
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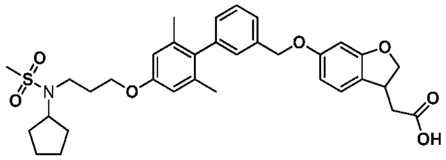
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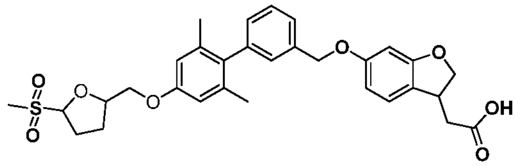
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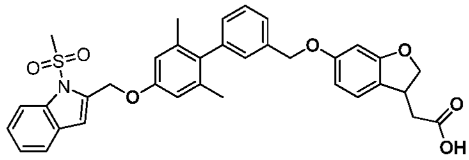
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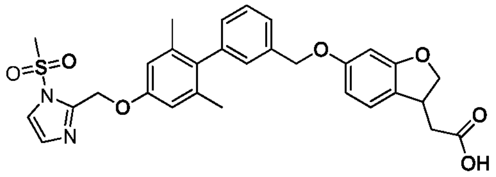
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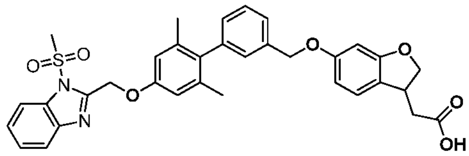
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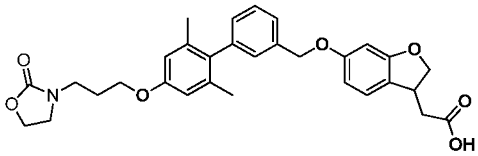
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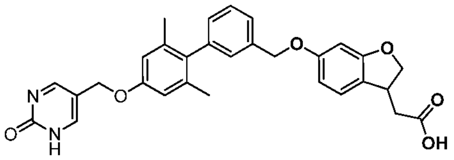
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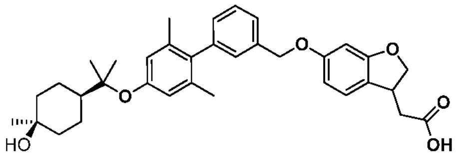
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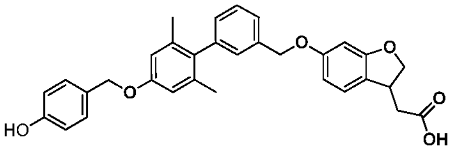
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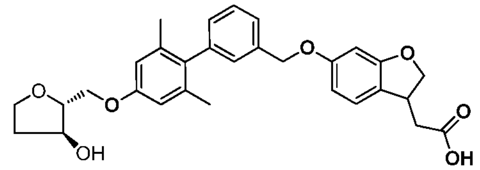
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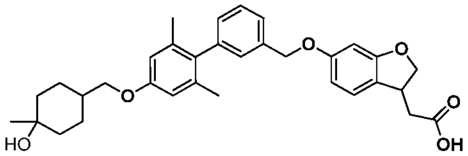
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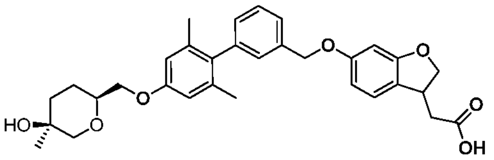
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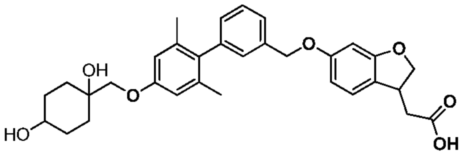
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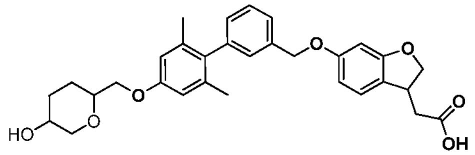
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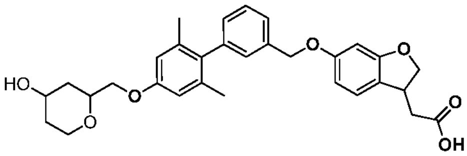
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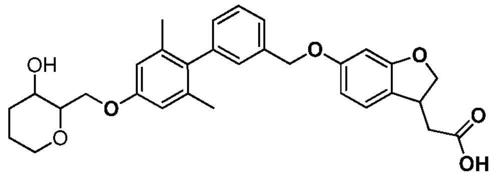
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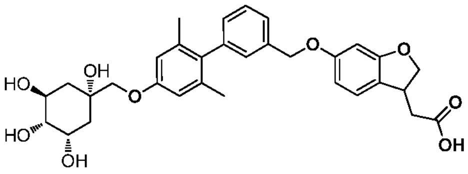
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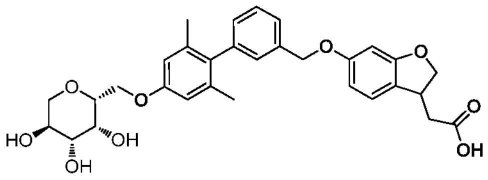
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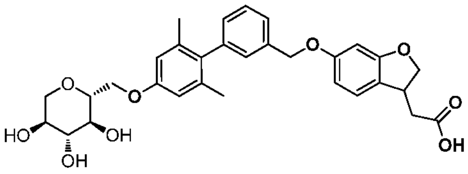
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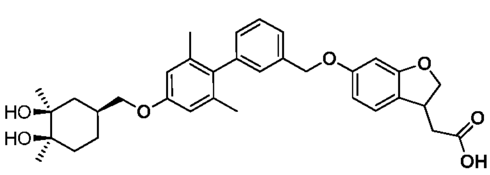
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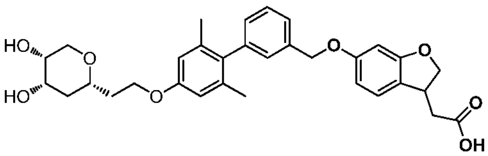
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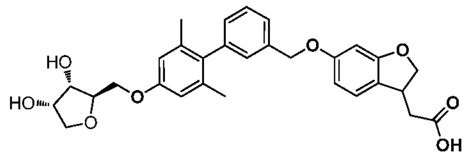
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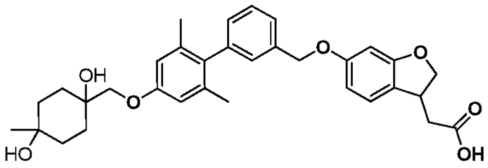
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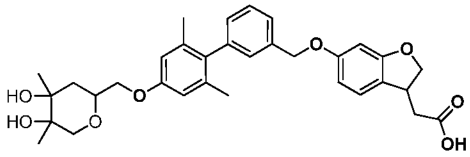
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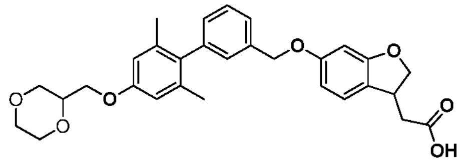
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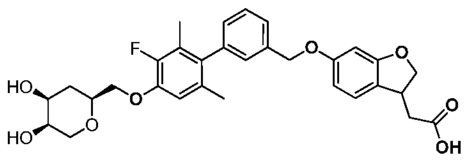
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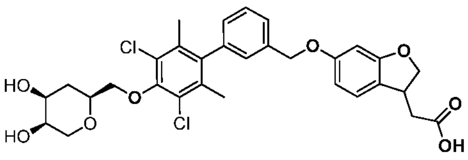
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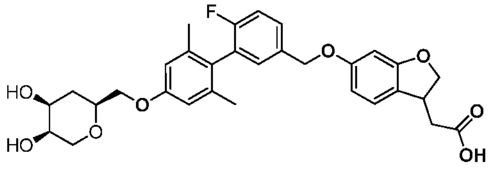
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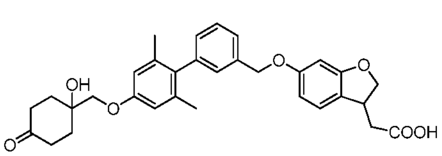
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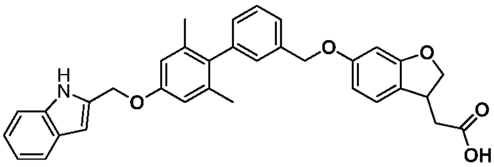
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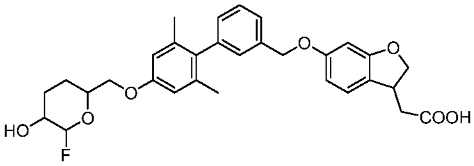
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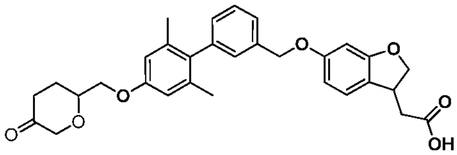
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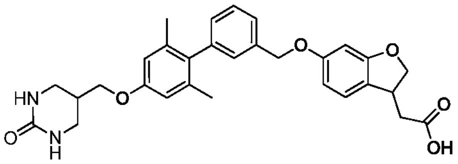
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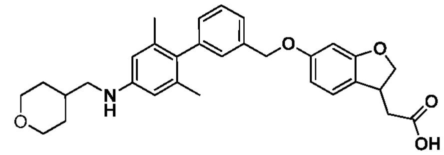
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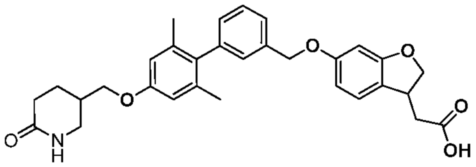
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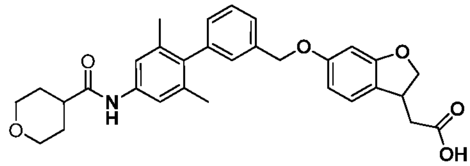
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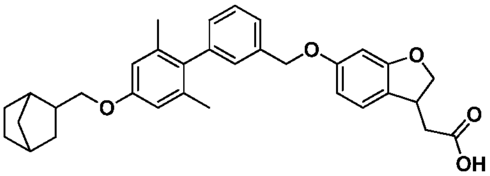
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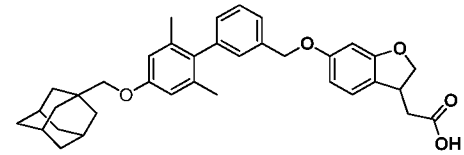
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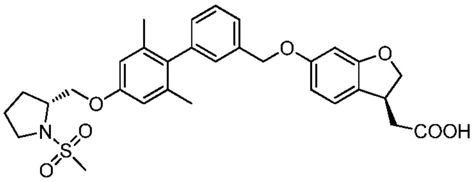
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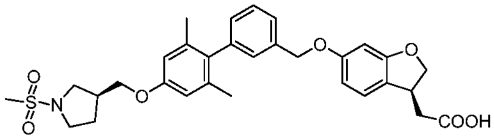
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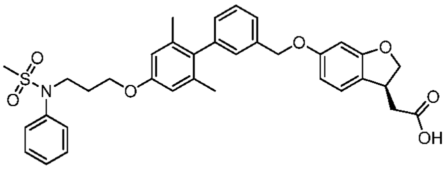
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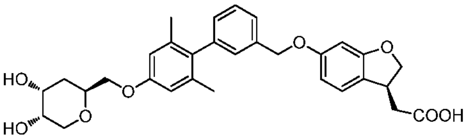
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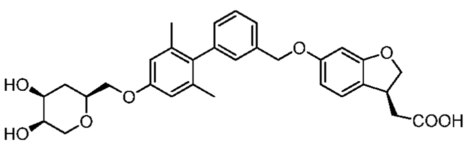
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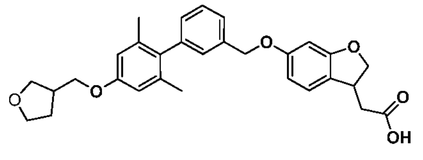
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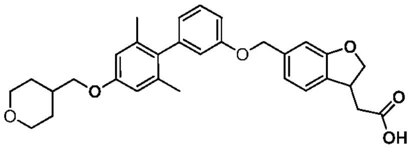
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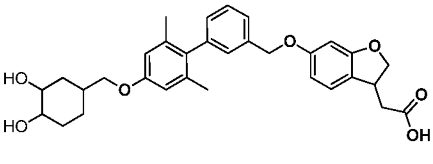
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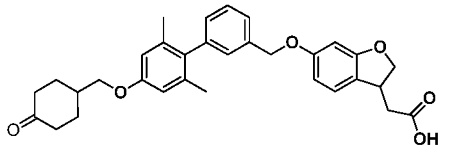
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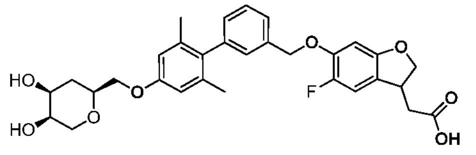
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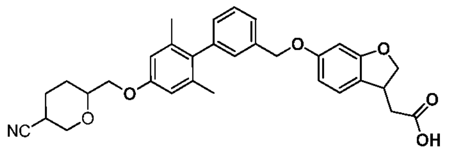
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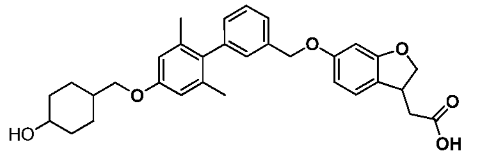
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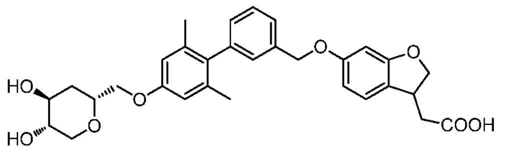
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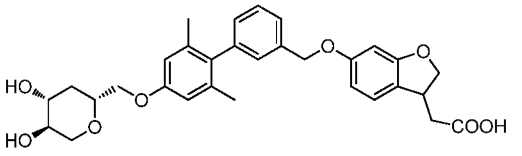
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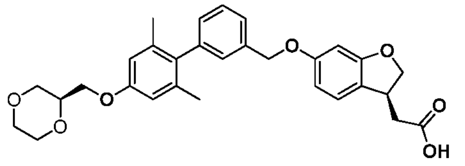
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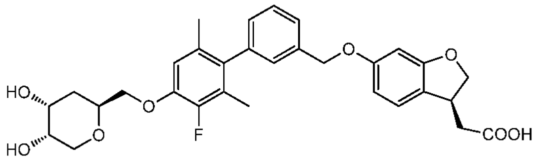
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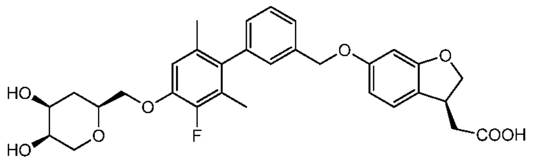
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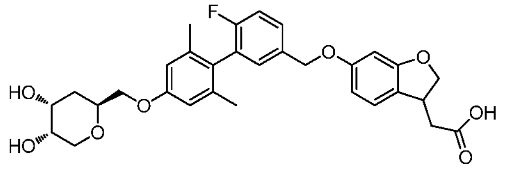
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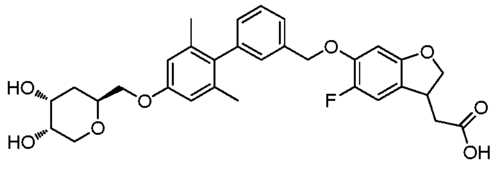
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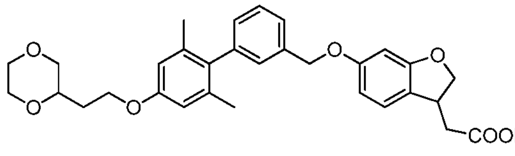

(86).

[0083] Provided herein includes the use of a compound disclosed herein (In present disclosure, "a compound disclosed herein" comprises a compound of formula (I) and a stereoisomer, a geometric isomer, a tautomer, an *N*-oxide, a hydrate, a solvate, a metabolite, a hydrolysate, a pharmaceutically acceptable salt and prodrug thereof.), in the manufacture of a medicament for the treatment of diabetes, diabetic retinopathy, diabetic neuropathy, diabetic nephropathy, insulin resistance, hyperglycemia, hyperinsulinemia, elevated blood levels of fatty acids or glycerol, hyperlipidemia, obesity, hypertriglyceridemia, syndrome X, ketosis acidosis, glucose intolerance, hypercholesterolemia, dyslipidemia, metabolic syndrome, cardiovascular disease, renal disease, thrombotic disorders, nephropathy, sexual dysfunction, skin disease, indigestion, hypoglycemia, cancer, edema, diabetes complications, atherosclerosis or hypertension, or increasing levels of HDL, including those described herein. Provided herein is use of the compound in the manufacture of a GPR40 modulating medicament. Provided herein is the use of the compounds disclosed herein, in the manufacture of a medicament to attenuate, prevent, manage or treat GPRs receptor-mediated diseases, especially GPR40 receptor-mediated diseases. Also provided herein is a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula (I) in association with at least one of pharmaceutically acceptable carriers, excipients, diluents, adjuvants and vehicles.

[0084] In certain embodiments, the salt is a pharmaceutically acceptable salt. The phrase "pharmaceutically acceptable" refers to that the substance or composition must be compatible chemically and/or toxicologically, with the other ingredients comprising a Formulation, and/or the mammal being treated therewith. The skills in the art could choose “pharmaceutically acceptable” substance or composition base on the other ingredients and the objects for treatment such as human.

[0085] If the compound disclosed herein is a base, the desired salt may be prepared by any suitable method available in the art, for example, treatment of the free base with an inorganic acid, such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like. Or with an organic acid, such as acetic acid, maleic acid, succinic acid, mandelic acid, fumaric acid, malonic acid, pyruvic acid, oxalic acid, glycolic acid, salicylic acid; a pyranosidyl acid, such as glucuronic acid or galacturonic acid; an alpha hydroxy acid, such as citric acid or tartaric acid; an amino acid, such as aspartic acid or glutamic acid; an aromatic acid, such as benzoic acid or cinnamic acid, a sulfonic acid, such as *p*-toluenesulfonic acid or ethanesulfonic acid, and the like.

[0086] If the compound disclosed herein is an acid, the desired salt may be prepared by any suitable method, for example, treatment of the free acid with an inorganic or organic base, such as an amine (primary, secondary or tertiary), an alkali metal hydroxide or alkaline earth metal hydroxide, and the like. Some non-limiting examples of suitable salts include organic salts derived from amino acids, such as glycine and arginine, ammonia, primary, secondary, and tertiary amines, and cyclic amines, such as piperidine, morpholine and piperazine, and inorganic salts derived from sodium, calcium, potassium, magnesium, manganese, iron, copper, zinc, aluminum, lithium, and the like.

COMPOSITIONS, FORMULATIONS AND ADMINISTRATION OF COMPOUNDS OF THE INVENTION

[0087] The invention provides the pharmaceutical composition suitable for pharmaceutical use comprising one or more compounds of the invention and a pharmaceutically acceptable carrier, excipient, diluent, adjuvant, vehicle or a combination thereof. The pharmaceutical composition can be used for treating diabetes, diabetic retinopathy, diabetic neuropathy, diabetic nephropathy, insulin resistance, hyperglycemia, hyperinsulinemia, elevated blood levels of fatty acids or glycerol, hyperlipidemia, obesity, hypertriglyceridemia, syndrome X, ketosis acidosis, glucose intolerance, hypercholesterolemia, dyslipidemia, metabolic syndrome, cardiovascular disease, renal disease, thrombotic disorders, nephropathy, sexual dysfunction, skin disease, indigestion, hypoglycemia, cancer, edema, diabetes complications, atherosclerosis or hypertension, or increasing high density lipoprotein level, specially, it has potent modulation ability to GPR40.

[0088] The compound of the invention may be administered alone or in combination with one or more other therapeutic agents. The pharmaceutical composition further comprises other antidiabetic agents, antihyperglycemic agents, antiadipositas drugs, antihypertensive agents, antiplatelet agents, antiatherosclerotic drugs, lipid-lowering agents, anti-inflammatories or a combination thereof. Said antidiabetic agents may be any other known antidiabetic agents that are different from the compound of the invention, for example, SGLT-2 inhibitor, biguanide, sulfonylurea, glucosidase inhibitor, PPAR agonist, αP2 inhibitor, PPARα/γ dual agonist, dipeptidyl peptidase (DPP-IV) inhibitor, ndinedglinide, insulin, glucagon like peptide-1 (GLP-1) inhibitor, PTP1B inhibitor, glycogen phosphorylase inhibitor or glucose-6-phosphatase inhibitor.

[0089] When it is possible that, for use in therapy, therapeutically effective amounts of a compound of Formula (I), as well as pharmaceutically acceptable salts thereof, may be administered as the raw chemical, it is possible to present the active ingredient as a pharmaceutical compositions, which include therapeutically effective amounts of compounds of Formula (I) or pharmaceutically acceptable salts thereof, and one or more pharmaceutically acceptable carriers, diluents, or excipients. The term "therapeutically effective amount," as used herein, refers to the total amount of each active component that is sufficient to show a meaningful patient benefit (*e.g.*, blood glucose falls). When applied to individual active ingredient, administered alone, the term refers to that ingredient alone. When applied to a combination, the term refers to combined amounts of the active ingredients that result in the therapeutic effect, whether administered in combination, serially, or simultaneously. The compounds of Formula (I) and pharmaceutically acceptable salts thereof, are as described above. The carrier(s), diluents(s), or excipient(s) must be acceptable in the sense of being compatible with the other ingredients of the formulation and not deleterious to recipient thereof. In accordance with another aspect of the present disclosure there is also provided a process for the preparation of a pharmaceutical formulation including admixing a compound of Formula(I), or a pharmaceutically acceptable salt thereof, with one or more pharmaceutically acceptable carriers, diluents, or excipients. The term "pharmaceutically acceptable," as used herein, refers to those compounds, materials, composition, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of patients without excessive toxicity, irritation, allergic response, or other problem complication commensurate with a reasonable benefit/risk ratio, and are effective for their intended use.

[0090] When the compositions of this disclosure comprise a combination of a compound of the present disclosure and one or more additional therapeutic or prophylactic agent, both the compound and the additional agent are usually present at dosage levels of between about 10 to 150%, and more preferably between about 10 and 80% of the dosage normally administered in a monotherapy regimen. Pharmaceutical formulations may be adapted for administration by any appropriate route, for example by the oral (including buccal or sublingual), rectal, nasal, topical (including buccal, sublingual, or transdermal), vaginal, or parenteral (including subcutaneous, intracutaneous, intramuscular, intra-articular, intrasynovial, intrasternal, intrathecal, intralesional, intravenous, or intradermal injections or infusions) route. Such formulations may be prepared by any method known in the art of pharmacy, for example by bringing into association the active ingredient with the carrier(s) or excipient(s). Oral administration or intravenous administration by injection is preferred.

[0091] The pharmaceutical compositions for the administration of the compounds of this invention may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art. All methods include the step of bringing the active ingredient into association with the carrier which constitutes one or more accessory ingredients. In general, the pharmaceutical compositions are prepared by uniformly and intimately bringing the active ingredient into association with a liquid carrier or finely divided solid carrier or both, and then, if necessary, shaping the product into the desired formulation. In the pharmaceutical composition, the active object compound is included in an amount sufficient to produce the desired effect upon the process or condition or diseases.

[0092] The pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions. Such compositions may contain one or more agents selected from sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations.

[0093] Tablets contain the active ingredient in admixture with other non-toxic pharmaceutical acceptable excipients which are suitable for the manufacture of tablets. These excipients may be, for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch or alginic acid; adhesive, such as starch, gelatin or acacia; and lubricating agents, for example, magnesium stearate, stearic acid, or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated by the techniques described in U.S. Patent Nos. 4256108, 4160452 and 4265874 to form osmotic therapeutic tablets for control release.

[0094] Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluents, for example, calcium carbonate, calcium phosphate, or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

[0095] Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxu-propylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example poplyoxy-ethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or *n*-propyl, *p*-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

[0096] Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil, or coconut oil, or in a mineral oil such as liquid paraffin. The oils suspensions may contain a thickening agent, for example beeswax, hard paraffin, or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

[0097] Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

[0098] The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

[0099] Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative, and flavoring and coloring agents.

[00100] The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, for example as a solution in 1,3-butane diol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acid such as oleic acid is find use in the preparation of injectables.

[00101] The pharmaceutical compositions may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will

therefore melt in the rectum to release the drug. Such materials include, for example, cocoa butter and polyethylene glycols.

[00102] For topical use, creams, ointments, jellies, solutions, or suspensions, *etc.*, containing the compounds of the invention are employed. As used herein, topical application is also meant to include the use of mouthwashes and gargles.

[00103] The pharmaceutical compositions and methods of the invention may further comprise other therapeutically active compounds, as noted herein, useful in the treatment of type II diabetes, obesity, hyperglycemia, glucose intolerance, insulin resistance, hyperinsulinemia, hypercholesterolemia, hypertension, hyperlipoproteinemia, hyperlipidemia, hypertriglylceridemia, dyslipidemia, metabolic syndrome, syndrome X, cardiovascular disease, atherosclerosis, kidney disease, ketoacidosis, thrombotic disorders, nephropathy, diabetic neuropathy, diabetic retinopathy, sexual dysfunction, dermatopathy, dyspepsia, hypoglycemia, cancer and edema.

[00104] In the treatment or precention type II diabetes, obesity, hyperglycemia, glucose intolerance, insulin resistance, hyperinsulinemia, hypercholesterolemia, hypertension, hyperlipoproteinemia, hyperlipidemia, hypertriglylceridemia, dyslipidemia, metabolic syndrome, syndrome X, cardiovascular disease, atherosclerosis, kidney disease, ketoacidosis, thrombotic disorders, nephropathy, diabetic neuropathy, diabetic retinopathy, sexual dysfunction, dermatopathy, dyspepsia, hypoglycemia, cancer and edema or other conditions or disorders associated with GPR40, an appropriate dosage level will generally be about 0.001 to 100 mg per kg patient body weight per day which can be administered in single or multiple doses. Preferably, the dosage level will be about 0.01 to about 25 mg/kg per day; more preferably about 0.05 to about 10 mg/kg per day. A suitable dosage level may be about 0.01 to 25 mg/kg per day, about 0.05 to about 10 mg/kg per day, or about 0.1 to about 5mg/kg per day. Within this range, the dosage may be 0.005 to 0.05, 0.05 to 0.5 or 0.5 to 5.0 mg/kg per day. For oral administration, the compositions are preferably provided in the form of tablets containing from 1.0 to 1000 milligrams of the active ingredient, particularly 1.0, 3.0, 5.0, 10.0, 15.0, 20.0, 25.0, 50.0, 75.0, 100.0, 150.0, 200.0, 300.0, 400.0, 500.0, 600.0, 750.0, 800.0, 900.0, and 1000.0 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. The compounds may be administered on a regimen of 1 to 4 times per day, preferably once or twice per day.

[00105] It will be understood, however, that the specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy.

[00106] The compounds of the invention can be combined or used in combination with other agents useful in the treatment, prevention, suppression or amelioration of the disease or conditions for which compounds of the invention are useful, including type II diabetes, obesity, hyperglycemia, glucose intolerance, insulin resistance,

hyperinsulinemia, hypercholesterolemia, hypertension, hyperlipoproteinemia, hyperlipidemia, hypertriglylceridemia, dyslipidemia, metabolic syndrome, syndrome X, cardiovascular disease, atherosclerosis, kidney disease, ketoacidosis, thrombotic disorders, nephropathy, diabetic neuropathy, diabetic retinopathy, sexual dysfunction, dermatopathy, dyspepsia, hypoglycemia, cancer and edema. Such other agents, or drugs, may be administered, by a route and in an amount commonly used therefore, simultaneously or sequentially with a compound of the invention. When a compound of the invention is used contemporaneously with one or more other drugs, a pharmaceutical composition containing such other drugs in addition to the compound of the invention is preferred. Accordingly, the pharmaceutical compositions of the invention include those that also contain one or more other active ingredients or therapeutic agents, in addition to a compound of the invention.

[00107] Examples of other therapeutic agents that may be combined with a compound of the invention, either administered separately or in the same pharmaceutical compositions, include, but are not limited to: (a) cholesterol lowering agents such as HMG-CoA reductase inhibitors (*e.g.*, lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin and other statins), bile acid sequestrants (*e.g.*, cholestyramine and colestipol), vitamin B_3 (also known as nicotinic acid, or niacin), vitamin B6 (pyridoxine), vitamin B12 (cyanocobalamin), fibric acid derivatives (*e.g.*, gemfibrozil, clofibrate, fenofibrate and benzafibrate), probucol, nitroglycerin, and inhibitors of cholesterol absorption (*e.g.*, betasitosterol and acylCoA-cholesterol acyltransferase (ACAT) inhibitors such as melinamide), HMG-CoA synthase inhibitors, squalene epoxidase inhibitors and squalene synthetase inhibitors; (b) antithrombotic agents, such as thrombolytic agents (*e.g.*, streptokinase, alteplase, anistreplase and reteplase), heparin, hirudin and warfarin derivatives, β-blockers (*e.g.*, atenolol), β-adrenergic agonists (*e.g.*, isoproterenol), ACE inhibitors and vasodilators (*e.g.*, sodium nitroprusside, nicardipine hydrochloride, nitroglycerin and enaloprilat); and (c) anti-diabetic agents such as insulin and insulin mimetics, sulfonylureas (*e.g.*, glyburide, meglinatide), biguanides, *e.g.*, metformin (GLUCOPHAGE®), α-glucosidase inhibitors (acarbose), insulin sensitizers, *e.g.*, thiazolidinone compounds, rodiglitazone (AVANDIA®), troglitazone (REZULIN®), ciglitazone, piolitazone (ACTOS®) and englitazone, DPP-IV inhibitors, *e.g.*, vildagliptin (Galvus®), sitagliptin (Januvia™), and GLP-1 analogs, *e.g.*, exenatide (Byetta®). In some embodiments, a compound of the invention may be administered along with a DPP-IV inhibitor or a GLP-1 analog. In some embodiments, a compound of the invention is administered with any of the DPP-IV inhibitors set forth in U.S. Patent Publication No. 20060270701 which is hereby incorporated by reference in its entirety and for all purposes as if specifically set forth herein.

[00108] The weight ratio of the compound of the invention to the second active ingredient may be varied and will depend upon the effective dose of each ingredient. Generally, an effective dose of each will be used. Combinations of the compound disclosed herein with other active ingredients will generally also be within the aforementioned range, but in each case, an effective dose of each active ingredient should be used.

USES OF THE COMPOUNDS AND COMPOSITIONS OF THE INVENTION

[00109] Provided herein is use of the compound or the pharmaceutical composition in the manufacture of a

medicament for modulating G-protein coupled receptor, G-protein coupled receptor 40 (GPR40) is preferred.

[00110] Also provided herein is a method, which comprises administering the compound or the pharmaceutical composition disclosed herein, further comprises administering additional GPR40 modulator, SGLT-2 inhibitor, biguanide, sulfonylurea, glucosidase inhibitor, PPAR agonist, αP2 inhibitor, PPARα/γ dual agonist, dipeptidyl peptidase (DPP-IV) inhibitor, ndinedglinide, insulin, glucagon like peptide-1(GLP-1) inhibitor, PTP1B inhibitor, glycogen phosphorylase inhibitor or glucose-6-phosphatase inhibitor to a patient, thus administering the compound of the invention may combination with additional GPR40 modulator, SGLT-2 inhibitor, biguanide, sulfonylurea, glucosidase inhibitor, PPAR agonist, αP2 inhibitor, PPARα/γ dual agonist, dipeptidyl peptidase (DPP-IV) inhibitor, ndinedglinide, insulin, glucagon like peptide-1(GLP-1) inhibitor, PTP1B inhibitor, glycogen phosphorylase inhibitor or glucose-6-phosphatase inhibitor, the compound of the invention as a single dosage form or separately from the compound or composition as part of a multiple dosage form. The additional antidiabetic agent may be administered at the same time as a compound disclosed herein or at a different time. In the latter case, administration may be staggered by, for example, 6 hours, 12 hours, 1 day, 2 days, 3 days, 1 week, 2 weeks, 3 weeks, 1 month, or 2 months.

[00111] In certain embodiments disclosed herein, an "effective amount" or "effective dose" of the compound or pharmaceutically acceptable composition is that amount effective for treating or lessening the severity of one or more of the aforementioned disorders. The compounds and compositions, according to the method disclosed herein, may be administered using any amount and any route of administration effective for treating or lessening the severity of the disorder or disease. The exact amount required will vary from subject to subject, depending on the species, age, and general condition of the subject, the severity of the infection, the particular agent, its mode of administration, and the like. A compound or composition can also be administered with one or more other therapeutic agents, as discussed above.

GENERAL SYNTHETIC PROCEDURES

[00112] Generally, the compounds disclosed herein may be prepared by methods described herein, wherein the substituents are as defined for Formula (I), above, except where further noted. The following non-limiting schemes and examples are presented to further exemplify the invention.

[00113] Persons skilled in the art will recognize that the chemical reactions described may be readily adapted to prepare a number of other compounds disclosed herein, and alternative methods for preparing the compounds disclosed herein are deemed to be within the scope disclosed herein. For example, the synthesis of non-exemplified compounds according to the invention may be successfully performed by modifications apparent to those skilled in the art, *e.g.*, by appropriately protecting interfering groups, by utilizing other suitable reagents known in the art other than those described, and/or by making routine modifications of reaction conditions. Alternatively, other reactions disclosed herein or known in the art will be recognized as having applicability for preparing other compounds disclosed herein.

[00114] In the examples described below, unless otherwise indicated all temperatures are set forth in degrees

Celsius. Reagents were purchased from commercial suppliers such as Aldrich Chemical Company, Arco Chemical Company and Alfa Chemical Company, and were used without further purification unless otherwise indicated. Common solvents were purchased from commercial suppliers such as Shantou XiLong Chemical Factory, Guangdong Guanghua Reagent Chemical Factory Co. Ltd., Guangzhou Reagent Chemical Factory, Tianjin YuYu Fine Chemical Ltd., Qingdao Tenglong Reagent Chemical Ltd., and Qingdao Ocean Chemical Factory.

[00115] Anhydrous tetrahydrofuran, dioxane, toluene, and ether were obtained by refluxing the solvent with sodium. Anhydrous dichloromethane and chloroform were obtained by refluxing the solvent with calcium hydride. Ethyl acetate, petroleum ether, hexane, *N,N*-dimethylacetamide and *N,N*-dimethylformamide were treated with anhydrous sodium sulfate prior to use.

[00116] The reactions set forth below were done generally under a positive pressure of nitrogen or argon or with a drying tube (unless otherwise stated) in anhydrous solvents, and the reaction flasks were typically fitted with rubber septa for the introduction of substrates and reagents via syringe. Glassware was oven dried and/or heat dried.

[00117] Column chromatography was conducted using a silica gel column. Silica gel (300 – 400 mesh) was purchased from Qingdao Ocean Chemical Factory. ^{1}H NMR spectra were recorded with a Bruker 400 MHz spectrometer at ambient temperature. ^{1}H NMR spectra were obtained as $CDCl_3$, DMSO-d_6, CD_3OD or acetone-d_6 solutions (reported in ppm), using TMS (0 ppm) or chloroform (7.25 ppm) as the reference standard. When peak multiplicities are reported, the following abbreviations are used: s (singlet), d (doublet), t (triplet), m (multiplet), br (broadened), dd (doublet of doublets), dt (doublet of triplets). Coupling constants, when given, are reported in Hertz (Hz).

[00118] Low-resolution mass spectral (MS) data were also determined on an Agilent 6320 series LC-MS spectrometer equipped with G1312A binary pumps, a G1316A TCC (Temperature Control of Column, maintained at 30 °C), a G1329A autosampler and a G1315B DAD detector were used in the analysis. An ESI source was used on the LC-MS spectrometer.

[00119] Low-resolution mass spectral (MS) data were also determined on an Agilent 6120 series LC-MS spectrometer equipped with G1311A Quaternary pump, a G1316A TCC (Temperature Control of Column, maintained at 30 °C), a G1329A autosampler and a G1315D DAD detector were used in the analysis. An ESI source was used on the LC-MS spectrometer.

[00120] Both LC-MS spectrometers were equipped with an Agilent Zorbax SB-C18, 2.1 x 30 mm, 5 μm column. Injection volume was decided by the sample concentration. The flow rate was 0.6 mL/min. The HPLC peaks were recorded by UV-Vis wavelength at 210 nm and 254 nm. The mobile phase was 0.1% formic acid in acetonitrile (phase A) and 0.1% formic acid in ultrapure water (phase B). The gradient condition is shown in Table 1:

Time (min)	A (CH_3CN, 0.1% HCOOH)	B (H_2O, 0.1% HCOOH)
0-3	5-100	95-0

3-6	100	0
6-6.1	100-5	0-95
6.1-8	5	95

[00121] Purities of compounds were assessed by Agilent 1100 Series high performance liquid chromatography (HPLC) with UV detection at 210 nm and 254 nm (Zorbax SB-C18, 2.1 × 30 mm, 4 micorn, 10 min, 0.6 mL/min flow rate, 5 to 95 % (0.1 % formic acid in CH_3CN) in (0.1 % formic acid in H_2O). Column was operated at 40 °C.

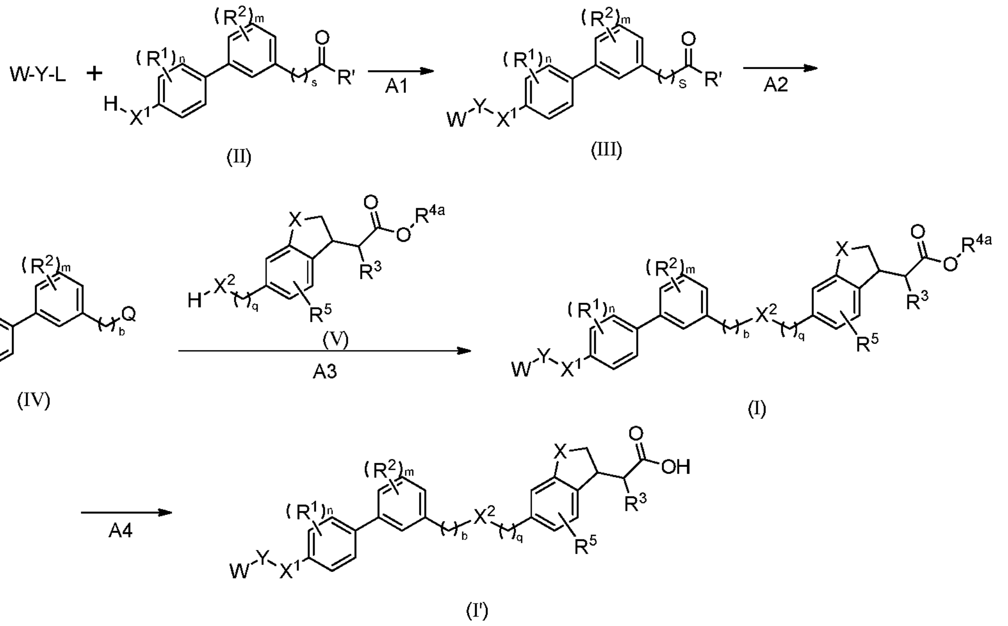
[00122] The following abbreviations are used throughout the specification:

AD-Mix-β	Sharpless asymmetric dihydroxylation mixture, which contains hydroquinidine 1,4-phthalazinediyl diether (0.0016 mol), potassium carbonate power (0.4988 mol), potassium ferricyanide (0.4988 mol), and potassium osmate (VI) dehydrate (0.0007 mol).
g	gram
mg	milligram
mmol	millimole
ml, mL	milliliter
L	liter
°C	degree centigrade
^1H NMR	^1H nuclear magnetic resonance spectrum
^{13}C NMR	^{13}C nuclear magnetic resonance spectrum
MS	mass spectrometry
MHz	megahertz
Hz	hertz
DMSO-d_6	dimethyl-d_6 sutfoxide
$CDCl_3$	chloroform-*d*
CD_3OD	methanol-*d*
DMSO	dimethylsulfoxide
pos.ion	positive ion
neg. ion	negative ion
ESI	electrospray ionization
m/z	mass electron ratio
DCM	dichloromethane
Pd/C	palladium on activated carbon
TLC	thin layer chromatography
TBSO	(*tert*-butyldimethylsilyl)oxy
Me	methyl
Bn	benzyl

TMS	trimethylsilyl
Cbz	carboxybenzyl
h	hour, hours
EtOAc	ethyl acetate
PET	petroleum ether
MeOH	methanol
THF	tetrahydrofuran
Na_2SO_4	sodium sulfate
$NaHCO_3$	sodium bicarbonate
DMF	*N,N*-dimethylformamide

SYNTHETIC TECHNIQUES

Scheme 1



[00123] W, Y, R^1, R^2, R^3, R^5, X, X^1, X^2, b, q, m and n are as defined in Formula (I); R^{4a} is C_{1-6} alkyl; s is 0, 1, 2 or 3; R' is H or optionally substituted C_{1-6} alkoxy.

Step A1:

[00124] When L is a leaving group, W-Y-L can react with compound II in the presence of a base in a solvent to give compound III. L may be halogen atom or methylsulfonyloxy, *p*-methylbenzenesulfonyloxy, *etc*. The base may be, for example, potassium carbonate, *etc*. The solvent is inert under the reaction conditions. Some non-limiting examples of the solvent include *N,N*-dimethylformamide, *etc*.

[00125] When L is hydroxy, Mitsunobu reaction of W-Y-L with compound II in the presence of azodicarbonyl compound (such as diisopropyl azodicarboxylate and 1,1'-(azodicarbonyl)-dipiperidine) and phosphine (such as triphenylphosphine and tributylphosphine) in a suitable solvent can give compound III. The suitable solvent

is preferably inert under the reaction conditions. Some non-limiting examples of the suitable solvent include toluene, *etc.*

Step A2:

[00126] When Q is hydroxy, compound III can be reduced to provide compound IV. The reduction reaction can be carried out in the presence of a reducing agent by using conventional method. The reducing agent may be, for example, sodium borohydride, lithium aluminium hydride, *etc.* The solvent is preferably inert under the reaction conditions. Some non-limiting examples of the solvent include methanol, tetrahydrofuran, *etc.*, and a mixture thereof.

[00127] When Q is a leaving group, compound III can be reduced in the presence of a reducing agent (such as sodium borohydride, lithium aluminium hydride) in an inert solvent (such as methanol, tetrahydrofuran) and then react with a halogenating agent or a sulfonated acylating agent to obtain compound IV, wherein the reaction can be carried out without solvent, or in inert solvent when react with a halogenating agent; the halogenating agent may be, for example, phosphoric trichloride, *etc*; some non-limiting examples of the inert solvent include *N,N*-dimethylformamide and dichloromethane, *etc.*, or excess halogenating agent can be added as solvent; and the reaction can be carried out in the presence of a base in an inert solvent when react with a sulfonated acylating agent; the sulfonated acylating agent may be, for example, methanesulfonyl chloride, *p*-methylbenzene sulfonyl chloride, *etc.*; the inert solvent may be the solvents which be listed in the above reaction with halogenating agent; the base may be, for example, triethylamine, *etc.*

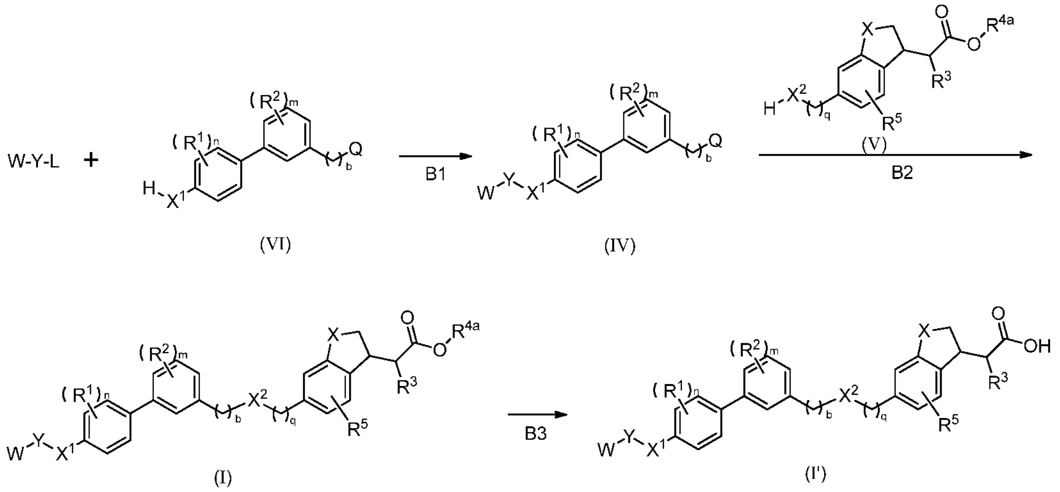
Step A3:

[00128] Compound I can be obtained from compound IV reacting with compound V by the method which is described in step A1or a similar method thereof.

Step A4:

[00129] Hydrolysis reaction of compound I in the presence of a base can provide compound I'. The base may be, for example, lithium hydrate, sodium hydroxide, *etc.* The hydrolysis reaction can be carried out without solvent, or in an inert solvent. Some non-limiting examples of the solvent include methanol, tetrahydrofuran, water, *etc.*, and a mixture thereof.

Scheme 2



[00130] W, Y, R^1, R^2, R^3, R^5, X, X^1, X^2, b, q, m and n are as defined in formula (I); R^{4a}, Q and L are as defined in scheme 1.

Step B1:

[00131] Compound IV can be obtianed from W-Y-L reacting with compound VI by the method which is described in step A1of Scheme 1 or a similar method thereof.

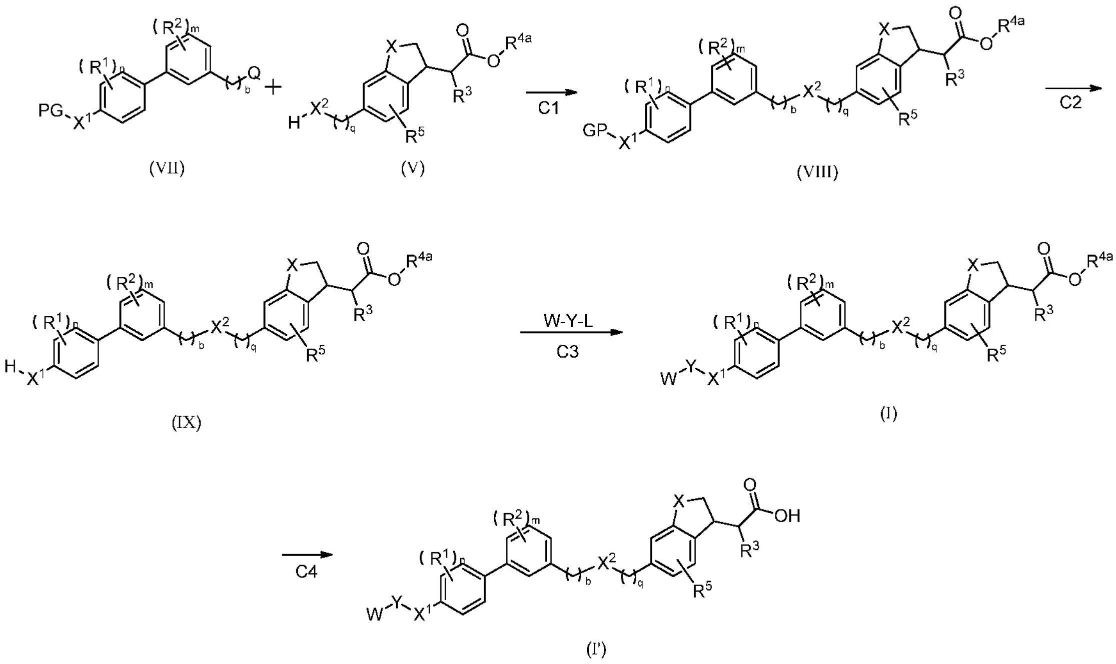
Step B2:

[00132] Compound I can be obtained from compound IV reacting with compound V by the method which is described in step A3 of Scheme 1 or a similar method thereof.

Step B3:

[00133] Compound I' can be obtained from compound I by the method which is described in step A4 of Scheme 1 or a similar method thereof.

Scheme 3



[00134] W, Y, R^1, R^2, R^3, R^5, X, X^1, X^2, b, q, m and n are as defined in formula (I); R^{4a}, Q and L are as defined

in scheme 1. When X^1 is oxygen atom or nitrogen atom, PG is a corresponding protecting group.

Step C1:

[00135] Compound VIII can be obtianed from compound VII reacting with compound V by the method which is described in step B2 of Scheme 2 or a similar method thereof.

Step C2:

[00136] The protecting group of compound VIII can be removed by a suitable method to provide compound IX. For example, deprotecdtion reaction of phenyl compound substituted with alkylsilyloxy ((*tert*-butyldimethylsilyl)oxyphenyl compound) can be carried out in the presence of a fluorinated reagent (tetrabutylammonium fluoride) and in an inert solvent. Some non-limiting examples of the inert solvent include tetrahydrofuran, *etc*.

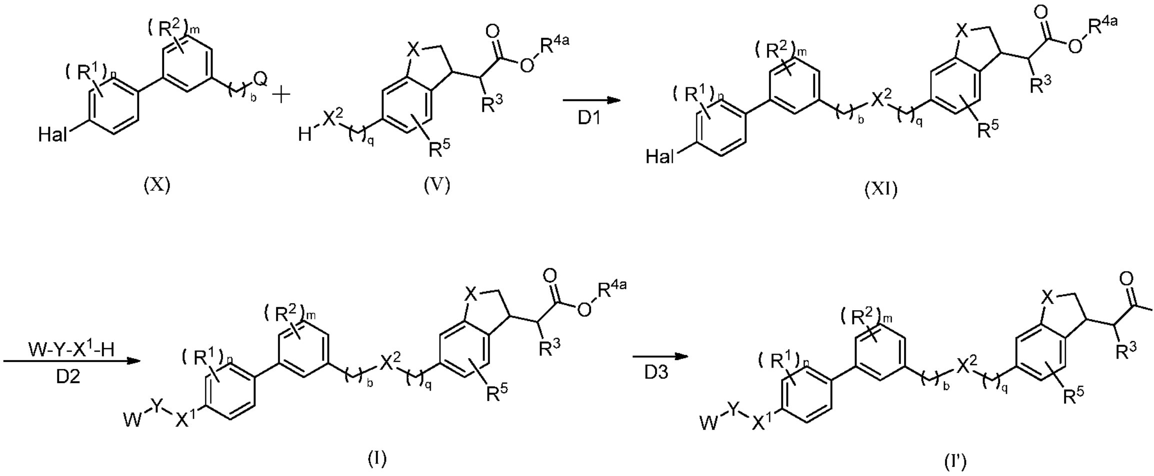
Step C3:

[00137] Compound I can be obtianed from compound IX reacting with W-Y-L by the method which is described in step A1 of Scheme 1 or a similar method thereof.

Step C4:

[00138] Compound I’ can be obtained from compound I by the method which is described in step A4 of Scheme 1 or a similar method thereof.

Scheme 4



[00139] W, Y, R^1, R^2, R^3, R^5, X, X^1, X^2, b, q, m and n are as defined in formula (I); Hal is Cl, Br or I; R^{4a} and Q are as defined in scheme 1.

Step D1:

[00140] Compound XI can be obtained from compound X reacting with compound V by the method which is described in step C1 of Scheme 3 or a similar method thereof.

Step D2:

[00141] The coupled reaction of compound XI with X-Y-X^1-H in the presence of a catalyst and a ligand in a solvent can obtain compound I. The catalyst may be a copper catalyst including, but not limited, cuprous iodide

and cuprous chloride, *etc*. The ligand may be, a ligand being used in match with the catalyst, including, but not limited, *L*-proline, trans-*N*,*N'*-diethyl-1,2-cyclohexanediamine, *etc*. The solvent is inert under the reaction conditions, including, but not limited to, dimethylsulfoxide, *etc*.

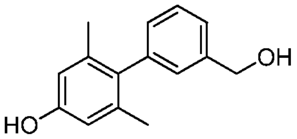
Step D3:

[00142] Compound I' can be obtained from compound I by the method which is described in step A4 of Scheme 1 or a similar method thereof.

EXAMPLES:

Example 1

3'-(Hydroxymethyl)-2,6-dimethyl-[1,1'-biphenyl]-4-ol



Step 1) 4'-hydroxy-2',6'-dimethyl-[1,1'-biphenyl]-3-carbaldehyde

[00143] To a solution of 4-bromo-3,5-dimethylphenol (10.2 g, 51 mmol) and (3-formylphenyl)boronic acid (7.67 g, 51.2 mmol) in sodium carbonate aqueous solution (150 mL, 1 M), ethanol (50 mL) and toluene (150 mL) was added tetrakis(triphenylphosphine)palladium (2.95 g, 2.55 mmol) under nitrogen atmosphere. The reaction mixture was stirred at 80 °C for 24 h. The reaction mixture was cooled to room temperature, and partitioned between ethyl acetate (200 mL) and water (50 mL). The organic phase was washed with brine (30 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PET/EtOAc (v/v) = 10/1) to give the title compound as a white solid (8.7 g, 75.4%).

MS (ESI, neg. Ion) *m/z*: 225.2 $[M-H]^-$.

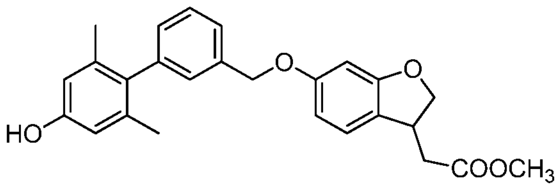
Step 2) 3'-(hydroxymethyl)-2,6-dimethyl-[1,1'-biphenyl]-4-ol

[00144] To a solution of 4'-hydroxy-2',6'-dimethyl-[1,1'-biphenyl]-3-carbaldehyde (7.3 g, 32 mmol) in THF (50 mL) and MeOH (25 mL) at 0 °C was added sodium borohydride (1.45 g, 38 mmol) portionwise. The resulting mixture was stirred at 0 °C overnight. The reaction mixture was quenched with water (10 mL) and extracted with EtOAc (50 mL × 2). The combined organic phases were washed with brine (20 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PET/EtOAc (v/v) = 4/1) to give the title compound as light yellow oil (6.0 g, 69%).

^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.43 (t, J = 7.6 Hz, 1H), 7.36 (d, J = 7.7 Hz, 1H), 7.15 (s, 1H), 7.09 (d, J = 7.5 Hz, 1H), 6.62 (s, 2H), 4.76 (s, 2H), 2.00 (s, 6H).

Example 2

Methyl 2-(6-((4'-hydroxy-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzo furan-3-yl)acetate



Step1) 4'-((*tert*-butyldimethylsilyl)oxy)-2',6'-dimethyl-[1,1'-biphenyl]-3-carbaldehyde

[00145] To a solution of 4'-hydroxy-2',6'-dimethyl-[1,1'-biphenyl]-3-carbaldehyde (10.2 g, 45.3 mmol) and imidazole (3.7 g, 54.3 mmol) in DCM (200 mL) at 0 °C under nitrogen atmosphere was added *tert*-butyldimethylsilyl chloride (8.2 g, 54.3 mmol) dropwise. The resulting mixture was stirred at room temperature overnight. The reaction mixture was quenched with water (50 mL) and extracted with DCM (100 mL × 2). The combined organic phases were washed with brine (50 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PET/EtOAc (v/v) = 30/1) to give the title compound as light yellow oil (15 g, 97.4%).

Step2) (4'-((*tert*-butyldimethylsilyl)oxy)-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methanol

[00146] To a solution of 4'-((*tert*-butyldimethylsilyl)oxy)-2',6'-dimethyl-[1,1'-biphenyl]-3- carbaldehyde (49 g, 143.9 mmol) in THF (200 mL) and MeOH (100 mL) at 0 °C was added sodium borohydride (5.7 g, 150 mmol) portionwise. The resulting mixture was stirred at 0 °C overnight. The reaction mixture was quenched with water (50 mL) and extracted with EtOAc (200 mL × 2). The combined organic phases were washed with brine (50 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PET / EtOAc (v/v) = 4/1) to give the title compound as light yellow oil (42 g, 85.2%).

Step3) Methyl 2-(6-((4'-((*tert*-butyldimethylsilyl)oxy)-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetate

[00147] To a solution of (4'-((*tert*-butyldimethylsilyl)oxy)-2',6'-dimethyl-[1,1'-biphenyl]-3-yl) methanol (6.9 g, 20 mmol) and methyl 2-(6-hydroxy-2,3- dihydrobenzofuran-3-yl)acetate (4.2 g, 20 mmol) in toluene (50 mL) were added tributylphosphine (8.1 mL, 32 mmol) and 1,1'-(azodicarbonyl)-dipiperidine (8.1 g, 32 mmol) at room temperature. The resulting mixture was stirred at room temperature for 1 h under nitrogen atmosphere. The reaction mixture was quenched with water (50 mL) and extracted with EtOAc (50 mL × 2). The combined organic phases were washed with of brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PET/EtOAc (v/v) = 10/1) to give the title compound as a white solid (9 g, 84%).

Step4) Methyl 2-(6-((4'-hydroxy-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl) acetate

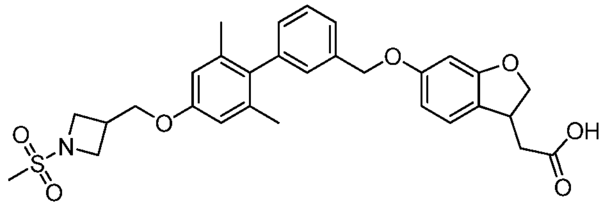
[00148] To a solution of methyl 2-(6-((4'-((*tert*-butyldimethylsilyl)oxy)-2',6'-dimethyl-[1,1'-biphenyl] -3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetate (9 g, 16.9 mmol) in tetrahydrofuran (30 mL) at room temperature was added tetrabutylammonium fluoride (26 mL, 26 mmol, 1M solution in tetrahydrofuran). The mixture was stirred for 1 h at room temperature. The reaction mixture was diluted with water (100 mL) and

extracted with EtOAc (100 mL × 2). The combined organic phases were washed with brine (30 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PET/EtOAc (v/v) = 2/1) to give the title compound as a white solid (6.7 g, 95%).

^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.44 (t, J = 7.5 Hz, 1H), 7.40 (d, J = 7.7 Hz, 1H), 7.19 (s, 1H), 7.10 (d, J = 7.4 Hz, 1H), 7.04 (d, J = 8.1 Hz, 1H), 6.62 (s, 2H), 6.53 – 6.45 (m, 2H), 5.08 (s, 2H), 4.77 (t, J = 9.0 Hz, 1H), 4.29 (dd, J = 9.1, 6.1 Hz, 1H), 3.87 – 3.79 (m, 1H), 3.74 (s, 3H), 2.77 (dd, J = 16.4, 5.4 Hz, 1H), 2.58 (dd, J = 16.4, 9.3 Hz, 1H), 1.99 (s, 6H).

Example 3

2-(6-((2',6'-Dimethyl-4'-((1-(methylsulfonyl)azetidin-3-yl)methoxy)-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



Step 1) (1-(methylsulfonyl)azetidin-3-yl)methyl methanesulfonate

[00149] To a solution of azetidin-3-ylmethanol hydrochloride (2 g, 16.18 mmol) and triethylamine (7.7 mL, 55 mmol) in DCM (50 mL) in an ice bath was added methanesulfonyl chloride (3 mL, 38.8 mmol) dropwise under nitrogen atmosphere. The mixture was stirred at room temperature for 2 h under nitrogen atmosphere. The mixture was quenched with saturated sodium hydrogen carbonate aqueous solution (20 mL) and extracted with DCM (30 mL × 2). The combined organic phases were washed with brine (5 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PET / EtOAc (v/v) = 4/1) to give the title compound as yellow oil (430 mg, 10.9 %).

Step 2) methyl 2-(6-((2',6'-dimethyl-4'-((1-(methylsulfonyl)azetidin-3-yl)methoxy)-[1,1'-biphenyl]-3-yl) methoxy) -2,3-dihydrobenzofuran-3-yl)acetate

[00150] A solution of (1-(methylsulfonyl)azetidin-3-yl)methyl methanesulfonate (407 mg, 1.67 mmol), methyl 2-(6-((4'-hydroxy-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydro benzofuran-3-yl)acetate (200 mg, 0.478 mmol) and potassium carbonate (264.2 mg, 1.91 mmol) in DMF (5 mL) was heated to 100 °C overnight. The reaction mixture was cooled to room temperature, and partitioned between EtOAc (10 mL) and water (10 mL). The organic phase was washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PET/EtOAc (v/v) = 2/1) to give the title compound as pale yellow oil (288 mg, 96.0 %).

Step 3) 2-(6-((2',6'-dimethyl-4'-((1-(methylsulfonyl)azetidin-3-yl)methoxy)-[1,1'-biphenyl]-3-yl)methoxy) -2,3-dihydrobenzofuran-3-yl)acetic acid

[00151] To a solution of methyl 2-(6-((2',6'-dimethyl-4'-((1-(methylsulfonyl)azetidin-3-yl)methoxy) -[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetate (288 mg, 0.51 mmol) in tetrahydrofuran

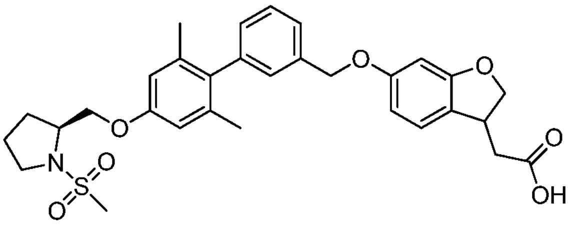
(4.8 mL) and methanol (2.4 mL) was added aqueous sodium hydroxide solution (0.51 mL, 2 M). The mixture was stirred at 50 °C for 2 h. The reaction mixture was diluted with water (10 mL), acidifed with aqueous hydrochloric acid (5 mL, 1 M). The resulting mixture was extracted with EtOAc (10 mL × 2). The combined organic phases were washed with brine (3 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give the title compound as a white solid (250 mg, 89.0%).

MS (ESI, pos. Ion) *m/z*: 552.2 $[M+H]^+$; and

^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.43 (dt, J = 15.1, 7.6 Hz, 2H), 7.19 (s, 1H), 7.12 – 7.04 (m, 2H), 6.68 (s, 2H), 6.56 – 6.45 (m, 2H), 5.09 (s, 2H), 4.77 (d, J = 9.0 Hz, 1H), 4.31 (dd, J = 9.2, 6.1 Hz, 1H), 4.18 – 4.10 (m, 4H), 3.95 (dd, J = 7.9, 6.2 Hz, 2H), 3.89 – 3.77 (m, 1H), 3.17 – 3.05 (m, 1H), 2.96 (s, 3H), 2.83 (dd, J = 16.9, 5.3 Hz, 1H), 2.64 (dd, J = 16.8, 9.3 Hz, 1H), 2.02 (s, 6H).

Example 4

2-(6-((2',6'-Dimethyl-4'-(((*S*)-1-(methylsulfonyl)pyrrolidin-2-yl)methoxy)-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



Step 1) (*S*)-(1-(methylsulfonyl)pyrrolidin-2-yl)methyl methanesulfonate

[00152] To an ice-cooled solution of *L*-prolinol (2 g, 19.77 mmol) and triethylamine (6.67 mL, 47.45 mmol) in DCM (50 mL) was added methanesulfonyl chloride (3.67 mL, 47.45 mmol) dropwise. The mixture was stirred at room temperature for 2 h under nitrogen atmosphere. The mixture was quenched with saturated sodium hydrogen carbonate solution (20 mL) and extracted with DCM (30 mL × 2). The combined organic phases were washed with brine (5 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (DCM/MeOH (v/v) = 20/1) to give the title compound as a yellow solid (2.1 g, 41.0%).

^1H NMR (400 MHz, $CDCl_3$) δ 4.33 – 4.23 (m, 2H), 3.99 (ddt, J = 7.8, 5.8, 4.1 Hz, 1H), 3.55 – 3.43 (m, 1H), 3.36 (dt, J = 9.9, 7.1 Hz, 1H), 3.07 (s, 3H), 2.91 (s, 3H), 2.17 – 1.87 (m, 4H).

Step 2) methyl 2-(6-((2',6'-dimethyl-4'-(((*S*)-1-(methylsulfonyl)pyrrolidin-2-yl)methoxy)-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetate

[00153] A mixture of (*S*)-(1-(methylsulfonyl)pyrrolidin-2-yl)methyl methanesulfonate (258 mg, 1.1 mmol), methyl 2-(6-((4'-hydroxy-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl) acetate (140 mg, 0.33 mmol) and potassium carbonate (138 mg, 1.1 mmol) in DMF (5 mL) was heated to 100 °C overnight. The reaction mixture was cooled to room temperature, and partitioned between EtOAc (10 mL) and water (10 mL). The organic phase was washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in*

vacuo. The residue was purified by silica gel column chromatography (PET/EtOAc (v/v) = 2/1) to give the title compound as a white solid (160 mg, 47.0%).

Step 3) 2-(6-((2',6'-dimethyl-4'-(((*S*)-1-(methylsulfonyl)pyrrolidin-2-yl)methoxy)-[1,1'-biphenyl]-3-yl) methoxy)-2,3-dihydrobenzofuran-3-yl)acetic acid

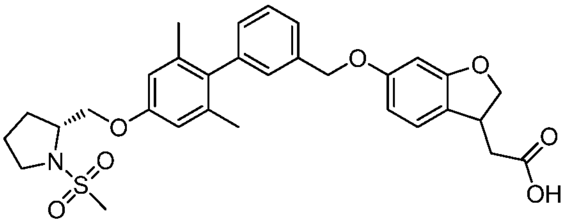
[00154] To a solution of methyl 2-(6-((2',6'-dimethyl-4'-(((*S*)-1-(methylsulfonyl)pyrrolidin-2-yl)methoxy)-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetate (140 mg, 0.24 mmol) in tetrahydrofuran (2.4 mL) and methanol (1.2 mL) was added aqueous sodium hydroxide solution (0.24 mL, 2 M). The mixture was stirred at 50 °C for 2 h. The reaction mixture was diluted with water (10 mL), acidifed with hydrochloric acid (2 mL, 1 M), and extracted with EtOAc (10 mL × 2). The combined organic phases were washed with brine (3 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give the title compound as a white solid (110 mg, 81.0%).

MS (ESI, pos. Ion) *m/z*: 566.2 $[M+H]^+$; and

^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.45 – 7.35 (m, 2H), 7.16 (s, 1H), 7.09 – 7.02 (m, 2H), 6.68 (s, 2H), 6.53 – 6.44 (m, 2H), 5.06 (s, 2H), 4.76 (t, J = 9.0 Hz, 1H), 4.29 (dd, J = 9.2, 6.1 Hz, 1H), 4.17 (dd, J = 9.3, 3.9 Hz, 1H), 4.13 – 4.04 (m, 1H), 3.93 (dd, J = 9.3, 7.5 Hz, 1H), 3.86 – 3.73 (m, 1H), 3.50 (dt, J = 6.7, 5.3 Hz, 1H), 3.45 – 3.31 (m, 1H), 2.90 (s, 3H), 2.81 (dd, J = 16.9, 5.3 Hz, 1H), 2.61 (dd, J = 16.8, 9.3 Hz, 1H), 2.17 – 2.03 (m, 3H), 2.03 – 1.87 (m, 7H).

Example 5

2-(6-((2',6'-Dimethyl-4'-(((*R*)-1-(methylsulfonyl)pyrrolidin-2-yl)methoxy)-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



Step 1) (*R*)-(1-(methylsulfonyl)pyrrolidin-2-yl)methyl methanesulfonate

[00155] To an ice-cooled solution of *D*-prolinol (2 g, 19.77 mmol) and triethylamine (6.67 mL, 47.45 mmol) in DCM (50 mL) was added methanesulfonyl chloride (3.67 mL, 47.45 mmol) dropwise. The mixture was stirred at room temperature for 2 h under nitrogen atmosphere. The mixture was quenched with saturated sodium hydrogen carbonate solution (20 mL) and extracted with DCM (30 mL × 2). The combined organic phases were washed with brine (5 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (DCM/MeOH (v/v) = 20/1) to give the title compound as a yellow solid (1.7 g, 34.0%).

Step 2) methyl 2-(6-((2',6'-dimethyl-4'-(((*R*)-1-(methylsulfonyl)pyrrolidin-2-yl)methoxy)-[1,1'-biphenyl] -3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetate

[00156] A mixture of (*R*)-(1-(methylsulfonyl)pyrrolidin-2-yl)methylmethanesulfonate (492 mg, 1.91 mmol), methyl 2-(6-((4'-hydroxy-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran -3-yl)acetate (200 mg, 0.48 mmol) and potassium carbonate (264 mg, 1.91 mmol) in DMF (5 mL) was heated to 100 °C overnight. The reaction mixture was cooled to room temperature, and diluted with water (10 mL). The resulting mixuter was extracted with EtOAc (10 mL). The organic phase was washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PET/EtOAc (v/v) = 2/1) to give the title compound as a yellow solid (150 mg, 55.6%).

Step 3) 2-(6-((2',6'-dimethyl-4'-(((*R*)-1-(methylsulfonyl)pyrrolidin-2-yl)methoxy)-[1,1'-biphenyl]-3-yl) methoxy)-2,3-dihydrobenzofuran-3-yl)acetic acid

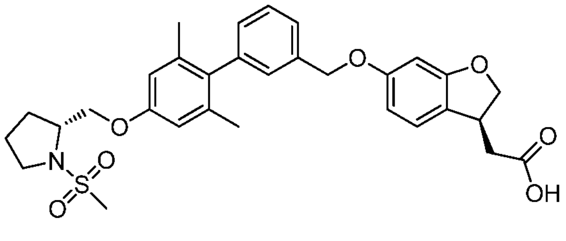
[00157] To a solution of methyl 2-(6-((2',6'-dimethyl-4'-(((*R*)-1-(methylsulfonyl)pyrrolidin-2-yl)methoxy) -[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetate (150 mg, 0.26 mmol) in tetrahydrofuran (2.4 mL) and methanol (1.2 mL) was added aqueous sodium hydroxide solution (0.26 mL, 2 M). The mixture was stirred at 50 °C for 2 h. The reaction mixture was diluted with water (10 mL), acidifed with hydrochloric acid (2 mL, 1 M). The resulting mixuture was extracted with EtOAc (10 mL × 2). The combined organic phases were washed with brine (3 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give the title compound as a white solid (130 mg, 89.0%).

MS (ESI, pos. Ion) *m/z*: 566.1 $[M+H]^+$; and

^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.40 (dt, *J* = 15.4, 7.7 Hz, 2H), 7.16 (s, 1H), 7.11 – 7.03 (m, 2H), 6.67 (s, 2H), 6.53 – 6.43 (m, 2H), 5.06 (s, 2H), 4.76 (t, *J* = 9.0 Hz, 1H), 4.29 (dd, *J* = 9.2, 6.0 Hz, 1H), 4.17 (dd, *J* = 9.4, 3.9 Hz, 1H), 4.13 – 4.05 (m, 1H), 3.92 (dd, *J* = 9.3, 7.5 Hz, 1H), 3.80 (td, *J* = 8.8, 4.4 Hz, 1H), 3.52 – 3.47 (m, 1H), 3.39 (dd, *J* = 12.0, 4.8 Hz, 1H), 2.89 (s, 3H), 2.81 (dd, *J* = 16.8, 5.4 Hz, 1H), 2.62 (dd, *J* = 16.8, 9.3 Hz, 1H), 2.15 – 2.03 (m, 3H), 1.98 (s, 6H), 1.95 (d, *J* = 4.8 Hz, 1H).

Example 6

2-((*S*)-6-((2',6'-Dimethyl-4'-(((*R*)-1-(methylsulfonyl)pyrrolidin-2-yl)methoxy)-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



Step 1) (*R*)-2',6'-dimethyl-4'-((1-(methylsulfonyl)pyrrolidin-2-yl) methoxy)-[1,1'-biphenyl]-3-carbaldehyde

[00158] A mixture of (*R*)-(1-(methylsulfonyl)pyrrolidin-2-yl)methyl methanesulfonate (4.55 g, 17.7 mmol), 4'-hydroxy-2',6'-dimethyl-[1,1'-biphenyl]-3-carbaldehyde (1 g, 4.4 mmol) and potassium carbonate (2.44 mg, 17.7 mmol) in DMF (5 mL) was heated to 100 °C overnight. The reaction mixture was cooled to room

temperature and diluted with water (10 mL). The resulting mixture was extracted with EtOAc (10 mL). The organic phase was washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PET/EtOAc (v/v) = 4/1) to give the title compound as a white solid (790 mg, 46.0%).

MS (ESI, pos. Ion) *m/z*: 388.2 $[M+H]^+$.

Step 2) (*R*)-(2',6'-dimethyl-4'-((1-(methylsulfonyl)pyrrolidin-2-yl) methoxy)-[1,1'-biphenyl] -3-yl)methanol

[00159] To a solution of (*R*)-2',6'-dimethyl-4'-((1-(methylsulfonyl)pyrrolidin-2-yl)methoxy)-[1,1'-biphenyl]-3-carbaldehyde (790 mg, 2.04 mmol) in THF (8 mL) and MeOH (4 mL) was added sodium borohydride (81 mg, 2.14 mmol) portionly at 0 °C. The mixture was stirred at 0 °C overnight. After removing of the solvent, water (10 mL) was added, and the mixture was extracted with EtOAc (10 mL × 2). The combined organic phases were washed with 10 mL of brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PET/EtOAc (v/v) = 1/1) to give the title compound as a white solid (463 mg, 58.0%).

^1H NMR (400 MHz, $CDCl_3$): *δ* (ppm) 7.43 (t, *J* = 7.5 Hz, 1H), 7.36 (d, *J* = 7.7 Hz, 1H), 7.14 (s, 1H), 7.08 (d, *J* = 7.4 Hz, 1H), 6.70 (s, 2H), 4.75 (s, 2H), 4.19 (dd, *J* = 9.4, 3.9 Hz, 1H), 4.11 (dt, *J* = 7.4, 4.4 Hz, 1H), 3.95 (dd, *J* = 9.3, 7.5 Hz, 1H), 3.51 (dt, *J* = 7.0, 5.5 Hz, 1H), 3.40 (dt, *J* = 9.8, 7.7 Hz, 1H), 2.91 (s, 3H), 2.14 - 2.10 (m, 4H), 2.02 (s, 6H).

Step 3) methyl 2-((*S*)-6-((2',6'-dimethyl-4'-(((*R*)-1-(methylsulfonyl)pyrrolidin-2-yl)methoxy)-[1,1'-biphenyl] -3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetate

[00160] To a solution of (*R*)-(2',6'-dimethyl-4'-((1-(methylsulfonyl)pyrrolidin-2-yl)methoxy)-[1,1'-biphenyl]-3-yl)methanol (187 mg, 0.48 mmol) and (*S*)-methyl 2-(6-hydroxy-2,3- dihydrobenzofuran-3-yl)acetate (100 mg, 0.48 mmol, purchased from Shanghai Kaipulin pharmaceutical development co., LTD) in toluene (5 mL) were added tributylphosphine (155 mg, 0.77 mmol) and 1,1'-(azodicarbonyl)-dipiperidine (194 mg, 0.77 mmol). The resulting mixture was stirred at room temperature for 1 h under nitrogen atmosphere. The reaction mixture was quenched with water (20 mL) and extracted with EtOAc (40 mL × 2). The combined organic phases were washed with brine (5 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PET / EtOAc (v/v) = 2/1) to give the title compound as a white solid (220 mg, 79%).

^1H NMR (400 MHz, $CDCl_3$): *δ* (ppm) 7.42 (dt, *J* = 15.1, 7.7 Hz, 2H), 7.18 (s, 1H), 7.06 (dd, *J* = 22.5, 7.5 Hz, 2H), 6.69 (s, 2H), 6.51 – 6.47 (m, 2H), 5.08 (s, 2H), 4.77 (t, *J* = 9.0 Hz, 1H), 4.28 (dd, *J* = 9.2, 6.1 Hz, 1H), 4.19 (dd, *J* = 9.8, 4.4 Hz, 1H), 4.12 – 4.08 (m, 1H), 3.97 (ddd, *J* = 16.7, 8.4, 6.5 Hz, 2H), 3.82 (td, *J* = 9.1, 4.5 Hz, 1H), 3.74 (s, 3H), 3.51 (dt, *J* = 6.9, 5.4 Hz, 1H), 3.440 - 3.36 (m, 1H), 2.91 (s, 3H), 2.77 (dd, *J* = 16.4, 5.5 Hz, 1H), 2.57 (dd, *J* = 16.4, 9.3 Hz, 1H), 2.16 (d, *J* = 4.2 Hz, 1H), 2.00 (s, 6H), 1.90-1.82 (m, 2H).

Step 4) 2-((*S*)-6-((2',6'-dimethyl-4'-(((*R*)-1-(methylsulfonyl)pyrrolidin-2-yl)methoxy)-[1,1'-biphenyl]-3-yl) methoxy)-2,3-dihydrobenzofuran-3-yl)acetic acid

[00161] To a solution of methyl 2-((*S*)-6-((2',6'-dimethyl-4'-(((*R*)-1-(mhylsulfonyl)pyrrolidin-2-yl)methoxy)

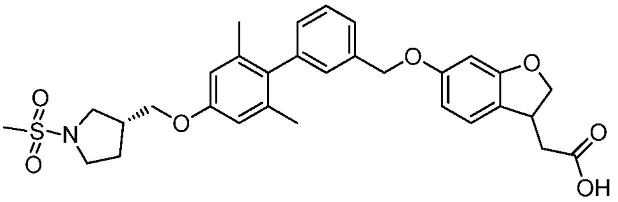
biphenyl-3-yl) methoxy)-2,3-dihydrobenzofuran-3-yl)acetate (220 mg, 0.38 mmol) in tetrahydrofuran (4 mL) was added aqueous lithium hydroxide solution (3.8 mL, 1 M). The mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with water (10 mL), acidifed with hydrochloric acid (5 mL, 1 M), and extracted with EtOAc (10 mL × 2). The combined organic phases were washed with brine (3 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give the title compound as a white solid (191 mg, 89.0%).

MS (ESI, pos. Ion) *m/z*: 566.3 $[M+H]^+$; and

^1H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.46 - 7.39 (m, 2H), 7.19 (s, 1H), 7.09 (dd, *J* = 14.7, 7.8 Hz, 2H), 6.70 (s, 2H), 6.52 (dd, *J* = 15.1, 6.9 Hz, 2H), 5.09 (s, 2H), 4.78 (t, *J* = 9.0 Hz, 1H), 4.31 (dd, *J* = 9.0, 6.2 Hz, 1H), 4.20 (dd, *J* = 9.4, 3.8 Hz, 1H), 4.12 (dd, *J* = 7.0, 3.5 Hz, 1H), 3.95 - 3.94 (m, 1H), 3.83 - 3.81 (m, 1H), 3.53 - 3.50 (m, 1H), 3.41 (dd, *J* = 16.6, 7.0 Hz, 1H), 2.92 (s, 3H), 2.83 (dd, *J* = 16.8, 5.2 Hz, 1H), 2.64 (dd, *J* = 16.8, 9.3 Hz, 1H), 2.13 - 2.08 (m, 3H), 2.01 (s, 6H), 1.99 -1.97 (m, 1H).

Example 7

2-(6-((2',6'-Dimethyl-4'-(((*R*)-1-(methylsulfonyl)pyrrolidin-3-yl)methoxy)-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



Step 1) (*R*)-(1-(methylsulfonyl)pyrrolidin-3-yl)methyl methanesulfonate

[00162] To an ice-cooled solution of (*R*)-pyrrolidin-3-ylmethanol (5 g, 49.4 mmol) and triethylamine (17 mL, 118.6 mmol) in DCM (200 mL) was added methanesulfonyl chloride (9.18 mL, 118.6 mmol) dropwise. The mixture was stirred at room temperature for 2 h under nitrogen atmosphere. The mixture was quenched with saturated sodium hydrogen carbonate solution (30 mL) and extracted with DCM (50 mL × 2). The combined organic phases were washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (DCM/MeOH (v/v) = 20/1) to give the title compound as a yellow solid (11 g, 86.6%).

Step 2) 2-(6-((2',6'-dimethyl-4'-(((*R*)-1-(methylsulfonyl)pyrrolidin-3-yl)methoxy)-[1,1'-biphenyl]-3-yl) methoxy)-2,3-dihydrobenzofuran-3-yl)acetate

[00163] A mixture of (*R*)-(1-(methylsulfonyl)pyrrolidin-3-yl)methyl methanesulfonate (739 mg, 2.87 mmol), methyl 2-(6-((4'-hydroxy-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydro benzofuran-3-yl)acetate (300 mg, 0.72 mmol) and potassium carbonate (396 mg, 2.87 mmol) in DMF (5 mL) was heated to 100 °C overnight. The reaction mixture was cooled to room temperature, and partitioned between EtOAc (10 mL) and water (10 mL). The organic phase was washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PET / EtOAc (v/v) = 2/1) to give the title compound as a yellow solid (379 mg, 91.0%).

MS (ESI, pos. Ion) *m/z*: 580.3 $[M+H]^+$.

Step 3) 2-(6-((2',6'-dimethyl-4'-(((*R*)-1-(methylsulfonyl)pyrrolidin-3-yl)methoxy)-[1,1'-biphenyl]-3-yl) methoxy)-2,3-dihydrobenzofuran-3-yl)acetic acid

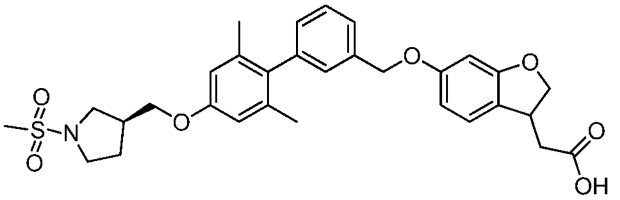
[00164] To a solution of methyl 2-(6-((2',6'-dimethyl-4'-(((*R*)-1-(methylsulfonyl)pyrrolidin-3-yl)methoxy) -[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetate (379 mg, 0.65 mmol) in tetrahydrofuran (6.5 mL) was added aqueous lithium hydroxide solution (6.5 mL, 1 M). The mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with water (10 mL), acidifed with hydrochloric acid (10 mL, 1 M), and extracted with EtOAc (20 mL × 2). The combined organic phases were washed with brine (5 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give the title compound as a white solid (349 mg, 94.0%).

MS (ESI, pos. Ion) *m/z*: 566.1 $[M+H]^+$; and

^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.42 (dt, J = 15.0, 7.6 Hz, 2H), 7.18 (s, 1H), 7.13 – 7.04 (m, 2H), 6.66 (s, 2H), 6.56 – 6.45 (m, 2H), 5.08 (s, 2H), 4.78 (t, J = 9.0 Hz, 1H), 4.31 (dd, J = 9.2, 6.1 Hz, 1H), 4.06 – 3.90 (m, 3H), 3.88 – 3.78 (m, 1H), 3.63 (dd, J = 10.0, 7.7 Hz, 1H), 3.58 – 3.48 (m, 1H), 3.46 – 3.37 (m, 1H), 3.31 (dd, J = 10.1, 6.7 Hz, 1H), 2.89 (s, 3H), 2.87 – 2.74 (m, 2H), 2.63 (dd, J = 16.8, 9.3 Hz, 1H), 2.21 (dd, J = 12.6, 5.2 Hz, 1H), 2.01 (s, 6H).

Example 8

2-(6-((2',6'-Dimethyl-4'-(((*S*)-1-(methylsulfonyl)pyrrolidin-3-yl)methoxy)-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



Step 1) (*S*)-(1-(methylsulfonyl)pyrrolidin-3-yl)methyl methanesulfonate

[00165] To an ice-cooled solution of (*S*)-pyrrolidin-3-ylmethanol (5 g, 49.4 mmol) and triethylamine (17 mL, 118.6 mmol) in DCM (200 mL) was added methanesulfonyl chloride (9.18 mL, 118.6 mmol) dropwise. The mixture was stirred at room temperature for 2 h under nitrogen atmosphere. The mixture was quenched with saturated sodium hydrogen carbonate solution (30 mL) and extracted with DCM (50 mL × 2). The combined organic phases were washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (DCM/MeOH (v/v) = 20/1) to give the title compound as a yellow solid (11.3 g, 89.0%).

Step 2) 2-(6-((2',6'-dimethyl-4'-(((*S*)-1-(methylsulfonyl)pyrrolidin-3-yl)methoxy)-[1,1'-biphenyl]-3-yl) methoxy)-2,3-dihydrobenzofuran-3-yl)acetate

[00166] A mixture of (*S*)-(1-(methylsulfonyl)pyrrolidin-3-yl)methyl methanesulfonate (739 mg, 2.87 mmol), methyl 2-(6-((4'-hydroxy-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydro benzofuran -3-yl)acetate

(300 mg, 0.72 mmol) and potassium carbonate (396 mg, 2.87 mmol) in DMF (5 mL) was heated to 100 °C overnight. The reaction mixture was cooled to room temperature, and partitioned between EtOAc (10 mL) and water (10 mL). The organic phase was washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PET/EtOAc (v/v) = 2/1) to give the title compound as a white solid (350 mg, 94.3%).

MS (ESI, pos. Ion) *m/z*: 580.3 $[M+H]^+$.

Step 3) 2-(6-((2',6'-dimethyl-4'-(((*S*)-1-(methylsulfonyl)pyrrolidin-3-yl)methoxy)-[1,1'-biphenyl]-3-yl) methoxy)-2,3-dihydrobenzofuran-3-yl)acetic acid

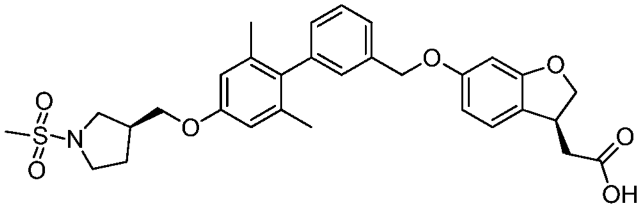
[00167] To a solution of methyl 2-(6-((2',6'-dimethyl-4'-(((*S*)-1-(methylsulfonyl)pyrrolidin-3-yl)methoxy) -[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetate (350 mg, 0.6 mmol) in tetrahydrofuran (6 mL) was added aqueous lithium hydroxide solution (6 mL, 1 M). The mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with water (10 mL), acidifed with hydrochloric acid (10 mL, 1 M), and extracted with EtOAc (20 mL × 2). The combined organic phases were washed with brine (5 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give the title compound as a white solid (323 mg, 94.6%).

MS (ESI, pos. Ion) *m/z*: 566.3 $[M+H]^+$; and

^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.51 – 7.36 (m, 2H), 7.19 (s, 1H), 7.08 (t, *J* = 7.9 Hz, 2H), 6.67 (s, 2H), 6.58 – 6.44 (m, 2H), 5.08 (s, 2H), 4.78 (t, *J* = 9.0 Hz, 1H), 4.30 (dd, *J* = 9.0, 6.2 Hz, 1H), 4.00 (ddd, *J* = 25.4, 12.7, 7.5 Hz, 3H), 3.88 – 3.77 (m, 1H), 3.62 (dd, *J* = 9.7, 7.9 Hz, 1H), 3.56 – 3.47 (m, 1H), 3.42 (dd, *J* = 17.0, 7.5 Hz, 1H), 3.31 (dd, *J* = 9.9, 6.7 Hz, 1H), 2.90 (s, 3H), 2.86 – 2.77 (m, 2H), 2.63 (dd, *J* = 16.8, 9.3 Hz, 1H), 2.20 (dt, *J* = 12.2, 6.1 Hz, 1H), 2.01 (s, 6H).

Example 9

2-((*S*)-6-((2',6'-Dimethyl-4'-(((*S*)-1-(methylsulfonyl)pyrrolidin-3-yl)methoxy)-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



Step 1) (*S*)-2',6'-dimethyl-4'-((1-(methylsulfonyl)pyrrolidin-3-yl)methoxy)-[1,1'-biphenyl] -3-carbaldehyde

[00168] A mixture of (*S*)-(1-(methylsulfonyl)pyrrolidin-3-yl)methyl methanesulfonate (6.8 g, 26.5 mmol), 4'-hydroxy-2',6'-dimethyl-[1,1'-biphenyl]-3-carbaldehyde (1.5 g, 6.63 mmol) and potassium carbonate (3.66 g, 26.5 mmol) in DMF (15 mL) was heated to 100 °C overnight. The reaction mixture was cooled to room temperature, and partitioned between EtOAc (15 mL) and water (15 mL). The organic phase was washed with brine (15 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PET/EtOAc (v/v) = 2/1) to give the title compound as yellow oil (2.0 g, 78.0%).

^1H NMR (600 MHz, $CDCl_3$): δ 10.07 (s, 1H), 7.88 (d, *J* = 7.7 Hz, 1H), 7.68 (s, 1H), 7.61 (t, *J* = 7.6 Hz, 1H), 7.46 – 7.40 (m, 1H), 6.68 (s, 2H), 4.04 (dd, *J* = 9.2, 5.9 Hz, 1H), 3.96 (dd, *J* = 9.2, 7.1 Hz, 1H), 3.63 (dd, *J* = 10.1, 7.6 Hz, 1H), 3.56 – 3.52 (m, 1H), 3.40 – 3.38 (m, 1H), 3.32 (dd, *J* = 10.1, 6.6 Hz, 1H), 2.90 (s, 3H), 2.82 (dt, *J* = 13.8, 6.9 Hz, 1H), 2.25 – 2.19 (m, 1H), 2.01 (s, 6H), 1.96 – 1.90 (m, 1H).

Step 2) (*S*)-(2',6'-dimethyl-4'-((1-(methylsulfonyl)pyrrolidin-3-yl)methoxy)-[1,1'-biphenyl] -3-yl)methanol

[00169] To a solution of (*S*)-2',6'-dimethyl-4'-((1-(methylsulfonyl)pyrrolidin-3-yl)methoxy)-[1,1'-biphenyl]-3-carbaldehyde (2.0 g, 5.16 mmol) in THF (20 mL) and MeOH (10 mL) was added sodium borohydride (206 mg, 5.42 mmol) portions at 0 °C. The mixture was stirred at 0 °C overnight. After removing of the solvent, water (20 mL) was added, and the mixture was extracted with EtOAc (20 mL × 2). The combined organic phases were washed with brine (30 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PET/EtOAc (v/v) = 1/1) to give the title compound as a white solid (1.7 g, 84.5%).

Step 3) methyl 2-((*S*)-6-((2',6'-dimethyl-4'-(((*S*)-1-(methylsulfonyl)pyrrolidin-3-yl)methoxy)-[1,1'-biphenyl] -3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetate

[00170] To a solution of (*S*)-(2',6'-dimethyl-4'-((1-(methylsulfonyl)pyrrolidin-3-yl)methoxy)-[1,1'-biphenyl]-3-yl)methanol (280 mg, 0.72 mmol) and (*S*)-methyl 2-(6-hydroxy-2,3-dihydrobenzofuran-3-yl)acetate (150 mg, 0.72 mmol) in toluene (10 mL) were added tributylphosphine (233 mg, 1.15 mmol) and 1,1'-(azodicarbonyl)-dipiperidine (290 mg, 1.15 mmol). The resulting mixture was stirred at room temperature for 1.5 h under nitrogen atmosphere. The reaction mixture was quenched with water (20 mL) and extracted with EtOAc (40 mL × 2). The combined organic phases were washed with brine (5 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PET/EtOAc (v/v) = 2/1) to give the title compound as a white solid (300 mg, 72%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.47 – 7.37 (m, 2H), 7.18 (s, 1H), 7.09 (d, *J* = 7.4 Hz, 1H), 7.04 (d, *J* = 8.2 Hz, 1H), 6.66 (s, 2H), 6.53 – 6.45 (m, 2H), 5.08 (s, 2H), 4.77 (t, *J* = 9.0 Hz, 1H), 4.28 (dd, *J* = 9.2, 6.1 Hz, 1H), 4.03 (dd, *J* = 9.2, 5.9 Hz, 1H), 3.95 (dd, *J* = 9.2, 7.0 Hz, 1H), 3.82 (ddd, *J* = 14.7, 9.0, 5.8 Hz, 1H), 3.74 (s, 3H), 3.63 (dd, *J* = 10.0, 7.6 Hz, 1H), 3.53 (ddd, *J* = 9.6, 8.1, 5.1 Hz, 1H), 3.42 (dt, *J* = 9.8, 7.5 Hz, 1H), 3.31 (dd, *J* = 10.1, 6.7 Hz, 1H), 2.89 (s, 3H), 2.85 – 2.73 (m, 2H), 2.58 (dd, *J* = 16.4, 9.3 Hz, 1H), 2.24 – 2.17 (m, 1H), 2.01 (s, 6H), 1.96 – 1.90 (m, 1H).

Step 4) 2-((*S*)-6-((2',6'-dimethyl-4'-(((*S*)-1-(methylsulfonyl)pyrrolidin-3-yl)methoxy)-[1,1'-biphenyl]-3-yl) methoxy)-2,3-dihydrobenzofuran-3-yl)acetic acid

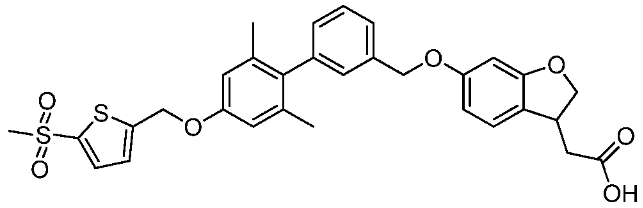
[00171] To a solution of methyl 2-((*S*)-6-((2',6'-dimethyl-4'-(((*S*)-1-(methylsulfonyl)pyrrolidin-3-yl)methoxy) biphenyl-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetate (300 mg, 0.52 mmol) in tetrahydrofuran (5.2 mL) was added aqueous lithium hydroxide solution (5.2 mL, 1 M). The mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with water (10 mL), acidifed with hydrochloric acid (10 mL, 1 M), and extracted with EtOAc (20 mL × 2). The combined organic phases were washed with brine (3 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give the title compound as a white solid (280 mg, 95.9%).

MS (ESI, pos. Ion) *m/z*: 566.1 $[M+H]^+$; and

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.48 – 7.36 (m, 2H), 7.18 (s, 1H), 7.08 (dd, *J* = 14.1, 7.8 Hz, 2H), 6.66 (s, 2H), 6.55 – 6.45 (m, 2H), 5.08 (s, 2H), 4.78 (t, *J* = 9.0 Hz, 1H), 4.30 (dd, *J* = 9.2, 6.1 Hz, 1H), 4.04 – 3.92 (m, 3H), 3.87 – 3.79 (m, 1H), 3.62 (dd, *J* = 10.0, 7.7 Hz, 1H), 3.56 – 3.48 (m, 1H), 3.46 – 3.38 (m, 1H), 3.30 (dd, *J* = 10.1, 6.7 Hz, 1H), 2.89 (s, 3H), 2.85 – 2.78 (m, 2H), 2.63 (dd, *J* = 16.8, 9.3 Hz, 1H), 2.01 (s, 6H), 1.96 – 1.90 (m, 1H).

Example 10

2-(6-((2',6'-Dimethyl-4'-((5-(methylsulfonyl)thiophen-2-yl)methoxy)-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



Step 1) (5-(methylsulfonyl)thiophen-2-yl)methanol

[00172] A mixture of (5-bromothiophen-2-yl)methanol (1 g, 5.18 mmol), cuprous iodide (99 mg, 0.52 mmol), Sodium methanesulphinate (794 mg, 7.77 mmol) and *L*-proline sodium salt (142 g, 1.03 mmol) in DMSO (10 mL) was heated to 95 °C for 24 h under nitrogen atmosphere. The reaction mixture was cooled to room temperature, and partitioned between EtOAc (40 mL) and water (20 mL). The organic phase was washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PET/EtOAc (v/v) = 1/1) to give the title compound as yellow oil (419 mg, 42.1%).

Step 2) 2-(chloromethyl)-5-(methylsulfonyl)thiophene

[00173] To a solution of (5-(methylsulfonyl)thiophen-2-yl)methanol (419 mg, 2.18 mmol) in DMF (5 mL) was added phosphorus oxychloride (0.25 mL, 2.70 mmol) dropwise. The mixture was stirred at room temperature for 5 h. The mixture was diluted with water (20 mL) and extracted with EtOAc (20 mL × 2). The combined organic phases were washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PET/EtOAc (v/v) = 6/1) to give the title compound as a yellow solid (438 mg, 95.4%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 (d, *J* = 3.7 Hz, 1H), 7.13 (d, *J* = 3.7 Hz, 1H), 4.79 (s, 2H), 3.20 (s, 3H).

Step 3) methyl 2-(6-((2',6'-dimethyl-4'-((5-(methylsulfonyl)thio-phen-2-yl)methoxy)-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetate

[00174] A mixture of 2-(chloromethyl)-5-(methylsulfonyl)thiophene (76 mg, 0.36 mmol), methyl 2-(6-((4'-hydroxy-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)meth-oxy)-2,3-dihydrobenzofuran-3-yl)acetate (100 mg, 0.24 mmol) and potassium phosphate (82 mg, 0.39 mmol) in DMF (5 mL) was stirred at 60 °C overnight under nitrogen atmosphere. The reaction mixture was quenched with water (5 mL) and extracted with EtOAc (20 mL

× 2). The combined organic phases were washed with brine (5 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PET / EtOAc (v/v) = 2/1) to give the title compound as a yellow solid (139 mg, 98.2%).

MS (ESI, pos. Ion) *m/z*: 593.1 $[M+H]^+$.

Step 4) 2-(6-((2',6'-dimethyl-4'-((5-(methylsulfonyl)thiophen-2-yl)methoxy)-[1,1'-biphenyl]-3-yl) methoxy)- 2,3-dihydrobenzofuran-3-yl)acetic acid

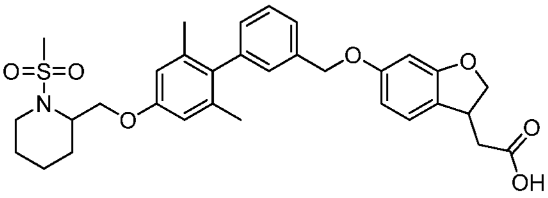
[00175] To a solution of methyl 2-(6-((2',6'-dimethyl-4'-((5-(methylsulfonyl)thiophen-2-yl)methoxy)-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetate (139 mg, 0.23 mmol) in tetrahydrofuran (2.4 mL) was added aqueous lithium hydroxide solution (2.4 mL, 1 M). The mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with water (10 mL), acidifed with hydrochloric acid (5 mL, 1 M), and extracted with EtOAc (20 mL × 2). The combined organic phases were washed with brine (3 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give the title compound as a white solid (90 mg, 66.3%).

MS (ESI, pos. Ion) *m/z*: 579.2 $[M+H]^+$; and

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.66 (d, J = 3.8 Hz, 1H), 7.45 (t, J = 7.5 Hz, 1H), 7.41 (d, J = 7.7 Hz, 1H), 7.19 (s, 1H), 7.15 (d, J = 3.7 Hz, 1H), 7.09 (dd, J = 16.5, 7.8 Hz, 2H), 6.75 (s, 2H), 6.53 – 6.47 (m, 2H), 5.29 (s, 2H), 5.08 (s, 2H), 4.78 (t, J = 9.0 Hz, 1H), 4.31 (dd, J = 9.2, 6.1 Hz, 1H), 3.83 (ddd, J = 14.6, 9.1, 5.7 Hz, 1H), 3.22 (s, 3H), 2.83 (dd, J = 16.8, 5.3 Hz, 1H), 2.64 (dd, J = 16.8, 9.3 Hz, 1H), 2.02 (s, 6H).

Example 11

2-(6-((2',6'-Dimethyl-4'-((1-(methylsulfonyl)piperidin-2-yl)methoxy)-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



Step 1) (1-(methylsulfonyl)piperidin-2-yl)methyl methanesulfonate

[00176] To an ice-cooled solution of 2-piperidylmethanol (4 g, 34.7 mmol) and triethylamine (12.0 mL, 85.0 mmol) in DCM (100 mL) was added methanesulfonyl chloride (7.0 mL, 88.6 mmol) dropwise. The mixture was stirred at room temperature for 1 h under nitrogen atmosphere. The mixture was quenched with saturated sodium hydrogen carbonate solution (50 mL) and extracted with DCM (50 mL × 2). The combined organic phases were washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (DCM/MeOH (v/v) = 60/1) to give the title compound as a yellow solid (7.0 g, 74.3%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 4.52 (dd, J = 10.3, 8.9 Hz, 1H), 4.36 (td, J = 8.7, 4.2 Hz, 1H), 4.21 (dd, J = 10.4, 5.8 Hz, 1H), 3.77 (d, J = 14.3 Hz, 1H), 3.11 – 3.04 (m, 4H), 2.95 (s, 3H), 1.82 – 1.68 (m, 4H), 1.61 – 1.46 (m, 2H).

Step 2) methyl 2-(6-((2',6'-dimethyl-4'-((1-(methylsulfonyl)piperidin-2-yl)methoxy)-[1,1'-biphenyl]-3-yl) methoxy)-2,3-dihydrobenzofuran-3-yl)acetate

[00177] A mixture of (1-(methylsulfonyl)piperidin-2-yl)methyl methanesulfonate (389 mg, 1.43 mmol), methyl 2-(6-((4'-hydroxy-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran -3-yl)acetate (400 mg, 0.96 mmol) and potassium carbonate (400 mg, 2.89 mmol) in DMF (10 mL) was heated to 80 °C overnight. The reaction mixture was cooled to room temperature, and partitioned between EtOAc (10 mL) and water (10 mL). The organic phase was washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PET/EtOAc (v/v) = 1/3) to give the title compound as yellow oil (220 mg, 38.8%).

Step 3) 2-(6-((2',6'-dimethyl-4'-((1-(methylsulfonyl)piperidin-2-yl)methoxy)-[1,1'-biphenyl]-3-yl)methoxy) -2,3-dihydrobenzofuran-3-yl)acetic acid

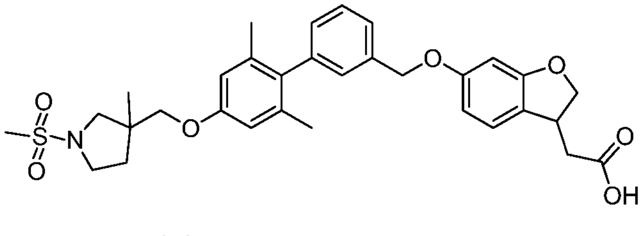
[00178] To a solution of methyl 2-(6-((2',6'-dimethyl-4'-((1-(methylsulfonyl)piperidin-2-yl)methoxy)-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetate (220 mg, 0.37 mmol) in tetrahydrofuran (4 mL) was added aqueous lithium hydroxide solution (4 mL, 1 M) The mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with water (10 mL), acidifed with hydrochloric acid (10 mL, 1 M), and extracted with EtOAc (20 mL × 2). The combined organic phases were washed with brine (5 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give the title compound as a white solid (160 mg, 79.1%).

MS (ESI, pos. Ion) *m/z*: 580.0 $[M+H]^+$; and

^1H NMR (600 MHz, $CDCl_3$): δ 7.47 – 7.38 (m, 2H), 7.18 (s, 1H), 7.08 (dd, *J* = 14.2, 7.8 Hz, 2H), 6.68 (s, 2H), 6.54 – 6.46 (m, 2H), 5.08 (s, 2H), 4.78 (t, *J* = 9.0 Hz, 1H), 4.52 – 4.46 (m, 1H), 4.36 – 4.27 (m, 2H), 4.01 (dd, *J* = 9.8, 5.6 Hz, 1H), 3.82 (dd, *J* = 13.3, 10.3 Hz, 2H), 3.13 – 3.06 (m, 1H), 3.03 (s, 3H), 2.82 (dd, *J* = 16.8, 5.3 Hz, 1H), 2.63 (dd, *J* = 16.8, 9.4 Hz, 1H), 2.02 (s, 6H), 1.92 (d, *J* = 13.4 Hz, 1H), 1.88 – 1.81 (m, 1H), 1.75 (t, *J* = 11.4 Hz, 2H), 1.63 (dd, *J* = 15.6, 6.2 Hz, 2H).

Example 12

2-(6-((2',6'-Dimethyl-4'-((3-methyl-1-(methylsulfonyl)pyrrolidin-3-yl)methoxy)-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



Step 1) methyl 1-benzyl-3-methylpyrrolidine-3-carboxylate

[00179] To an ice-cooled solution of *N*-benzyl-1-methoxy-*N*-((trimethylsilyl)methyl) methanamine (10.8 mL, 44.9 mmol) and methyl methacrylate (4.78 mL, 44.8 mmol) in dry DCM (50 mL) was slowly added a solution of trifluoroacetic acid (0.33 mL, 4.4 mmol) in dry DCM (4 mL). The mixture was stirred at room temperature for 4 h under nitrogen atmosphere. The mixture was quenched with saturated sodium hydrogen carbonate

solution (20 mL) and extracted with DCM (50 mL × 2). The combined organic phases were washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PET/EtOAc (v/v) = 5/1) to give the title compound as colorless liquid (8.2 g, 78.0%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 – 7.24 (m, 5H), 3.71 (s, 3H), 3.63 (s, 2H), 2.97 (d, J = 9.4 Hz, 1H), 2.76 – 2.58 (m, 2H), 2.49 – 2.36 (m, 2H), 1.74 – 1.62 (m, 1H), 1.37 (s, 3H).

Step 2) (1-benzyl-3-methylpyrrolidin-3-yl)methanol

[00180] To an ice-cooled suspension of lithium aluminium hydride (2.0 g, 52.6 mmol) in tetrahydrofuran (60 mL) was added a solution of methyl 1-benzyl-3-methylpyrrolidine-3-carboxylate (8.2 g, 35 mmol) dropwise in tetrahydrofuran (20 mL). The resulting mixture was stirred at room temperature overnight. And then water (2 mL) and 10% aqueous sodium hydroxide solution (20 mL) were slowly added to the mixture at 0 °C, and then the mixture was filtered. The filter cake was washed with tetrahydrofuran (20 mL) and the combined filtrates were concentrated *in vacuo*. The residue was diluted with water (10 mL), and extracted with EtOAc (20 mL × 2). The combined organic phases were washed with brine (5 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PET/EtOAc (v/v) = 1/1) to give the title compound as yellow oil (5.5 g, 76.0%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 – 7.22 (m, 5H), 3.56 (dd, J = 11.3, 6.9 Hz, 3H), 3.36 (d, J = 9.6 Hz, 1H), 3.03 (td, J = 9.0, 2.9 Hz, 1H), 2.85 (d, J = 9.0 Hz, 1H), 2.31 (dd, J = 17.7, 9.0 Hz, 1H), 2.15 (d, J = 9.0 Hz, 1H), 2.10 – 2.01 (m, 1H), 1.69 – 1.57 (m, 1H), 1.02 (s, 3H).

Step 3) (3-methylpyrrolidin-3-yl)methanol

[00181] A solution of (1-benzyl-3-methyl-pyrrolidin-3-yl)methanol (5.5 g, 27.0 mmol) and 10% Palladium on carbon (0.6 g) in methanol (150 mL) was stirred at room temperature under hydrogen atmosphere overnight. The reaction mixture was filtered and the filtrate was concentrated *in vacuo* to give the title compound as light yellow oil (3.0 g, 97.0%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.46 (dd, J = 16.0, 10.0 Hz, 2H), 3.08 – 2.98 (m, 1H), 2.98 – 2.89 (m, 2H), 2.56 (d, J = 10.5 Hz, 1H), 1.82 – 1.69 (m, 1H), 1.56 – 1.44 (m, 1H), 1.06 (s, 3H).

Step 4) (3-methyl-1-(methylsulfonyl)pyrrolidin-3-yl) methyl methanesulfonate

[00182] To an ice-cooled solution of (3-methylpyrrolidin-3-yl)methanol (1.0 g, 8.68 mmol) and triethylamine (2.9 mL, 21.0 mmol) in DCM (60 mL) was added methanesulfonyl chloride (1.65 mL, 20.9 mmol) dropwise. The mixture was stirred at room temperature for 1 h under nitrogen atmosphere. The mixture was quenched with saturated sodium hydrogen carbonate solution (30 mL) and extracted with DCM (50 mL × 2). The combined organic phases were washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (DCM/MeOH (v/v) = 30/1) to give the title compound as yellow oil (1.75 g, 74.3%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.10 (s, 2H), 3.48 (t, J = 7.2 Hz, 2H), 3.39 (d, J = 10.1 Hz, 1H), 3.18 – 3.02 (m, 4H), 2.89 (s, 3H), 2.01 (dt, J = 13.8, 8.9 Hz, 1H), 1.88 – 1.75 (m, 1H), 1.25 (s, 3H).

Step 5) methyl 2-(6-((2',6'-dimethyl-4'-((3-methyl-1-(methylsulfonyl)pyrrolidin-3-yl)methoxy)-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetate

[00183] A solution of (3-methyl-1-(methylsulfonyl)pyrrolidin-3-yl) methyl methanesulfonate (518 mg, 1.91 mmol), methyl 2-(6-((4'-hydroxy-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)-acetate (400 mg, 0.96 mmol) and potassium carbonate (400 mg, 2.89 mmol) in DMF (5 mL) was heated to 80 °C overnight. The reaction mixture was cooled to room temperature, and partitioned between EtOAc (10 mL) and water (10 mL). The organic phase was washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PET / EtOAc (v/v) = 2/1) to give the title compound as yellow oil (171 mg, 30.1%).

MS (ESI, pos. Ion) *m/z*: 594.2 $[M+H]^+$.

Step 6) 2-(6-((2',6'-dimethyl-4'-((3-methyl-1-(methylsulfonyl)pyrrolidin-3-yl)methoxy) -[1,1'-biphenyl] -3-yl) methoxy)-2,3-dihydrobenzofuran-3-yl)acetic acid

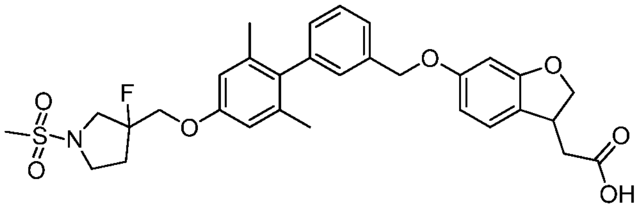
[00184] To a solution of methyl 2-(6-((2',6'-dimethyl-4'-((3-methyl-1-(methylsulfonyl)pyrrolidin-3-yl) methoxy)-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetate (171 mg, 0.29 mmol) in tetrahydrofuran (3 mL) was added aqueous lithium hydroxide solution (3 mL, 1 M). The mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with of water (10 mL), acidifed with hydrochloric acid (10 mL, 1 M), and extracted with EtOAc (20 mL × 2). The combined organic phases were washed with brine (5 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give the title compound as a pale yellow solid (100 mg, 59.9%).

MS (ESI, pos. Ion) *m/z*: 580.3 $[M+H]^+$; and

^1H NMR (600 MHz, $CDCl_3$): δ 7.45 (t, *J* = 7.5 Hz, 1H), 7.40 (d, *J* = 7.6 Hz, 1H), 7.19 (s, 1H), 7.09 (dd, *J* = 14.2, 7.8 Hz, 2H), 6.68 (s, 2H), 6.56 – 6.46 (m, 2H), 5.09 (s, 2H), 4.78 (t, *J* = 9.0 Hz, 1H), 4.31 (dd, *J* = 9.1, 6.1 Hz, 1H), 3.86 (dd, *J* = 21.0, 8.9 Hz, 3H), 3.56 – 3.46 (m, 3H), 3.20 (d, *J* = 9.9 Hz, 1H), 2.90 (s, 3H), 2.83 (dd, *J* = 16.8, 5.2 Hz, 1H), 2.64 (dd, *J* = 16.8, 9.4 Hz, 1H), 2.19 – 2.11 (m, 1H), 2.02 (s, 6H), 1.87 – 1.79 (m, 1H), 1.30 (s, 3H).

Example 13

2-(6-((4'-((3-Fluoro-1-(methylsulfonyl)pyrrolidin-3-yl)methoxy)-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



Step 1) methyl 1-benzyl-3-fluoropyrrolidine-3-carboxylate

[00185] To a solution of *N*-benzyl-1-methoxy-*N*-((trimethylsilyl)methyl) methanamine (2.6 mL, 10.0 mmol) and methyl 2-fluoroacrylate (0.9 mL, 10.0 mmol) in dry DCM (30 mL) in an ice bath was slowly added a

solution of trifluoroacetic acid (0.1 mL, 1.0 mmol) in dry DCM (2 mL). The mixture was stirred at room temperature for 4 h under nitrogen atmosphere. The mixture was quenched with saturated sodium hydrogen carbonate solution (20 mL) and extracted with DCM (30 mL × 2). The combined organic phases were washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PET / EtOAc (v/v) = 20/1) to give the title compound as colorless liquid (1.8 g, 80.0%).

MS (ESI, pos. Ion) *m/z*: 238.2 $[M+H]^+$.

Step 2) (1-benzyl-3-fluoropyrrolidin-3-yl)methanol

[00186] To an ice-cooled suspension of lithium aluminium hydride (2.14 g, 56.3 mmol) in tetrahydrofuran (60 mL) was added a solution of methyl 1-benzyl-3-fluoro pyrrolidine-3-carboxylate (8.91 g, 37.5 mmol) dropwise in tetrahydrofuran (20 mL). The mixture was stirred at room temperature overnight. Then water (2 mL) and 10% aqueous sodium hydroxide solution (20 mL) were slowly added to the mixture at 0 °C, and then the resulting mixture was filtered. The filter cake was washed with tetrahydrofuran (20 mL) and the combined filtrates were concentrated *in vacuo*. The residue was diluted with water (10 mL), and extracted with EtOAc (20 mL × 2). The combined organic phases were washed with brine (5 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PET / EtOAc (v/v) = 3/1) to give the title compound as yellow oil (7.0 g, 89.1%).

Step 3) (3-fluoropyrrolidin-3-yl)methanol

[00187] To a solution of (1-benzyl-3-fluoropyrrolidin-3-yl)methanol (5.62 g, 26.9 mmol) in methanol (50 mL) was added 10% Palladium on carbon (1.0 g). The mixture was stirred at room temperature under hydrogen atmosphere overnight. The reaction mixture was filtered and the filtrate was concentrated *in vacuo* to give the title compound as light yellow oil (2.78 g, 86.7%).

Step 4) (3-fluoro-1-(methylsulfonyl)pyrrolidin-3-yl)methyl methanesulfonate

[00188] To an ice-cooled solution of (3-fluoropyrrolidin-3-yl)methanol (500 mg, 4.2 mmol) and triethylamine (1.4 mL, 10.0 mmol) in DCM (60 mL) was added methanesulfonyl chloride (0.8 mL, 10.0 mmol) dropwise. The mixture was stirred at room temperature for 1 h under nitrogen atmosphere. The mixture was quenched with saturated sodium hydrogen carbonate solution (15 mL) and extracted with DCM (25 mL × 2). The combined organic phases were washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (DCM/MeOH (v/v) = 30/1) to give the title compound as yellow oil (880 mg, 76.2%).

^{1}H NMR (400 MHz, DMSO-d_6): δ 4.58 (s, 1H), 4.53 (s, 1H), 3.57 (s, 1H), 3.51 (t, J = 9.2 Hz, 2H), 3.46 – 3.39 (m, 1H), 3.26 (s, 3H), 2.95 (s, 3H), 2.17 (ddd, J = 24.2, 15.4, 6.2 Hz, 2H).

Step 5) methyl 2-(6-((4'-((3-fluoro-1-(methylsulfonyl)pyrrolidin-3-yl)methoxy)-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetate

[00189] A mixture of (3-fluoro-1-(methylsulfonyl)pyrrolidin-3-yl)methyl methanesulfonate (160 mg, 0.58

mmol), methyl 2-(6-((4'-hydroxy-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl) acetate (200 mg, 0.48 mmol) and potassium carbonate (200 mg, 1.45 mmol) in DMF (10 mL) was heated to 80 °C overnight. The reaction mixture was cooled to room temperature, and partitioned between EtOAc (10 mL) and water (10 mL). The organic phase was washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PET/EtOAc (v/v) = 2/1) to give the title compound as yellow oil (130 mg, 45.5%).

MS (ESI, pos. Ion) *m/z*: 598.2 $[M+H]^+$.

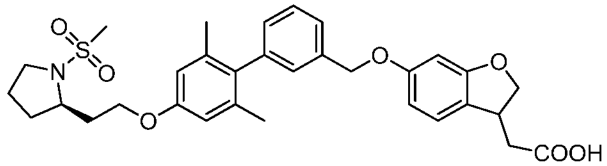
Step 6) 2-(6-((4'-((3-fluoro-1-(methylsulfonyl)pyrrolidin-3-yl)methoxy)-2',6'-dimethyl-[1,1'-biphenyl]-3-yl) methoxy)-2,3-dihydrobenzofuran-3-yl)acetic acid

[00190] To a solution of methyl 2-(6-((4'-((3-fluoro-1-(methylsulfonyl)pyrrolidin-3-yl)methoxy)-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetate (260 mg, 0.44 mmol) in tetrahydrofuran (4 mL) was added aqueous lithium hydroxide solution (4 mL, 1 M). The mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with water (10 mL), acidifed with hydrochloric acid (10 mL, 1 M), and extracted with EtOAc (20 mL × 2). The combined organic phases were washed with brine (5 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give the title compound as a white solid (90 mg, 35.5%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.49 – 7.37 (m, 2H), 7.18 (s, 1H), 7.08 (dd, J = 11.0, 8.0 Hz, 2H), 6.69 (s, 2H), 6.57 – 6.41 (m, 2H), 5.08 (s, 2H), 4.78 (t, J = 9.0 Hz, 1H), 4.29 (ddd, J = 23.9, 11.4, 8.2 Hz, 2H), 4.22 – 4.12 (m, 1H), 3.83 (ddd, J = 14.6, 9.0, 5.8 Hz, 1H), 3.79 – 3.68 (m, 3H), 3.56 (td, J = 10.1, 6.8 Hz, 1H), 2.93 (s, 3H), 2.83 (dd, J = 16.8, 5.3 Hz, 1H), 2.64 (dd, J = 16.8, 9.3 Hz, 1H), 2.42 – 2.24 (m, 2H), 2.02 (s, 6H).

Example 14

2-(6-((2',6'-Dimethyl-4'-(2-((*R*)-1-(methylsulfonyl)pyrrolidin-2-yl)ethoxy)-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



Step 1) (*R*)-1-((benzyloxy)carbonyl)pyrrolidine-2-carboxylic acid

[00191] To an ice-cooled solution of (*R*)-pyrrolidine-2-carboxylic acid (4.0 g, 34.7 mmol) in toluene (50 mL) was added aqueous sodium hydroxide solution (50 mL, 2 M) followed by a solution of benzyl carbonochloridate (10.0 mL, 71.1 mmol) in toluene (50 mL). The mixture was stirred at room temperature for 1 h under nitrogen atmosphere. The mixture was quenched with water (50 mL). The aquous layer was acidified with hydrochloric acid (100 mL, 4 M) and extracted with EtOAc (200 mL × 2). The combined organic phases were washed with brine (30 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PET/EtOAc (v/v) = 1/1) to give the title compound as yellow oil (8.66 g, 100%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 (dd, J = 27.0, 13.5 Hz, 5H), 5.20 (dd, J = 22.9, 13.0 Hz, 2H), 4.43 (dd, J = 12.9, 9.9 Hz, 1H), 3.71 – 3.41 (m, 2H), 2.40 – 2.07 (m, 4H), 2.06 – 1.85 (m, 2H).

Step 2) (*R*)-benzyl 2-(2-diazoacetyl)pyrrolidine-1-carboxylate

[00192] To a solution of (*R*)-1-((benzyloxy)carbonyl)pyrrolidine-2- carboxylic acid (2 g, 8.02 mmol) in anhydrous *N,N*-dimethylformamide (0.3 mL) and anhydrous DCM (20 mL) in an ice bath was added oxalyl dichloride (0.92 mL, 11.0 mmol) dropwise under nitrogen atmosphere. The reaction mixture was allowed to warm up to room temperature and stirred for 2 h. The solvent was evaporated under reduced pressure to yield yellow oil. This crude product was immediately dissolved in a mixture of tetrahydrofuran (30 mL) and acetonitrile (30 mL) and cooled to 0 °C under nitrogen atmosphere. Anhydrous triethylamine (1.6 g, 16.04 mmol) and (trimethylsilyl)diazomethane (9 mL,18 mmol, 2.0 M solution in hexane) were added in turn, and the reaction mixture stirred for 5 h at 0 °C. The mixture was quenched with glacial acetic acid and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PET/EtOAc (v/v) = 4/1) to give the title compound as yellow oil (1.54 g, 70.2%).

MS (ESI, pos. Ion) *m/z*: 296.1 $[M+Na]^+$.

Step 3) (*R*)-benzyl 2-(2-methoxy-2-oxoethyl)pyrrolidine-1-carboxylate

[00193] To a solution of (*R*)-benzyl 2-(2-diazoacetyl)pyrrolidine-1-carboxylate (1.54 g, 5.63 mmol) in anhydrous methanol (25 mL) was added the solution of silver benzoate (130 mg, 0.57 mmol) in anhydrous triethylamine (2.3 mL) dropwise. The mixture was stirred at room temperature for 3 h. The reaction mixture was quenched with saturated sodium sulfite solution (50 mL) and filtered. The filtrate was extracted with EtOAc (100 mL × 2). The combined organic phases were washed with brine (30 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PET/EtOAc (v/v) = 5/1) to give the title compound as colorless oil (825 mg, 52.8%).

MS (ESI, pos. Ion) *m/z*: 278.2 $[M+H]^+$.

Step 4) (*R*)-benzyl 2-(2-hydroxyethyl)pyrrolidine-1-carboxylate

[00194] To a solution of (*R*)-benzyl 2-(2-methoxy-2-oxoethyl)pyrrolidine-1-carboxylate (1.9 g, 6.9 mmol) in ethanol (50 mL) was slowly added the solution of sodium borohydride (2.6 g, 68 mmol) in H_2O (20 mL) at room temperature. The mixture was stirred at room temperature overnight and then refluxed for 1 h. After removal of the solvent under reduced pressure, water (10 mL) was added and the mixture was extracted with EtOAc (20 mL × 2). The combined organic phases were washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PET/EtOAc (v/v) = 1/1) to give the title compound as yellow oil (510 mg, 30.0%).

Step 5) (*R*)-2-(pyrrolidin-2-yl)ethanol

[00195] To a solution of (*R*)-benzyl 2-(2-hydroxyethyl)pyrrolidine-1-carboxylate (510 mg, 0.5 mmol) in methanol (10 mL) was added 10% Palladium on carbon (50 mg). The mixture was stirred at room temperature under hydrogen atmosphere overnight. The reaction mixture was filtered and the filtrate was

concentrated *in vacuo* to give the title compound as light yellow oil (230 mg, 97.6%).

^{1}H NMR (600 MHz, CDCl$_3$): δ 3.84 (dd, J = 10.1, 5.1 Hz, 1H), 3.80 – 3.73 (m, 1H), 3.52 – 3.41 (m, 1H), 3.13 – 2.99 (m, 2H), 2.03 – 1.94 (m, 1H), 1.94 – 1.86 (m, 1H), 1.82 – 1.70 (m, 3H), 1.54 (dt, J = 20.5, 8.0 Hz, 1H).

Step 6) (*R*)-2-(1-(methylsulfonyl)pyrrolidin-2-yl)ethyl methanesulfonate

[00196] To a solution of (*R*)-2-(pyrrolidin-2-yl)ethanol (230 mg, 2.0 mmol) and triethylamine (0.67 mL, 4.8 mmol) in DCM (20 mL) in an ice bath was added methanesulfonyl chloride (0.4 mL, 5.0 mmol) dropwise. The mixture was stirred at room temperature for 1 h under nitrogen atmosphere. The mixture was quenched with saturated sodium hydrogen carbonate solution (10 mL) and extracted with DCM (20 mL × 2). The combined organic phases were washed with brine (5 mL), dried over Na$_2$SO$_4$ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (DCM/MeOH (v/v) = 30/1) to give the title compound as yellow oil (350 mg, 64.6%).

Step 7) methyl 2-(6-((2',6'-dimethyl-4'-(2-((*R*)-1-(methylsulfonyl)pyrrolidin-2-yl)ethoxy)-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetate

[00197] A solution of (*R*)-2-(1-(methylsulfonyl)pyrrolidin-2-yl)ethyl methanesulfonate (340 mg, 1.25 mmol), methyl 2-(6-((4'-hydroxy-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3- dihydrobenzofuran-3-yl)acetate (400 mg, 0.96 mmol) and potassium carbonate (400 mg, 2.89 mmol) in DMF (10 mL) was heated to 80 °C overnight. The reaction mixture was cooled to room temperature, and partitioned between EtOAc (10 mL) and water (10 mL). The organic phase was washed with brine (10 mL), dried over Na$_2$SO$_4$ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PET/EtOAc (v/v) = 3/1) to give the title compound as light yellow oil (375 mg, 66.1%).

MS (ESI, pos. Ion) *m/z*: 594.2 [M+H]$^+$.

Step 8) 2-(6-((2',6'-dimethyl-4'-(2-((*R*)-1-(methylsulfonyl)pyrrolidin-2-yl)ethoxy)-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetic acid

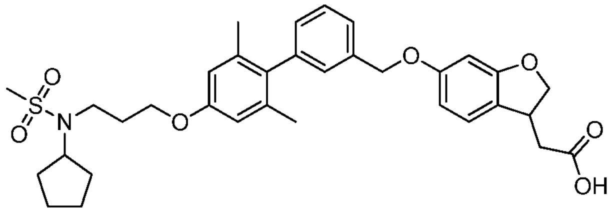
[00198] To a solution of methyl 2-(6-((2',6'-dimethyl-4'-(2-((*R*)-1-(methylsulfonyl)pyrrolidin-2-yl)ethoxy)-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetate (375 mg, 0.63 mmol) in tetrahydrofuran (6 mL) was added aqueous lithium hydroxide solution (6 mL, 1 M). The mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with water (10 mL), acidified with aqueous hydrochloric acid (20 mL, 1 M), and extracted with EtOAc (20 mL × 2). The combined organic phases were washed with brine (5 mL), dried over Na$_2$SO$_4$ and concentrated *in vacuo* to give the title compound as a yellow solid (170 mg, 46.4%).

MS (ESI, pos. Ion) *m/z*: 580.3 [M+H]$^+$; and

^{1}H NMR (600 MHz, CDCl$_3$): δ 7.48 – 7.37 (m, 2H), 7.19 (s, 1H), 7.09 (dd, J = 18.2, 7.8 Hz, 2H), 6.67 (s, 2H), 6.55 – 6.46 (m, 2H), 5.08 (s, 2H), 4.78 (t, J = 9.0 Hz, 1H), 4.31 (dd, J = 9.1, 6.1 Hz, 1H), 4.10 (t, J = 6.1 Hz, 2H), 3.96 (dt, J = 8.0, 6.4 Hz, 1H), 3.83 (ddd, J = 14.5, 9.1, 5.8 Hz, 1H), 3.46 (dt, J = 11.8, 6.0 Hz, 1H), 3.39 (dt, J = 10.4, 7.0 Hz, 1H), 2.90 – 2.78 (m, 4H), 2.63 (dd, J = 16.8, 9.4 Hz, 1H), 2.30 (dt, J = 19.8, 5.8 Hz, 1H), 2.10 (dt, J = 12.9, 7.9 Hz, 1H), 2.05 – 1.92 (m, 10H).

Example 15

2-(6-((4'-(3-(*N*-Cyclopentylmethylsulfonamido)propoxy)-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



Step 1) *N*-(3-(benzyloxy)propyl)cyclopentanamine

[00199] To a solution of cyclopentanamine (0.4 mL, 4.1 mmol) and potassium carbonate (553 mg, 4.1 mmol) in acetonitrile (15 mL) was added ((3-bromopropoxy)methyl) benzene (0.36 mL, 2.0 mmol). The mixture was stirred at 60 °C overnight. The mixture was cooled to rt and concentrated *in vacuo* to give the title compound as light yellow oil (467 mg, 98.0%).

Step 2) *N*-(3-(benzyloxy)propyl)-*N*-cyclopentylmethanesulfonamide

[00200] To an ice-cooled solution of *N*-(3-(benzyloxy)propyl)cyclopentanamine (467 mg, 2.0 mmol) and triethylamine (1.1 mL, 7.8 mmol) in DCM (20 mL) was added methanesulfonyl chloride (0.62 mL, 8.0 mmol) dropwise. The mixture was stirred at room temperature for 1 h under nitrogen atmosphere. The mixture was quenched with saturated sodium hydrogen carbonate solution (15 mL) and extracted with DCM (45 mL × 2). The combined organic phases were washed with brine (5 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PET/EtOAc (v/v) = 4/1) to give the title compound as light yellow oil (477 mg, 76.6%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.36 – 7.26 (m, 5H), 4.48 (s, 2H), 4.16 – 4.07 (m, 1H), 3.51 (t, J = 5.9 Hz,2H), 3.16 (dd, J = 8.5, 6.8 Hz, 2H), 2.81 (s, 3H), 2.01 – 1.94 (m, 2H), 1.87 (t, J = 10.0 Hz, 2H), 1.66 (dd, J= 8.2, 5.9 Hz, 2H), 1.59 – 1.48 (m, 4H).

Step 3) *N*-cyclopentyl-*N*-(3-hydroxypropyl)methanesulfonamide

[00201] To a solution of *N*-(3-(benzyloxy)propyl)-*N*-cyclopentylmethanesulfonamide (477 mg, 1.5 mmol) in methanol (20 mL) was added 10% Palladium on carbon (85 mg). The mixture was stirred at room temperature under hydrogen atmosphere overnight. The reaction mixture was filtered and the filtrate was concentrated *in vacuo* to give the title compound as light yellow oil (333 mg, 98.3%).

Step 4) 3-(*N*-cyclopentylmethylsulfonamido)propyl methanesulfonate

[00202] To a solution of *N*-cyclopentyl-*N*-(3-hydroxypropyl)methane sulfonamide (333 mg, 1.5 mmol) and triethylamine (0.3 mL, 2.3 mmol) in DCM (10 mL) in an ice bath was added methanesulfonyl chloride (0.18 mL, 2.3 mmol) dropwise. The mixture was stirred at room temperature for 1 h under nitrogen atmosphere. The

mixture was quenched with saturated sodium hydrogen carbonate solution (8 mL) and extracted with DCM (20 mL × 2). The combined organic phases were washed with brine (5 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (DCM/MeOH (v/v) = 50/1) to give the title compound as light yellow oil (239 mg, 53.1%).

Step 5) methyl 2-(6-((4'-(3-(*N*-cyclopentylmethylsulfonamido)propoxy)-2',6'-dimethyl-[1,1'-biphenyl]-3-yl) methoxy)-2,3-dihydrobenzofuran-3-yl)acetate

[00203] A solution of 3-(*N*-cyclopentylmethylsulfonamido)propyl methanesulfonate (259 mg, 0.9 mmol), methyl 2-(6-((4'-hydroxy-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3- dihydrobenzofuran-3-yl)acetic acid (241 mg, 0.6 mmol) and potassium carbonate (239 mg, 1.7 mmol) in DMF (5 mL) was heated to 80 °C overnight. The reaction mixture was cooled to room temperature, and partitioned between EtOAc (10 mL) and water (10 mL). The organic phase was washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (DCM/MeOH (v/v) = 40/1) to give the title compound as light yellow oil (260 mg, 72.5%).

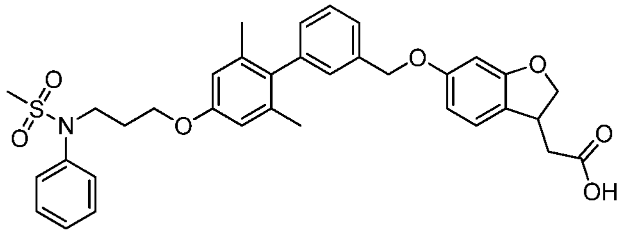
Step 6) 2-(6-((4'-(3-(*N*-cyclopentylmethylsulfonamido)propoxy)-2',6'-dimethyl-[1,1'-biphenyl]-3-yl) methoxy)-2,3-dihydrobenzofuran-3-yl)acetic acid

[00204] To a solution of methyl 2-(6-((4'-(3-(*N*-cyclopentylmethylsulfonamido)propoxy)-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetate (260 mg, 0.42 mmol) in tetrahydrofuran (4.2 mL) was added aqueous lithium hydroxide solution (4.2 mL, 1 M). The mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with of water (10 mL), acidifed with aqueous hydrochloric acid (10 mL, 1 M), and extracted with EtOAc (20 mL × 2). The combined organic phases were washed with brine (3 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give the title compound as a white solid (140 mg, 55.1%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.46 – 7.38 (m, 2H), 7.18 (s, 1H), 7.09 (dd, *J* = 16.5, 7.8 Hz, 2H), 6.66 (s, 2H), 6.54 – 6.44 (m, 2H), 5.08 (s, 2H), 4.78 (t, *J* = 9.0 Hz, 1H), 4.31 (dd, *J* = 9.2, 6.1 Hz, 1H), 4.21 – 4.14 (m, 1H), 4.04 (t, *J* = 5.6 Hz, 2H), 3.86 – 3.79 (m, 1H), 3.33 – 3.23 (m, 2H), 2.88 (s, 3H), 2.82 (dd, *J* = 16.8, 5.3 Hz, 1H), 2.63 (dd, *J* = 16.8, 9.3 Hz, 1H), 2.19 (dt, *J* = 11.9, 5.8 Hz, 2H), 2.01 (s, 6H), 1.98 – 1.85 (m, 4H), 1.79 – 1.68 (m, 4H).

Example 16

2-(6-((2',6'-Dimethyl-4'-(3-(*N*-phenylmethylsulfonamido)propoxy)-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



Step 1) 3-(phenylamino)propan-1-ol

[00205] A mixture of iodobenzene (5.46 mL, 49.0 mmol), 3-aminopropan-1-ol (5.6 mL, 74 mmol), cuprous iodide (0.93 g, 4.9 mmol), *L*-proline (1.2 g, 9.9 mmol) and potassium carbonate (13.54 g, 97.9 mmol) in DMSO (30 mL) was stirred at 80 °C for 12 h under nitrogen atmosphere. The reaction mixture was cooled to room temperature, and partitioned between EtOAc (100 mL) and water (50 mL). The organic phase was washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PET/EtOAc (v/v) = 2/1) to give the title compound as yellow oil (6.5 g, 88.0%).

Step 2) 3-(*N*-phenylmethylsulfonamido)propyl methanesulfonate

[00206] To a solution of 3-(phenylamino)propan-1-ol (500 mg, 3.31 mmol) and triethylamine (1.2 mL, 8.5 mmol) in DCM (15 mL) in an ice bath was added methanesulfonyl chloride (0.6 mL, 8 mmol) dropwise. The mixture was stirred at room temperature overnight under nitrogen atmosphere. The mixture was quenched with saturated sodium hydrogen carbonate solution (10 mL) and extracted with DCM (20 mL × 2). The combined organic phases were washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PET/EtOAc (v/v) = 1/1) to give the title compound as a light yellow solid (700 mg, 68.9%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.46 – 7.32 (m, 5H), 4.29 (t, J = 5.9 Hz, 2H), 3.84 (t, J = 6.4 Hz, 2H), 2.99 (s, 3H), 2.89 (s, 3H), 1.95 – 1.89 (m, 2H).

Step 3) methyl 2-(6-((2',6'-dimethyl-4'-(3-(*N*-phenylmethylsulfonamido)propoxy)-[1,1'-biphenyl]-3-yl) methoxy)-2,3-dihydrobenzofuran-3-yl)acetate

[00207] A solution of 3-(*N*-phenylmethylsulfonamido)propyl methanesulfonate (280 mg, 0.92 mmol), methyl 2-(6-((4'-hydroxy-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetate (250 mg, 0.60 mmol) and potassium carbonate (250 mg, 1.81 mmol) in DMF (10 mL) was heated to 80 °C overnight. The reaction mixture was cooled to room temperature, and partitioned between EtOAc (30 mL) and water (10 mL). The organic phase was washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PET/EtOAc (v/v) = 3/1) to give the title compound as yellow oil (320 mg, 85.1%).

Step 4) 2-(6-((2',6'-dimethyl-4'-(3-(*N*-phenylmethylsulfonamido)propoxy)-[1,1'-biphenyl]-3-yl)methoxy) -2,3-dihydrobenzofuran-3-yl)acetic acid

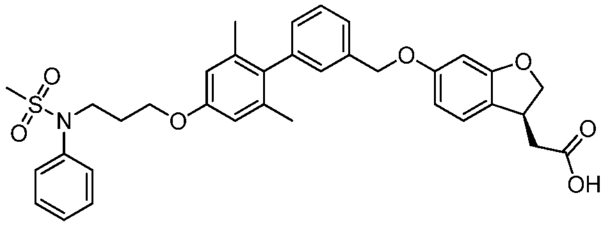
[00208] To a solution of methyl 2-(6-((2',6'-dimethyl-4'-(3-(*N*-phenylmethylsulfonamido)propoxy)-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetate (320 mg, 0.51 mmol) in tetrahydrofuran (5 mL) was added aqueous lithium hydroxide solution (5 mL, 1 M). The mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with water (10 mL), acidifed with aqueous hydrochloric acid (10 mL, 1 M), and extracted with EtOAc (20 mL × 2). The combined organic phases were washed with brine (5 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give the title compound as a white solid (166 mg, 53.1%).

MS (ESI, neg. Ion) *m/z*: 614.3 $[M-H]^-$; and

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.50 – 7.33 (m, 7H), 7.19 (s, 1H), 7.09 (dd, J = 13.1, 7.8 Hz, 2H), 6.62 (s, 2H), 6.55 – 6.47 (m, 2H), 5.08 (s, 2H), 4.78 (t, *J* = 9.0 Hz, 1H), 4.31 (dd, *J* = 9.1, 6.2 Hz, 1H), 4.05 (t, *J* = 6.0 Hz, 2H), 3.97 – 3.90 (m, 2H), 3.86 – 3.79 (m, 1H), 2.93 (s, 3H), 2.83 (dd, *J* = 16.9, 5.3 Hz, 1H), 2.64 (dd, *J* = 16.8, 9.4 Hz, 1H), 2.05 – 1.94 (m, 8H).

Example 17

(*S*)-2-(6-((2',6'-Dimethyl-4'-(3-(*N*-phenylmethylsulfonamido)propoxy)-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



Step 1) *N*-(3-((3'-formyl-2,6-dimethyl-[1,1'-biphenyl]-4-yl)oxy)propyl)-*N*-phenylmethane-sulfonamide

[00209] A solution of 3-(*N*-phenylmethylsulfonamido)propyl methanesulfonate (2 g, 6.51mmol), 4'-hydroxy-2',6'-dimethyl-[1,1'-biphenyl]-3-carbaldehyde (1 g, 4.42 mmol) and potassium carbonate (2.0 g, 14.5 mmol) in DMF (15 mL) was heated to 80 °C overnight. The reaction mixture was cooled to room temperature, and partitioned between EtOAc (10 mL) and water (10 mL). The organic phase was washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PET/EtOAc (v/v) = 3/1) to give the title compound as yellow oil (1.5 g, 78.0%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 10.07 (s, 1H), 7.88 (d, *J* = 7.7 Hz, 1H), 7.67 (s, 1H), 7.61 (t, *J* = 7.6 Hz, 1H), 7.47 – 7.36 (m, 6H), 6.63 (s, 2H), 4.06 (t, *J* = 6.1 Hz, 2H), 3.95 (t, *J* = 6.9 Hz, 2H), 2.93 (s, 3H), 2.03 (dd, *J* = 13.1, 6.4 Hz, 2H), 1.99 (s, 6H).

Step 2) *N*-(3-((3'-(hydroxymethyl)-2,6-dimethyl-[1,1'-biphenyl]-4-yl)oxy)propyl)-*N*- phenylmethanesulfon amide

[00210] To a solution of *N*-(3-((3'-formyl-2,6-dimethyl-[1,1'-biphenyl]-4-yl)oxy)propyl)-*N*-phenylmethanesulfon amide (1.5 g, 3.4 mmol) in THF (16 mL) and MeOH (8 mL) was added sodium borohydride (140 mg, 3.68 mmol) portionwise at 0 °C. The mixture was stirred at 0 °C overnight. After removing of the solvent, water (10 mL) was added to the residue. The resulting mixture was extracted with EtOAc (10 mL × 2). The combined organic phases were washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PET/EtOAc (v/v) = 2/1) to give the title compound as light yellow oil (1.0 g, 66.0%).

Step 3) *N*-(3-((3'-(chloromethyl)-2,6-dimethyl-[1,1'-biphenyl]-4-yl)oxy)propyl)-*N*-phenylmethanesulfon amide

[00211] To a solution of *N*-(3-((3'-(hydroxymethyl)-2,6-dimethyl-[1,1'-biphenyl]-4-yl)oxy)propyl)-*N*-phenylmethanesulfonamide (500 mg, 1.14 mmol) in DMF (10 mL) was added phosphorus oxychloride (0.13 mL, 1.37 mmol) dropwise. The mixture was stirred at room temperature for 3 h. The mixture was diluted with

water (10 mL) and extracted with EtOAc (10 mL × 2). The combined organic phases were washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PET/EtOAc (v/v) = 4/1) to give the title compound as light yellow oil (450 mg, 86.4%).

MS (ESI, pos. Ion) *m/z*: 458.1 $[M+H]^+$.

Step 4) (*S*)-methyl 2-(6-((2',6'-dimethyl-4'-(3-(*N*-phenylmethylsulfonamido)propoxy)-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetate

[00212] A solution of *N*-(3-((3'-(chloromethyl)-2,6-dimethyl-[1,1'-biphenyl]-4-yl)oxy)propyl)-*N*-phenylmethanesulfonamide (120 mg, 0.26 mmol), (*S*)-methyl 2-(6-hydroxy-2,3-dihydro benzofuran-3-yl)acetate (50 mg, 0.24 mmol) and potassium phosphate (76 mg, 0.36 mmol) in DMF (5 mL) was heated to 60 °C for 3 h. The reaction mixture was cooled to room temperature, and partitioned between EtOAc (10 mL) and water (10 mL). The organic phase was washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PET/EtOAc (v/v) = 2/1) to give the title compound as yellow oil (140 mg, 92.6%).

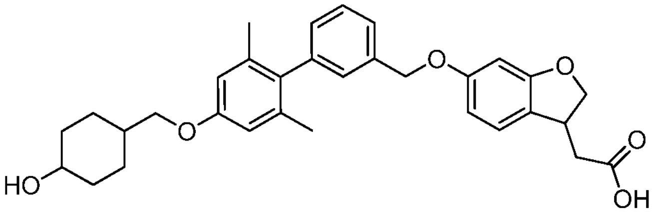
Step 5) (*S*)-2-(6-((2',6'-dimethyl-4'-(3-(*N*-phenylmethylsulfonamido)propoxy)-[1,1'-biphenyl]-3-yl) methoxy)-2,3-dihydrobenzofuran-3-yl)acetic acid

[00213] To a solution of (*S*)-methyl 2-(6-((2',6'-dimethyl-4'-(3-(*N*-phenylmethylsulfonamido) propoxy)-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetate (140 mg, 0.22 mmol) in tetrahydrofuran (2.5 mL) was added aqueous lithium hydroxide solution (2.5 mL, 1 M). The mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with water (10 mL), acidifed with aqueous hydrochloric acid (5 mL, 1 M), and extracted with EtOAc (20 mL × 2). The combined organic phases were washed with brine (3 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give the title compound as a white solid (120 mg, 87.7%).

^1H NMR (600 MHz, $CDCl_3$): δ 7.48 – 7.35 (m, 7H), 7.19 (s, 1H), 7.09 (dd, J = 13.2, 7.8 Hz, 2H), 6.62 (s, 2H), 6.56 – 6.46 (m, 2H), 5.09 (s, 2H), 4.78 (t, J = 9.0 Hz, 1H), 4.31 (dd, J = 9.1, 6.1 Hz, 1H), 4.05 (t, J = 6.0 Hz, 2H), 3.95 (t, J = 6.9 Hz, 2H), 3.83 (ddd, J = 14.5, 9.1, 5.8 Hz, 1H), 2.93 (s, 3H), 2.83 (dd, J = 16.9, 5.3 Hz, 1H), 2.64 (dd, J = 16.8, 9.4 Hz, 1H), 2.06 – 1.94 (m, 8H).

Example 18

2-(6-((4'-((4-Hydroxycyclohexyl)methoxy)-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



Step 1) (4-hydroxycyclohexyl)methyl 4-methylbenzenesulfonate

[00214] To a solution of 4-(hydroxymethyl)cyclohexanol (130 mg, 0.98 mmol), triethylamine (0.21 mL, 1.50 mmol) and *N,N,N',N'*-tetramethyl-1,6-hexane diamine (0.02 mL, 0.09 mmol) in toluene (5 mL) in an ice bath was added tosyl chloride (190 mg, 1.0 mmol). The mixture was stirred at 0 °C for 3 h. The reaction mixture was quenched with water (10 mL) and extracted with EtOAc (30 mL × 2). The combined organic phases were washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PET/EtOAc (v/v) = 2/1) to give the title compound as a white solid (80 mg, 28.5%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.80 (d, J = 8.2 Hz, 2H), 7.37 (d, J = 8.0 Hz, 2H), 3.85 (d, J = 6.4 Hz, 2H), 3.54 (ddd, J = 15.1, 10.8, 4.2 Hz, 1H), 2.47 (s, 3H), 2.03 – 1.94 (m, 2H), 1.82 – 1.75 (m, 2H), 1.64 – 1.60 (m, 1H), 1.26 – 1.19 (m,2H), 1.02 (ddd, J = 25.6, 13.3, 3.3 Hz, 2H).

Step 2) methyl 2-(6-((4'-((4-hydroxycyclohexyl)methoxy)-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetate

[00215] A solution of (4-hydroxycyclohexyl)methyl 4-methylbenzenesulfonate (80 mg, 0.28 mmol), methyl 2-(6-((4'-hydroxy-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetate (141 mg, 0.34 mmol) and potassium carbonate (115 mg, 0.84 mmol) in DMF (3 mL) was heated to 100 °C overnight. The reaction mixture was cooled to room temperature, and partitioned between EtOAc (10 mL) and water (10 mL). The organic phase was washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PET/EtOAc (v/v) = 3/1) to give the title compound as yellow oil (50 mg, 33.5%).

MS (ESI, pos. Ion) *m/z*: 531.3 $[M+H]^+$.

Step 3) 2-(6-((4'-((4-hydroxycyclohexyl)methoxy)-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetic acid

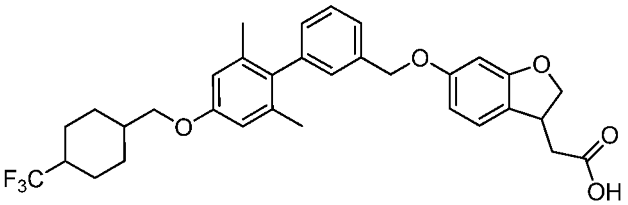
[00216] To a solution of methyl 2-(6-((4'-((4-hydroxycyclohexyl)methoxy)-2',6'-dimethyl-[1,1'-biphenyl]-3-yl) methoxy)-2,3-dihydrobenzofuran-3-yl)acetate (50 mg, 0.1 mmol) in tetrahydrofuran (1 mL) and methanol (0.5 mL) was added aqueous sodium hydroxide solution (0.1 mL, 2 M). The mixture was stirred at 50 °C for 2 h. The reaction mixture was diluted with water (5 mL), acidifed with hydrochloric acid (1 mL, 1 M), and extracted with EtOAc (10 mL × 2). The combined organic phases were washed with brine (3 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give the title compound as a yellow solid (36 mg, 73.7%).

MS (ESI, neg. Ion) *m/z*: 515.2 $[M-H]^-$; and

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 (dt, J = 15.3, 7.7 Hz, 2H), 7.19 (s, 1H), 7.08 (dd, J = 12.2, 7.8 Hz, 2H), 6.66 (s, 2H), 6.54 – 6.45 (m, 2H), 5.08 (s, 2H), 4.78 (t, J = 9.0 Hz, 1H), 4.31 (dd, J = 9.2, 6.1 Hz, 1H), 3.88 – 3.82 (m, 1H), 3.80 (d, J = 6.3 Hz, 2H), 3.69 – 3.58 (m, 1H), 2.82 (dd, J = 16.8, 5.4 Hz, 1H), 2.63 (dd, J = 16.8, 9.3 Hz, 1H), 2.08 (d, J = 7.6 Hz,2H), 1.99 (d, J = 14.1 Hz, 8H), 1.39 – 1.32 (m, 3H), 1.17 (d, J = 15.0 Hz, 2H).

Example 19

2-(6-((2',6'-Dimethyl-4'-((4-(trifluoromethyl)cyclohexyl)methoxy)-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



Step 1) methyl 2-(6-((2',6'-dimethyl-4'-((4-(trifluoromethyl)cyclohexyl)methoxy)-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetate

[00217] To a solution of (4-(trifluoromethyl)cyclohexyl)methanol (0.14 mL, 0.92 mmol) and methyl 2-(6-((4'-hydroxy-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetate (250 mg, 0.6 mmol) in toluene (10 mL) were added triphenylphosphine (240 mg, 0.9 mmol) and diisopropyl azodicarboxylate (0.2 mL, 1.0 mmol) at 0 °C. The mixture was stirred at 0 °C for 1 h under nitrogen atmosphere. The reaction mixture was quenched with water (10 mL) and extracted with EtOAc (20 mL × 2). The combined organic phases were washed with brine (5 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PET/EtOAc (v/v) = 15/1) to give the title compound as light yellow oil (150 mg, 43.1%).

Step 2) 2-(6-((2',6'-Dimethyl-4'-((4-(trifluoromethyl)cyclohexyl)methoxy)-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetic acid

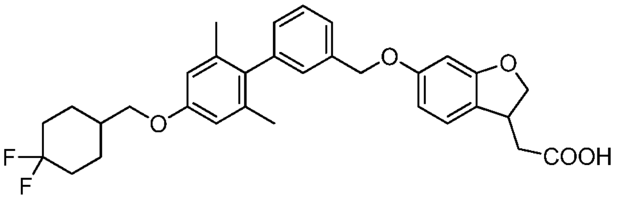
[00218] To a solution of methyl 2-(6-((2',6'-dimethyl-4'-((4-(trifluoromethyl)cyclohexyl)methoxy)-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetate (143 mg, 0.25 mmol) in tetrahydrofuran (3 mL) was added aqueous lithium hydroxide solution (3 mL, 1 M). The mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with water (5 mL), acidifed with aqueous hydrochloric acid (10 mL, 1 M), and extracted with EtOAc (20 mL × 2). The combined organic phases were washed with brine (3 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give the title compound as a light yellow solid (125 mg, 89.6%).

MS (ESI, pos. Ion) *m/z*: 569.3 $[M+H]^+$; and

^1H NMR (400 MHz, $CDCl_3$): δ 7.43 (dt, *J* = 15.3, 7.6 Hz, 2H), 7.20 (s, 1H), 7.14 – 7.05 (m, 2H), 6.68 (d, *J* = 7.5 Hz, 2H), 6.56 – 6.46 (m, 2H), 5.09 (s, 2H), 4.79 (t, *J* = 9.0 Hz, 1H), 4.31 (dd, *J* = 9.2, 6.1 Hz, 1H), 3.95 (d, *J* = 7.2 Hz, 1H), 3.87 – 3.78 (m, 2H), 2.84 (dd, *J* = 16.8, 5.3 Hz, 1H), 2.64 (dd, *J* = 16.8, 9.3 Hz, 1H), 2.17 (dd, *J* = 11.3, 7.1 Hz, 1H), 2.02 (s, 6H), 1.89 – 1.72 (m, 3H), 1.66 (m,3H), 1.41 (m, 1H), 1.23 – 1.07 (m, 1H), 0.96 – 0.80 (m, 1H).

Example 20

2-(6-((4'-((4,4-Difluorocyclohexyl)methoxy)-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



Step 1) (4,4-difluorocyclohexyl)methanol

[00219] To a solution of 4,4-difluorocyclohexanecarboxylic acid (500 mg, 3.1 mmol) in tetrahydrofuran (6 mL) in an ice bath was added a solution of sodium borohydride (120 mg, 3.2 mmol) in tetrahydrofuran (6 mL) dropwise. The mixture was stirred at room temperature for 1 h. Then Boron trifluoride etherate (0.38 mL, 3.1 mmol) was added dropwise and the resulting white slurry was stirred at room temperature overnight. The mixture was quenched with ethanol (12 mL), diluted with water (10 mL) and extracted with DCM (10 mL × 2). The combined organic phases were washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give the title compound as yellow liquid (450 mg, 98.0%).

Step 2) (4,4-difluorocyclohexyl)methyl methanesulfonate

[00220] To a solution of (4,4-difluorocyclohexyl)methanol (450 mg, 3.0 mmol) and triethylamine (0.7 mL, 5.0 mmol) in DCM (20 mL) in an ice bath was added methanesulfonyl chloride (0.4 mL, 5.0 mmol) dropwise. The mixture was stirred at room temperature for 1 h under nitrogen atmosphere. The mixture was quenched with saturated sodium hydrogen carbonate solution (10 mL) and extracted with DCM (15 mL × 2). The combined organic phases were washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PET/EtOAc (v/v) = 2/1) to give the title compound as yellow oil (130 mg, 20.0%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.10 (d, J = 6.2 Hz, 2H), 3.04 (s, 3H), 2.22 – 2.09 (m, 2H), 1.93 – 1.67 (m, 5H), 1.48 – 1.37 (m, 2H).

Step 3) methyl 2-(6-((4'-((4,4-difluorocyclohexyl)methoxy)-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy) -2,3-dihydrobenzofuran-3-yl)acetate

[00221] A solution of (4,4-difluorocyclohexyl)methyl methanesulfonate (130 mg, 0.57 mmol), methyl 2-(6-((4'-hydroxy-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetate (350 mg, 0.84 mmol) and potassium carbonate (240 mg, 1.74 mmol) in DMF (10 mL) was heated to 100 °C overnight. The reaction mixture was cooled to room temperature, and partitioned between EtOAc (10 mL) and water (10 mL). The organic phase was washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PET/EtOAc (v/v) = 10/1) to give the title compound as yellow oil (170 mg, 54.2%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.48 – 7.37 (m, 2H), 7.19 (s, 1H), 7.07 (dd, J = 37.1, 7.8 Hz, 2H), 6.67 (s, 2H), 6.53 – 6.43 (m, 2H), 5.08 (s, 2H), 4.77 (t, J = 9.0 Hz, 1H), 4.28 (dd, J = 9.1, 6.1 Hz, 1H), 3.91 – 3.78 (m, 3H), 3.74 (s, 3H), 2.77 (dd, J = 16.4, 5.4 Hz, 1H), 2.58 (dd, J = 16.4, 9.3 Hz, 1H), 2.22 – 2.13 (m, 2H), 2.00 (d, J = 13.9 Hz, 7H), 1.91 (d, J = 8.5 Hz, 1H), 1.87 – 1.72 (m, 2H), 1.52 – 1.41 (m, 2H), 1.31 (s, 1H).

Step 4) 2-(6-((4'-((4,4-difluorocyclohexyl)methoxy)-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetic acid

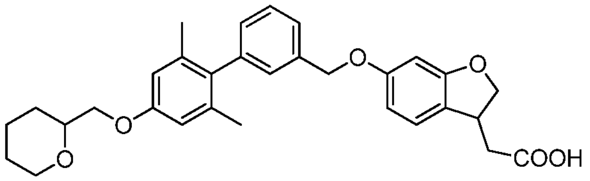
[00222] To a solution of methyl 2-(6-((4'-((4,4-difluorocyclohexyl)methoxy)-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetate (170 mg, 0.3 mmol) in tetrahydrofuran (3 mL) was added 1 M aqueous lithium hydroxide solution (3 mL). The mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with water (10 mL), acidifed with hydrochloric acid (10 mL, 1 M), and extracted with EtOAc (20 mL × 2). The combined organic phases were washed with brine (5 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give the title compound as a white solid (130 mg, 78.5%).

MS (ESI, pos. Ion) *m/z*: 537.3 $[M+H]^+$; and

^1H NMR (400 MHz, $CDCl_3$): δ 7.43 (dt, J = 15.1, 7.6 Hz, 2H), 7.20 (s, 1H), 7.10 (dd, J = 12.6, 7.7 Hz, 2H), 6.68 (s, 2H), 6.57 – 6.44 (m, 2H), 5.09 (s, 2H), 4.79 (t, J = 9.0 Hz, 1H), 4.32 (dd, J = 9.2, 6.1 Hz, 1H), 3.89 – 3.78 (m, 3H), 2.84 (dd, J = 16.8, 5.3 Hz, 1H), 2.65 (dd, J = 16.8, 9.3 Hz, 1H), 2.19 (ddd, J = 11.0, 8.7, 4.3 Hz, 2H), 2.05 – 1.72 (m, 11H), 1.55 – 1.42 (m, 2H).

Example 21

2-(6-((2',6'-Dimethyl-4'-((tetrahydro-2*H*-pyran-2-yl)methoxy)-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



Step 1) methyl 2-(6-((2',6'-dimethyl-4'-((tetrahydro-2*H*-pyran-2-yl)methoxy)-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetate

[00223] To a solution of (tetrahydro-2*H*-pyran-2-yl)methanol (146 mg, 1.3 mmol) and methyl 2-(6-((4'-hydroxy-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl) acetate (350 mg, 0.8 mmol) in toluene (20 mL) were added tributylphosphine (0.33 mL, 1.3 mmol) and 1,1'-(azodicarbonyl)-dipiperidine (338 mg, 1.3 mmol). The resulting mixture was stirred at room temperature for 1 h under nitrogen atmosphere. The reaction mixture was quenched with water (20 mL) and extracted with EtOAc (40 mL × 2). The combined organic phases were washed with brine (5 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PET/EtOAc (v/v) = 10/1) to give the title compound as light yellow oil (72 mg, 16.7%).

MS (ESI, pos. Ion) *m/z*: 517.2 $[M+H]^+$.

Step 2) 2-(6-((2',6'-dimethyl-4'-((tetrahydro-2*H*-pyran-2-yl)methoxy)-[1,1'-Biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetic acid

[00224] To a solution of methyl 2-(6-((2',6'-dimethyl-4'-((tetrahydro-2*H*-pyran-4-yl)methoxy)-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetate (72 mg, 0.14 mmol) in tetrahydrofuran (2 mL) was added

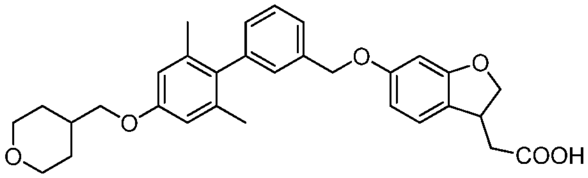
aqueous lithium hydroxide solution (2 mL, 1 M). The mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with water (5 mL), acidifed with hydrochloric acid (5 mL, 1 M), and extracted with EtOAc (40 mL × 2). The combined organic phases were washed with brine (2 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give the title compound as a light yellow solid (44 mg, 62.8%).

MS (ESI, pos. Ion) *m/z*: 503.2 $[M+H]^+$; and

^1H NMR (600 MHz, $CDCl_3$): δ 7.42 (d, J = 21.7 Hz, 2H), 7.19 (s, 1H), 7.09 (dd, J = 20.4, 7.1 Hz, 2H), 6.71 (s, 2H), 6.57 – 6.44 (m, 2H), 5.08 (s, 2H), 4.78 (t, J = 8.5 Hz, 1H), 4.30 (d, J = 7.0 Hz, 1H), 4.10 (d, J = 9.0 Hz, 1H), 4.02 (d, J = 6.2 Hz, 1H), 3.92 (d, J = 5.8 Hz, 1H), 3.79 (d, J = 40.4 Hz, 2H), 3.56 (t, J = 11.1 Hz, 1H), 2.86 – 2.77 (m, 1H), 2.63 (dd, J = 16.3, 9.3 Hz, 1H), 2.01 (s, 6H), 1.94 (d, J = 6.4 Hz, 1H), 1.75 (d, J = 12.0 Hz, 1H), 1.70 – 1.61 (m, 1H), 1.59 (s, 2H), 1.49 (dd, J = 23.0, 11.7 Hz, 1H).

Example 22

2-(6-((2',6'-Dimethyl-4'-((tetrahydro-2*H*-pyran-4-yl)methoxy)-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



Step 1) methyl 2-(6-((2',6'-dimethyl-4'-((tetrahydro-2*H*-pyran-4-yl)methoxy)-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetate

[00225] To a solution of (tetrahydro-2*H*-pyran-4-yl)methanol (104 mg, 0.90 mmol) and methyl 2-(6-((4'-hydroxy-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl) acetate (250 mg, 0.60 mmol) in toluene (8 mL) were added tributylphosphine (0.24 mL, 0.96 mmol) and 1,1'-(azodicarbonyl)-dipiperidine (244 mg, 0.96 mmol). The resulting mixture was stirred at room temperature for 1 h under nitrogen atmosphere. The reaction mixture was quenched with water (20 mL) and extracted with EtOAc (40 mL × 2). The combined organic phases were washed with brine (5 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PET/EtOAc (v/v) = 10/1) to give the title compound as a light yellow solid (143 mg, 46.3%).

^1H NMR (600 MHz, $CDCl_3$): δ 7.48 – 7.34 (m, 2H), 7.19 (s, 1H), 7.07 (dd, J = 37.9, 7.8 Hz, 2H), 6.67 (s, 2H), 6.53 – 6.45 (m, 2H), 5.08 (s, 2H), 4.77 (t, J = 9.0 Hz, 1H), 4.28 (dd, J = 9.1, 6.1 Hz, 1H), 4.05 (dd, J= 11.1, 3.6 Hz, 2H), 3.88 – 3.79 (m, 3H), 3.74 (s, 3H), 3.48 (dd, J = 11.5, 10.4 Hz, 2H), 2.76 (dd, J = 16.4,5.4 Hz, 1H), 2.57 (dd, J = 16.4, 9.3 Hz, 1H), 2.14 – 2.08 (m, 1H), 2.01 (s, 6H), 1.80 (dd, J = 12.9, 1.4 Hz, 2H), 1.52 – 1.42 (m, 2H).

Step 2) 2-(6-((2',6'-dimethyl-4'-((tetrahydro-2*H*-pyran-4-yl)methoxy)-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetic acid

[00226] To a solution of methyl 2-(6-((2',6'-dimethyl-4'-((tetrahydro-2*H*-pyran-4-yl)methoxy)-[1,1'-biphenyl]-

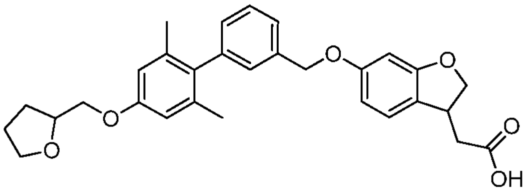
3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetate (200 mg, 0.39 mmol) in tetrahydrofuran (4 mL) was added aqueous lithium hydroxide solution (4 mL, 1 M). The mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with water (5 mL), acidifed with aqueous hydrochloric acid (5 mL, 1 M), and extracted with EtOAc (40 mL × 2). The combined organic phases were washed with brine (2 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give the title compound as a light yellow solid (180 mg, 92.5%).

MS (ESI, pos. Ion) *m/z*: 503.2 $[M+H]^+$; and

^1H NMR (600 MHz, $CDCl_3$): δ 7.48 – 7.36 (m, 2H), 7.19 (s, 1H), 7.09 (dd, *J* = 19.4, 7.7 Hz, 2H), 6.68 (s, 2H), 6.57 – 6.45 (m, 2H), 5.08 (s, 2H), 4.79 (t, *J* = 9.0 Hz, 1H), 4.31 (dd, *J* = 9.1, 6.1 Hz, 1H), 4.07 (dd, *J* = 10.9, 3.2 Hz, 2H), 3.86 – 3.82 (m, 3H), 3.50 (t, *J* = 11.1 Hz, 2H), 2.83 (dd, *J* = 16.8, 5.2 Hz, 1H), 2.64 (dd, *J* = 16.8, 9.4 Hz, 1H), 2.16 – 2.06 (m, 1H), 2.02 (s, 6H), 1.81 (d, *J* = 12.0 Hz, 2H), 1.55 – 1.44 (m, 2H).

Example 23

2-(6-((2',6'-Dimethyl-4'-((tetrahydrofuran-2-yl)methoxy)-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



Step 1) methyl 2-(6-((2',6'-dimethyl-4'-((tetrahydrofuran-2-yl)methoxy)-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetate

[00227] To a solution of (tetrahydrofuran-2-yl)methanol (0.07 mL, 0.72 mmol) and methyl 2-(6-((4'-hydroxy-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl) acetate (200 mg, 0.48 mmol) in toluene (5 mL) were added triphenylphosphine (188 mg, 0.72 mmol) and diisopropyl azodicarboxylate (0.14 mL, 0.72 mmol) at 0 °C. The mixture was stirred at 0 °C for 1 h under nitrogen atmosphere. The reaction mixture was quenched with water (10 mL) and extracted with EtOAc (20 mL × 2). The combined organic phases were washed with brine (5 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PET/EtOAc (v/v) = 20/1) to give the title compound as light yellow oil (195 mg, 81.2%).

MS (ESI, pos. Ion) *m/z*: 503.2 $[M+H]^+$.

Step 2) 2-(6-((2',6'-dimethyl-4'-((tetrahydrofuran-2-yl)methoxy)-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetic acid

[00228] To a solution of methyl 2-(6-((2',6'-dimethyl-4'-((tetrahydrofuran-2-yl)methoxy)-[1,1'-biphenyl]-3-yl) methoxy)-2,3-dihydrobenzofuran-3-yl)acetate (195 mg, 0.39 mmol) in tetrahydrofuran (4 mL) was added 1 M aqueous lithium hydroxide solution (4 mL). The mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with water (5 mL), acidifed with aqueous hydrochloric acid (10 mL, 1 M), and extracted with EtOAc (20 mL × 2). The combined organic phases were washed with brine (3 mL), dried over Na_2SO_4 and

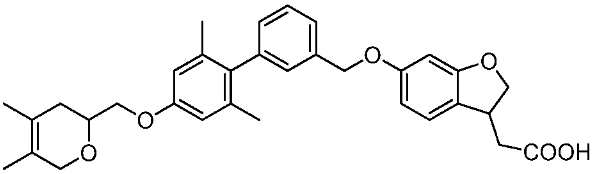
concentrated *in vacuo* to give the title compound as a light yellow solid (100 mg, 52.7%).

MS (ESI, pos. Ion) *m/z*: 489.2 $[M+H]^+$; and

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.45 – 7.37 (m, 2H), 7.18 (s, 1H), 7.08 (dd, *J* = 18.1, 7.8 Hz, 2H), 6.70 (s, 2H), 6.52 – 6.47 (m, 2H), 5.07 (s, 2H), 5.00 (dt, *J* = 12.5, 6.2 Hz, 3H), 4.77 (t, *J* = 9.0 Hz, 1H), 4.35 – 4.27 (m, 2H), 4.03 – 3.95 (m, 3H), 3.89 – 3.79 (m, 2H), 2.81 (dd, *J* = 16.8, 5.3 Hz, 1H), 2.61 (dd, *J* = 16.8, 9.4 Hz, 1H), 2.10 (dt, *J* = 7.2, 4.1 Hz, 1H), 2.00 (s, 6H).

Example 24

2-(6-((4'-((4,5-Dimethyl-3,6-dihydro-2*H*-pyran-2-yl)methoxy)-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



Step 1) ethyl 4,5-dimethyl-3,6-dihydro-2*H*-pyran-2-carboxylate

[00229] To a solution of ethyl 2-oxoacetate (6.3 mL, 30 mmol) in chloroform (150 mL) was added bismuth trichloride (500 mg, 1.6 mmol) followed by a solution of 2,3-dimethylbuta-1,3-diene (10 mL, 88.4 mmol) in chloroform (50 mL) dropwise under nitrogen atmosphere. The resulting mixture was stirred at 60 °C for 2 h under nitrogen atmosphere. The mixture was quenched with saturated sodium bicarbonate solution (20 mL) and extracted with DCM (80 mL × 2). The combined organic phases were washed with brine (30 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PET/EtOAc (v/v) = 50/1) to give the title compound as colorless liquid (2.3 g, 41.0%).

Step 2) (4,5-dimethyl-3,6-dihydro-2*H*-pyran-2-yl)methanol

[00230] To a suspension of lithium aluminium hydride (93 mg, 2.5 mmol) in tetrahydrofuran (5 mL) in an ice bath was added slowly a solution of ethyl 4,5-dimethyl-3,6-dihydro-2*H*-pyran-2-carboxylate (300 mg, 1.6 mmol) in tetrahydrofuran (5 mL). The resulting mixture was stirred at room temperature overnight. Then to the mixture were slowly added water (5 mL) and 10% aqueous sodium hydroxide solution (25 mL) at 0 °C. The resulting mixture was filtered. The filter cake was washed with tetrahydrofuran (20 mL). The combined filtrates were concentrated *in vacuo*. The residue was diluted with water (10 mL), and extracted with EtOAc (20 mL × 2). The combined organic phases were washed with brine (5 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PET/EtOAc (v/v) = 3/1) to give the title compound as yellow oil (220 mg, 95.0%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 4.07 (d, *J* = 15.4 Hz, 1H), 3.99 (d, *J* = 15.4 Hz, 1H), 3.70 – 3.62 (m, 2H), 3.57 (dd, *J* = 11.4, 7.3 Hz, 1H), 2.36 (s, 1H), 2.08 – 2.00 (m, 1H), 1.73 (d, *J* = 16.6 Hz, 1H), 1.66 (s, 3H), 1.55 (s, 3H).

Step 3) (4,5-dimethyl-3,6-dihydro-2*H*-pyran-2-yl)methyl 4-methyl benzenesulfonate

[00231] To a solution of (4,5-dimethyl-3,6-dihydro-2*H*-pyran-2-yl)methanol (1.33 g, 9.4 mmol), triethylamine (2.0 mL, 14.2 mmol) and *N,N,N',N'*-tetramethyl-1,6-hexanediamine (0.2 mL, 0.96 mmol) in toluene (25 mL) in an ice bath was added tosyl chloride (2.7 g, 14.0 mmol). The mixture was stirred at 0 °C for 3 h. The reaction mixture was quenched with water (10 mL) and extracted with EtOAc (30 mL × 2). The combined organic phases were washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PET/EtOAc (v/v) = 10/1) to give the title compound as light yellow oil (2.4 g, 86.0%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.83 (d, *J* = 8.3 Hz, 2H), 7.36 (d, *J* = 8.0 Hz, 2H), 4.06 – 4.02 (m, 2H), 3.98 (d, *J* = 15.6 Hz, 1H), 3.91 (d, *J* = 15.5 Hz, 1H), 3.79 (ddd, *J* = 10.5, 9.2, 5.1 Hz, 1H), 2.47 (s, 3H), 2.02 – 1.94 (m, 1H), 1.79 (d, *J* = 16.4 Hz, 1H), 1.64 (s, 3H), 1.53 (s, 3H).

Step 4) methyl 2-(6-((4'-((4,5-dimethyl-3,6-dihydro-2*H*-pyran-2-yl)methoxy)-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetate

[00232] A solution of (4,5-dimethyl-3,6-dihydro-2*H*-pyran-2-yl)methyl 4-methyl benzenesulfonate (425 mg, 1.43 mmol), methyl 2-(6-((4'-hydroxy-2',6'-dimethyl-[1,1'- biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran -3-yl) acetate (400 mg, 0.96 mmol) and potassium carbonate (400 mg, 2.89 mmol) in DMF (10 mL) was heated to 90 °C overnight. The reaction mixture was cooled to room temperature, and partitioned between EtOAc (10 mL) and water (10 mL). The organic phase was washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PET/EtOAc (v/v) = 12/1) to give the title compound as yellow oil (282 mg, 54.4%).

MS (ESI, pos. Ion) *m/z*: 543.3 $[M+H]^+$.

Step 5) 2-(6-((4'-((4,5-dimethyl-3,6-dihydro-2*H*-pyran-2-yl)methoxy)-2',6'-dimethyl-[1,1'-biphenyl]-3-yl) methoxy)-2,3-dihydrobenzofuran-3-yl)acetic acid

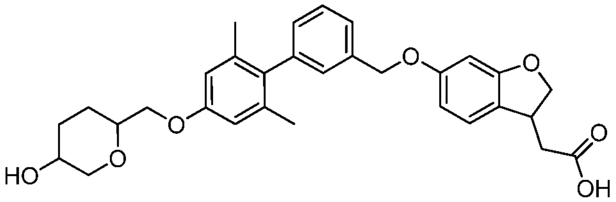
[00233] To a solution of methyl 2-(6-((4'-((4,5-dimethyl-3,6-dihydro-2*H*-pyran-2-yl)methoxy)-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl) acetate (77 mg, 0.14 mmol) in tetrahydrofuran (2 mL) was added aqueous lithium hydroxide solution (2 mL, 1 M). The mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with water (5 mL), acidified with aqueous hydrochloric acid (5 mL, 1 M), and extracted with EtOAc (10 mL × 2). The combined organic phases were washed with brine (5 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give the title compound as a yellow solid (41 mg, 54.5%).

MS (ESI, pos. Ion) *m/z*: 529.3 $[M+H]^+$; and

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.46 – 7.37 (m, 2H), 7.19 (s, 1H), 7.09 (dd, *J* = 20.7, 7.7 Hz, 2H), 6.72 (s, 2H), 6.54 – 6.46 (m, 2H), 5.08 (s, 2H), 4.78 (t, *J* = 9.0 Hz, 1H), 4.31 (dd, *J* = 8.9, 6.2 Hz, 1H), 4.16 (d, *J* = 15.2 Hz, 1H), 4.12 – 4.03 (m, 2H), 4.03 – 3.95 (m, 2H), 3.83 (d, *J* = 5.0 Hz, 1H), 2.83 (dd, *J* = 16.8, 5.0 Hz, 1H), 2.63 (dd, *J* = 16.8, 9.4 Hz, 1H), 2.27 – 2.15 (m, 1H), 2.01 (s, 6H), 1.95 (d, *J* = 16.5 Hz, 1H), 1.71 (s, 3H), 1.59 (s, 3H).

Example 25

2-(6-((4'-((5-Hydroxytetrahydro-2*H*-pyran-2-yl)methoxy)-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



Step1 (3,4-dihydro-2*H*-pyran-2-yl)methyl 4-methylbenzenesulfonate

[00234] To a solution of (3,4-dihydro-2*H*-pyran-2-yl)methanol (3 g, 26.3 mmol), triethylamine (5.5 mL, 39 mmol) and *N,N,N',N'*-tetramethyl-1,6-hexane diamine (0.56 mL, 2.6 mmol) in toluene (50 mL) in an ice bath was added tosyl chloride (7.6 g, 40 mmol). The mixture was stirred at 0 °C for 3 h. The reaction mixture was quenched with water (30 mL) and extracted with EtOAc (50 mL × 2). The combined organic phases were washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PET/EtOAc (v/v) = 50/1) to give the title compound as yellow oil (7 g, 99.3%).

^1H NMR (600 MHz, $CDCl_3$): δ 7.83 (d, J = 8.2 Hz, 2H), 7.37 (d, J = 8.1 Hz, 2H), 6.28 (d, J = 6.1 Hz, 1H), 4.69 (dd, J = 6.8, 5.7 Hz, 1H), 4.16 – 3.99 (m, 3H), 2.47 (s, 3H), 2.11 – 2.04 (m, 1H), 2.01 – 1.92 (m, 1H), 1.88 – 1.81 (m, 1H), 1.71 – 1.62 (m, 1H).

Step2 (5-hydroxytetrahydro-2*H*-pyran-2-yl)methyl 4-methylbenzenesulfonate

[00235] To a solution of (3,4-dihydro-2*H*-pyran-2-yl)methyl 4-methylbenzenesulfonate (3 g, 11.2 mmol) in dry THF (20 mL) at 0 °C was added borane-tetrahydrofuran complex (33.6 mL, 1 M) dropwise. The reaction was stirred overnight at room temperature. The reaction was treated with aqueous sodium hydroxide solution (26 mL, 2.5 M) dropwise, followed by hydrogen peroxide (4.6 mL, 30 wt% solution in water). The mixture was stirred at 60 °C for 1 h. The mixture was cooled to 0 °C and potassium carbonate (14 g) was added. The resulting mixture was extracted with EtOAc (40 mL × 2). The combined organic phases were washed with brine (30 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PET/EtOAc (v/v) = 2/1) to give the title compound as pale oil (2 g, 62.5%).

^1H NMR (600 MHz, $CDCl_3$): δ 7.80 (d, J = 8.2 Hz, 2H), 7.36 (d, J = 8.3 Hz, 2H), 4.01 – 3.93 (m, 3H), 3.68 (t, J = 6.4 Hz, 1H), 3.54 – 3.47 (m, 1H), 3.07 (t, J = 10.5 Hz, 1H), 2.46 (s, 3H), 2.19 – 2.10 (m, 1H), 1.65 – 1.55 (m, 2H), 1.43 – 1.33 (m, 2H).

Step 3) methyl 2-(6-((4'-((5-hydroxytetrahydro-2*H*-pyran-2-yl)methoxy)-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetate

[00236] A mixture of (5-hydroxytetrahydro-2*H*-pyran-2-yl)methyl 4-methylbenzenesulfonate (200 mg, 0.70 mmol), methyl 2-(6-((4'-hydroxy-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl) acetate (200 mg, 0.48 mmol), and potassium carbonate (200 mg, 1.45 mmol) in DMF (10 mL) was stirred at 100 °C overnight. The mixture was partitioned between EtOAc (10 mL) and water (10 mL), washed with water (10 mL) and brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica

gel column chromatography (PET/ EtOAc (v/v) = 10/1) to give the title compound as light yellow oil (200 mg, 78.6%).

MS (ESI, pos. Ion) *m/z*: 533.2 $[M+H]^+$.

Step 4) 2-(6-((4'-((5-hydroxytetrahydro-2*H*-pyran-2-yl)methoxy)-2',6'-dimethyl-[1,1'-biphenyl]-3-yl) methoxy)-2,3-dihydrobenzofuran-3-yl)acetic acid

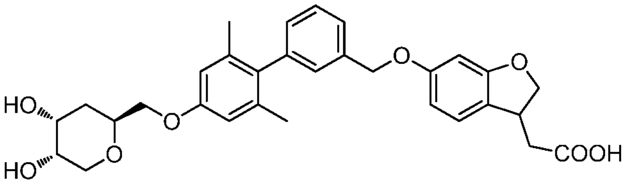
[00237] To a solution of methyl 2-(6-((4'-((5-hydroxytetrahydro-2*H*-pyran-2-yl)methoxy)-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetate (200 mg, 0.39 mmol) in tetrahydrofuran (4 mL) was added aqueous lithium hydroxide solution (4 mL, 1 M). The mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with water (4 mL), acidifed with aqueous hydrochloric acid (10 mL, 1 M), and extracted with EtOAc (40 mL × 2). The combined organic phases were washed with brine (5 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give the title compound as a light yellow solid (77 mg, 39.5%).

MS (ESI, pos. Ion) *m/z*: 519.2 $[M+H]^+$; and

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49 – 7.35 (m, 2H), 7.18 (s, 1H), 7.08 (dd, *J* = 11.8, 7.7 Hz, 2H), 6.70 (s, 2H), 6.59 – 6.37 (m, 2H), 5.08 (s, 2H), 4.77 (t, *J* = 9.0 Hz, 1H), 4.30 (dd, *J* = 9.2, 6.1 Hz, 1H), 4.15 – 4.08 (m, 1H), 4.04 (dd, *J* = 9.9, 6.1 Hz, 1H), 3.94 (dd, *J* = 9.9, 4.3 Hz, 1H), 3.87 – 3.75 (m, 2H), 3.75 – 3.66 (m, 1H), 3.24 (t, *J* = 10.4 Hz, 1H), 2.82 (dd, *J* = 16.8, 5.3 Hz, 1H), 2.62 (dd, *J* = 16.8, 9.3 Hz, 1H), 2.22 (dd, *J* = 10.6, 5.5 Hz, 1H), 2.00 (s, 6H), 1.91 (dd, *J* = 8.8, 6.0 Hz, 1H), 1.64 – 1.45 (m, 2H).

Example 26

2-(6-((4'-(((2*S*,4*R*,5*S*)-4,5-Dihydroxytetrahydro-2*H*-pyran-2-yl)methoxy)-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



Step 1) (*S*)-1-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)but-3-en-1-ol

[00238] To a mixture of Zn powder (20 g, 307 mmol) in tetrahydrofuran (100 mL) at 0 °C under nitrogen atmosphere was added (*R*)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde (20 g, 153 mmol), followed by allyl bromide (26 mL, 307 mmol) dropwise. The resulting mixture was stirred at 0 °C for 4 h. The reaction mixture was quenched with saturated ammonium chloride solution (30 mL) and filtered. The filtrate was extracted with EtOAc (80 mL × 2). The combined organic phases were washed with brine (80 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PET/EtOAc (v/v) = 60/1) to give the title compound as light yellow liquid (22.2 g, 83.9 %).

^{1}H NMR (600 MHz, $CDCl_3$): *δ* 5.92 – 5.81 (m, 1H), 5.16 (ddd, *J* = 21.3, 14.5, 5.6 Hz, 2H), 4.04 (ddd, *J* = 14.6, 10.7, 6.3 Hz, 2H), 3.95 (td, *J* = 9.3, 5.2 Hz, 1H), 3.84 – 3.75 (m, 1H), 2.42 – 2.31 (m, 1H), 2.28 – 2.21 (m, 1H), 1.45 (s, 3H), 1.38 (s, 3H).

Step 2) (*R*)-4-((*S*)-1-(allyloxy)but-3-en-1-yl)-2,2-dimethyl-1,3-dioxolane

[00239] To a suspension of sodium hydride (60% in mineral oil, 10.3 g, 258 mmol) in DMF (100 mL) at 0 °C was added a solution of (*S*)-1-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)but-3-en-1-ol (20 g, 129 mmol) in tetrahydrofuran (200 mL) dropwise. The resulting mixture was stirred at 0 °C for 19 h. Then allyl bromide (112 mL, 1.29 mol) was added at 0 °C. The resulting mixture was stirred at room temperature for another 3 h. The reaction mixture was quenched with saturated aqueous ammonium chloride solution (30 mL) and extracted with EtOAc (100 mL × 2). The combined organic phases were washed with brine (50 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PET/EtOAc (v/v) = 10/1) to give the title compound as light yellow liquid (14 g, 51.2 %).

Step 3) (2*R*,3*S*)-3-(allyloxy)hex-5-ene-1,2-diol

[00240] To a solution of ((*R*)-4-((*S*)-1-(allyloxy)but-3-enyl)-2,2-dimethyl-1,3-dioxolane (14 g, 66 mmol) in THF (150 mL) was added aqueous hydrochloric acid (150 mL, 2.0 M) at 0 °C. The resulting mixture was stirred at room temperature until the starting material was consumed fully (indicated by TLC). The mixture was extracted with EtOAc (50 mL × 2). The combined organic phases were washed with brine (50 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give the title compound as yellow oil (9.0 g, 79.2 %).

Step 4) (*S*)-2-(allyloxy)pent-4-enal

[00241] To a solution of (2*R*,3*S*)-3-(allyloxy)hex-5-ene-1,2-diol (9 g, 52 mmol) in DCM (200 mL) at room temperature were added sodium periodate (28 g, 131 mmol) and saturated sodium hydrogen carbonate solution (15 mL). After 5 min, additional $NaHCO_3$ (2.2 g) was added. The resulting mixture was stirred for 2 h and Na_2SO_4 (30 g) was added. The resulting mixture was stirred for 15 min and filtered. The filtrate was concentrated *in vacuo* to give the title compound as yellow oil (7.3 g, 100 %).

Step 5) (*S*)-2-(allyloxy)pent-4-en-1-ol

[00242] To a solution of (*S*)-2-(allyloxy)pent-4-enal (7.3 g, 52 mmol) in THF (60 mL) and MeOH (30 mL) at 0 °C was added sodium borohydride (2.1 g, 55 mmol). The resulting mixture was stirred at 0 °C overnight. The reaction mixture was quenched with water (5 mL) and extracted with EtOAc (20 mL × 2). The combined organic phases were washed with brine (20 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PET/EtOAc (v/v) = 5/1) to give the title compound as light yellow oil (5.1 g, 69%).

Step 6) (*S*)-2-(allyloxy)pent-4-en-1-yl4-methylbenzene sulfonate

[00243] To a solution of (*S*)-2-(allyloxy)pent-4-en-1-ol (4.64 g, 32.6 mmol), triethylamine (6.9 mL, 49 mmol) and *N,N,N',N'*-tetramethyl-1,6-hexanediamine (0.7 mL, 3 mmol) in toluene (50 mL) was added tosyl chloride (9.3 g, 49 mmol) at 0 °C. The resulting mixture was stirred at 0 °C for 3 h. The reaction mixture was quenched with water (30 mL) and extracted with EtOAc (30 mL × 2). The combined organic phases were washed with brine (30 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PET/EtOAc (v/v) = 50/1) to give the title compound as light yellow oil (6.7 g, 69%).

Step 7) (*S*)-(3,6-dihydro-2*H*-pyran-2-yl)methyl 4-methylbenzenesulfonate

[00244] To a solution of (*S*)-2-(allyloxy)pent-4-en-1-yl 4-methylbenzenesulfonate (6.7 g, 23 mmol) in DCM (200 mL) was added Grubb's Catalyst I (380 mg, 2 mol%). The resulting mixture was stirred at room temperature for 1.5 h. The mixture was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PET/EtOAc (v/v) = 20/1) to give the title compound as black oil (5.76 g, 95%).

Step 8) (*S*)-(4'-((3,6-dihydro-2*H*-pyran-2-yl)methoxy)-2',6'-dimethyl-[1,1'-biphenyl]-3-yl) methanol

[00245] A mixture of (*S*)-(3,6-dihydro-2*H*-pyran-2-yl)methyl-4-methylbenzenesulfonate (5.76 g, 21.5 mmol), 3'-(hydroxymethyl)-2,6-dimethyl-[1,1'-biphenyl]-4-ol (5.88 g, 25.8 mmol) and potassium carbonate (8.9 g, 64 mmol) in DMF (50 mL) was stirred at 100 °C overnight. The reaction mixture was diluted with water (30 mL) and extracted with EtOAc (30 mL). The organic phase was washed with brine (30 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PET/EtOAc (v/v) = 1/1) to give the title compound as light yellow oil (4.7 g, 67.0 %).

MS (ESI, pos. Ion) *m/z*: 325.2 $[M + H]^+$.

Step 9) (*S*)-2-(((3'-(chloromethyl)-2,6-dimethyl-[1,1'-biphenyl]-4-yl)oxy)methyl)-3,6- dihydro-2*H*-pyran

[00246] To a solution of (*S*)-(4'-((3,6-dihydro-2*H*-pyran-2-yl)methoxy)-2',6'-dimethyl-[1,1'-biphenyl]-3-yl) methanol (4.7 g, 14 mmol) in DMF (20 mL) was added dropwise phosphorus oxychloride (1.6 mL, 17 mmol) at room temperature. The resulting mixture was stirred at room temperature for 1.5 h. The reaction mixture was quenched with water (20 mL) and extracted with EtOAc (20 mL × 2). The combined organic phases were washed with brine (20 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PET/EtOAc (v/v) = 10/1) to give the title compound as light yellow oil (4.57 g, 92 %).

Step 10) methyl 2-(6-((4'-(((*S*)-3,6-dihydro-2*H*-pyran-2-yl)methoxy)-2',6'-dimethyl-[1,1'-biphenyl]-3-yl) methoxy)-2,3-dihydrobenzofuran-3-yl)acetate

[00247] A mixture of (*S*)-2-(((3'-(chloromethyl)-2,6-dimethyl-[1,1'-biphenyl]-4-yl)oxy)methyl)-3,6-dihydro -2*H*-pyran (500 mg, 1.46 mmol), methyl 2-(6-hydroxy-2,3- dihydrobenzofuran-3-yl)acetate (303 mg, 1.46 mmol) and potassium phosphate (500 mg, 2.36 mmol) in DMF (40 mL) was stirred at 60 °C under nitrogen atmosphere for 3 h. The reaction mixture was quenched with water (10 mL) and extracted with EtOAc (10 mL × 2). The combined organic phases were washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PET/EtOAc (v/v) = 1/1) to give the title compound as light yellow oil (690 mg, 92.0 %).

Step 11) methyl 2-(6-((4'-(((2*S*,4*R*,5*S*)-4,5-dihydroxytetrahydro-2*H*-pyran-2-yl)methoxy)-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetate

[00248] To a solution of methyl 2-(6-((4'-(((*S*)-3,6-dihydro-2*H*-pyran-2-yl)methoxy)-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetate (690 mg, 1.34 mmol) in *t*-BuOH (10 mL) and H_2O (10 mL) was added AD-Mix-β (2 g) at room temperature. The resulting mixture was stirred at room

temperature overnight. The reaction mixture was quenched with sodium sulfite and extracted with EtOAc (10 mL × 2). The combined organic phases were washed with brine (30 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PET/EtOAc (v/v) = 2/3) to give the title compound as colorless oil (200 mg, 27.2 %).

MS (ESI, pos. Ion) *m/z*: 549.2 $[M + H]^+$.

Step 12) 2-(6-((4'-(((2*S*,4*R*,5*S*)-4,5-dihydroxytetrahydro-2*H*-pyran-2-yl)methoxy)-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetic acid

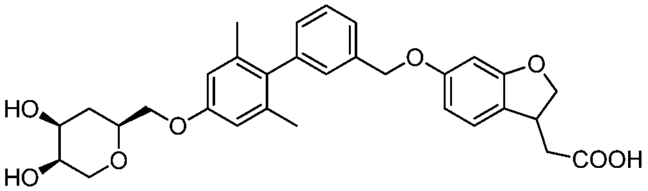
[00249] To a solution of methyl 2-(6-((4'-(((2*S*,4*R*,5*S*)-4,5-dihydroxytetrahydro-2*H*-pyran-2-yl)methoxy)-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetate (200 mg, 0.36 mmol) in tetrahydrofuran (4 mL) was added aqueous lithium hydroxide solution (4 mL, 1 M). The mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with water (5 mL), acidifed with aqueous hydrochloric acid (5 mL, 1 M), and extracted with EtOAc (10 mL × 2). The combined organic phases were washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give the title compound as a white solid (160 mg, 82.1%).

MS (ESI, pos. Ion) *m/z*: 535.2 $[M + H]^+$; and

^{1}HNMR (600 MHz, $CDCl_3$): δ 7.36 – 7.26 (m, 2H), 7.08 (s, 1H), 6.98 (dd, *J* = 16.5, 7.8 Hz, 2H), 6.59 (s, 2H), 6.45 – 6.34 (m, 2H), 5.01 – 4.94 (m, 2H), 4.67 (t, *J* = 9.0 Hz, 1H), 4.20 (dd, *J* = 9.1, 6.1 Hz, 1H), 4.15 (d, *J* = 2.1 Hz, 1H), 4.05 – 4.01 (m, 1H), 3.92 – 3.88 (m, 2H), 3.79 – 3.68 (m, 3H), 3.61 – 3.56 (m, 1H), 2.71 (dd, *J* = 16.8, 5.3 Hz, 1H), 2.52 (dd, *J* = 16.8, 9.3 Hz, 1H), 1.95 – 1.84 (m, 7H), 1.74 (t, *J* = 12.0 Hz, 1H).

Example 27

2-(6-((4'-(((2*S*,4*S*,5*R*)-4,5-Dihydroxytetrahydro-2*H*-pyran-2-yl)methoxy)-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



Step 1) methyl 2-(6-((4'-(((2*S*,4*S*,5*R*)-4,5-dihydroxytetrahydro-2*H*-pyran-2-yl)methoxy)-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetate

[00250] The title compound was prepared according to the procedure described in step 11 of Example 26. The reaction yielded the product as colorless oil (151 mg, 41%).

MS (ESI, pos. ion) *m/z*: 549.2 $[M+H]^+$.

Step 2) 2-(6-((4'-(((2*S*,4*S*,5*R*)-4,5-dihydroxytetrahydro-2*H*-pyran-2-yl)methoxy)-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetic acid

[00251] The title compound was prepared according to the procedure described in step 12 of Example 26 using methyl 2-(6-((4'-(((2*S*,4*S*,5*R*)-4,5-dihydroxytetrahydro-2*H*-pyran-2-yl)methoxy)-2',6'-dimethyl-[1,1'-biphenyl]

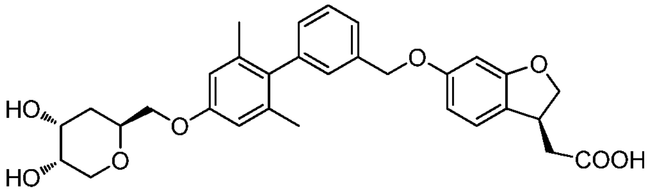
-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetate (151 mg, 0.28 mmol). The reaction yielded the product as a white solid (90 mg, 61.1%).

MS (ESI, pos. Ion) *m/z*: 535.2 $[M+H]^+$; and

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.37 – 7.26 (m, 2H), 7.07 (s, 1H), 6.97 (dd, *J* = 15.6, 7.8 Hz, 2H), 6.59 (s, 2H), 6.45 – 6.35 (m, 2H), 4.97 (s, 2H), 4.67 (t, *J* = 9.0 Hz, 1H), 4.20 (dd, *J* = 9.2, 6.1 Hz, 1H), 4.08 – 4.05 (m, 1H), 3.99 (dd, *J* = 10.1, 6.1 Hz, 1H), 3.90 (dd, *J* = 10.1, 3.9 Hz, 1H), 3.78 – 3.65 (m, 4H), 3.54 (d, *J* = 12.6 Hz, 1H), 2.71 (dd, *J* = 16.8, 5.4 Hz, 1H), 2.52 (dd, *J* = 16.8, 9.3 Hz, 1H), 1.95 – 1.80 (m, 7H), 1.70– 1.67 (m, 1H).

Example 28

2-((*S*)-6-((4'-(((2*S*,4*R*,5*S*)-4,5-Dihydroxytetrahydro-2*H*-pyran-2-yl)methoxy)-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



Step 1) methyl 2-((*S*)-6-((4'-(((*S*)-3,6-dihydro-2*H*-pyran-2-yl)methoxy)-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetate

[00252] The title compound was prepared according to the procedure described in step 10 of Example 26 using (*S*)-methyl 2-(6-hydroxy-2,3-dihydrobenzofuran-3-yl)acetate (1.3 g, 6.2 mmol) and (*S*)-2-(((3'-(chloromethyl)-2,6-dimethyl-[1,1'-biphenyl]-4-yl)oxy)methyl)-3,6-dihydro-2*H*-pyran (2.1 g, 6.1 mmol). The reaction yielded the product as pale yellow oil (2.87 g, 89%).

MS (ESI, pos. ion) *m/z*: 515.2 $[M+H]^+$.

Step 2) methyl 2-((*S*)-6-((4'-(((2*S*,4*R*,5*S*)-4,5-dihydroxytetrahydro-2*H*-pyran-2-yl)methoxy)-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetate

[00253] The title compound was prepared according to the procedure described in step 11 of Example 26 using methyl 2-((*S*)-6-((4'-(((*S*)-3,6-dihydro-2*H*-pyran-2-yl)methoxy)-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetate (3.1 g, 6 mmol). The reaction yielded the product as colorless oil (1.19 g, 36%).

MS (ESI, pos. ion) *m/z*: 549.2 $[M+H]^+$.

Step3) 2-((*S*)-6-((4'-(((2*S*,4*R*,5*S*)-4,5-dihydroxytetrahydro-2*H*-pyran-2-yl)methoxy)-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetic acid

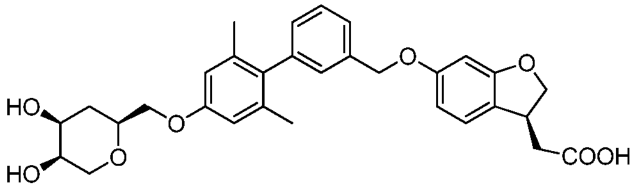
[00254] The title compound was prepared according to the procedure described in step 12 of Example 26 using methyl 2-((*S*)-6-((4'-(((2*S*,4*R*,5*S*)-4,5-dihydroxytetrahydro-2*H*-pyran-2-yl)methoxy)-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetate (1.19 g, 2.17 mmol). The reaction yielded the product as a white solid (1.16 g, 100%).

MS (ESI, pos. Ion) *m/z*: 535.2 $[M+H]^+$; and

^{1}H NMR (600 MHz, CDCl$_3$): δ 7.45 – 7.36 (m, 2H), 7.18 (s, 1H), 7.08 (dd, J = 16.4, 7.8 Hz, 2H), 6.69 (s, 2H), 6.56 – 6.45 (m, 2H), 5.08 (s, 2H), 4.78 (t, J = 9.0 Hz, 1H), 4.30 (dd, J = 9.2, 6.1 Hz, 1H), 4.25 (d, J = 2.2 Hz, 1H), 4.16 – 4.10 (m, 1H), 4.03 – 3.96 (m, 2H), 3.86 – 3.83 (m, 3H), 3.71 – 3.65 (m, 1H), 2.82 (dd, J = 16.8, 5.4 Hz, 1H), 2.63 (dd, J = 16.8, 9.3 Hz, 1H), 2.06 – 1.95 (m, 7H), 1.87 – 1.82 (m, 1H).

Example 29

2-((*S*)-6-((4'-(((2*S*,4*S*,5*R*)-4,5-Dihydroxytetrahydro-2*H*-pyran-2-yl)methoxy)-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



Step 1) methyl 2-((*S*)-6-((4'-(((2*S*,4*S*,5*R*)-4,5-dihydroxytetrahydro-2*H*-pyran-2-yl)methoxy)-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetate

[00255] The title compound was prepared according to the procedure described in step 2 of Example 28. The reaction yielded the product as colorless oil (1.38 g, 42%).

MS (ESI, pos. ion) *m/z*: 549.2 $[M+H]^+$.

Step 2) 2-((*S*)-6-((4'-(((2*S*,4*S*,5*R*)-4,5-dihydroxytetrahydro-2*H*-pyran-2-yl)methoxy)-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetic acid

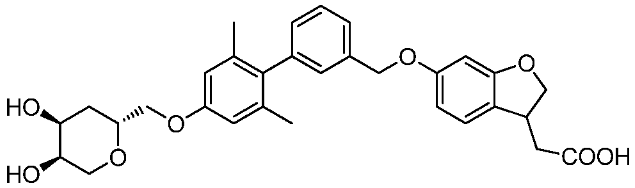
[00256] The title compound was prepared according to the procedure described in step 12 of Example 26 using methyl 2-((*S*)-6-((4'-(((2*S*,4*S*,5*R*)-4,5-dihydroxytetrahydro-2*H*-pyran-2-yl)methoxy)-2',6'-dimethyl-[1,1'-biphenyl] -3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetate (1.38 g, 2.52 mmol). The reaction yielded the product as a white solid (1.29 g, 95.9%).

MS (ESI, pos. Ion) *m/z*: 535.2 $[M+H]^+$; and

^{1}H NMR (600 MHz, CDCl$_3$): δ 7.46 – 7.35 (m, 2H), 7.17 (s, 1H), 7.08 (dd, J = 15.5, 7.8 Hz, 2H), 6.69 (s, 2H), 6.54 – 6.45 (m, 2H), 5.07 (s, 2H), 4.77 (t, J = 9.0 Hz, 1H), 4.30 (dd, J = 9.1, 6.1 Hz, 1H), 4.18 – 4.15 (m, 1H), 4.09 (dd, J = 10.0, 6.1 Hz, 1H), 3.99 (dd, J = 10.1, 3.9 Hz, 1H), 3.89 – 3.74 (m, 4H), 3.64 (d, J = 12.7 Hz, 1H), 2.81 (dd, J = 16.8, 5.4 Hz, 1H), 2.62 (dd, J = 16.8, 9.3 Hz, 1H), 1.98 – 1.95 (m 7H), 1.78 – 1.72 (m, 1H).

Example 30

2-(6-((4'-(((2*R*,4*S*,5*R*)-4,5-Dihydroxytetrahydro-2*H*-pyran-2-yl)methoxy)-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



Step 1) (*R*)-1-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)but-3-en-1-ol

[00257] The title compound was prepared according to the procedure described in step 1 of Example 26 using (*S*)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde (20 g, 153 mmol) and 3-bromoprop-1-ene (26 mL, 307 mmol). The reaction yielded the product as pale yellow liquid (22.2 g, 83.9%).

Step 2) (*S*)-4-((*R*)-1-(allyloxy)but-3-en-1-yl)-2,2-dimethyl-1,3-dioxolane

[00258] The title compound was prepared according to the procedure described in step 2 of Example 26 using (*R*)-1-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)but-3-en-1-ol (20 g, 129 mmol) and 3-bromoprop-1-ene (112 mL, 1.29 mol). The reaction yielded the product as a pale yellow solid (14 g, 51.2%).

Step 3) (2*S*,3*R*)-3-(allyloxy)hex-5-ene-1,2-diol

[00259] The title compound was prepared according to the procedure described in step 3 of Example 26 using (*S*)-4-((*R*)-1-(allyloxy)but-3-en-1-yl)-2,2-dimethyl-1,3-dioxolane (14 g, 66 mmol). The reaction yielded the product as yellow liquid (9.0 g, 79.2%).

Step 4) (*R*)-2-(allyloxy)pent-4-enal

[00260] The title compound was prepared according to the procedure described in step 4 of Example 26 using (2*S*,3*R*)-3-(allyloxy)hex-5-ene-1,2-diol (9.0 g, 52 mmol) and sodium periodate (28 g, 131 mmol). The reaction yielded the product as yellow liquid (7.3 g, 100%).

Step 5) (*R*)-2-(allyloxy)pent-4-en-1-ol

[00261] The title compound was prepared according to the procedure described in step 5 of Example 26 using (*R*)-2-(allyloxy)pent-4-enal (7.3 g, 52 mmol). The reaction yielded the product as pale yellow oil (5.1 g, 69%).

Step 6) (*R*)-2-(allyloxy)pent-4-en-1-yl 4-methylbenzenesulfonate

[00262] The title compound was prepared according to the procedure described in step 6 of Example 26 using (*R*)-2-(allyloxy)pent-4-en-1-ol (4.64 g, 32.6 mmol) and *p*-toluensulfonyl chloride (9.3 g, 49 mmol). The reaction yielded the product as yellow oil (6.7 g, 69%).

Step 7) (*R*)-(3,6-dihydro-2*H*-pyran-2-yl)methyl 4-methylbenzenesulfonate

[00263] The title compound was prepared according to the procedure described in step 7 of Example 26 using (*R*)-2-(allyloxy)pent-4-en-1-yl 4-methylbenzenesulfonate (6.7 g, 23 mmol). The reaction yielded the product as brownness oil (5.76 g, 95%).

Step 8) (*R*)-(4'-((3,6-dihydro-2*H*-pyran-2-yl)methoxy)-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methanol

[00264] The title compound was prepared according to the procedure described in step 8 of Example 26 using (*R*)-(3,6-dihydro-2*H*-pyran-2-yl)methyl 4-methylbenzenesulfonate (5.76 g, 21.5 mmol) and 3'-(hydroxymethyl)- 2,6-dimethyl-[1,1'-biphenyl]-4-ol (5.88 g, 25.8 mmol). The reaction yielded the product as yellow liquid (4.7 g, 67.0%).

Step 9) (*R*)-2-(((3'-(chloromethyl)-2,6-dimethyl-[1,1'-biphenyl]-4-yl)oxy)methyl)-3,6-dihydro-2*H*-pyran

[00265] The title compound was prepared according to the procedure described in step 9 of Example 26 using (*R*)-(4'-((3,6-dihydro-2*H*-pyran-2-yl)methoxy)-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methanol (4.7 g, 14 mmol) and phosphorus oxychloride (1.6 mL, 17 mmol). The reaction yielded the product as yellow oil (4.57 g, 92 %).

Step 10) methyl 2-(6-((4'-(((*R*)-3,6-dihydro-2*H*-pyran-2-yl)methoxy)-2',6'-dimethyl-[1,1'-biphenyl]-3-yl) methoxy)-2,3-dihydrobenzofuran-3-yl)acetate

[00266] The title compound was prepared according to the procedure described in step 10 of Example 26 using (*R*)-2-(((3'-(chloromethyl)-2,6-dimethyl-[1,1'-biphenyl]-4-yl)oxy)methyl)-3,6-dihydro-2*H*-pyran (500 mg, 1.46 mmol) and methyl 2-(6-hydroxy-2,3-dihydrobenzofuran-3-yl)acetate (303 mg, 1.46 mmol). The reaction yielded the product as pale yellow oil (690 mg, 92.0%).

Step 11) methyl 2-(6-((4'-(((2*R*,4*S*,5*R*)-4,5-dihydroxytetrahydro-2*H*-pyran-2-yl)methoxy)-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetate

[00267] The title compound was prepared according to the procedure described in step 11 of Example 26 using methyl 2-(6-((4'-(((*R*)-3,6-dihydro-2*H*-pyran-2-yl)methoxy)-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3 -dihydrobenzofuran-3-yl)acetate (690 mg, 1.34 mmol). The reaction yielded the product as colorless oil (200 mg, 27%).

MS (ESI, pos. ion) *m/z*: 549.2 $[M+H]^+$.

Step 12) 2-(6-((4'-(((2*R*,4*S*,5*R*)-4,5-dihydroxytetrahydro-2*H*-pyran-2-yl)methoxy)-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetic acid

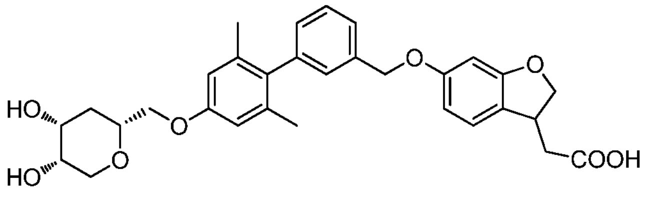
[00268] The title compound was prepared according to the procedure described in step 12 of Example 26 using methyl 2-(6-((4'-(((2*R*,4*S*,5*R*)-4,5-dihydroxytetrahydro-2*H*-pyran-2-yl)methoxy)-2',6'-dimethyl-[1,1'-biphenyl] -3-yl) methoxy)-2,3-dihydrobenzofuran-3-yl)acetate (200 mg, 0.36 mmol). The reaction yielded the product as a white solid (160 mg, 82.1%).

MS (ESI, pos. Ion) *m/z*: 535.2 $[M+H]^+$; and

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.48 – 7.35 (m, 2H), 7.18 (s, 1H), 7.08 (dd, *J* = 16.1, 7.8 Hz, 2H), 6.69 (s, 2H), 6.55 – 6.42 (m, 2H), 5.08 (s, 2H), 4.77 (t, *J* = 9.0 Hz, 1H), 4.30 (dd, *J* = 9.2, 6.1 Hz, 1H), 4.25 (d, *J* = 2.2 Hz, 1H), 4.14 – 4.10 (m, 1H), 4.04 – 3.96 (m, 2H), 3.90 – 3.78 (m, 3H), 3.71 – 3.65 (m, 1H), 2.82 (dd, *J* = 16.9, 5.2 Hz, 1H), 2.63 (dd, *J* = 16.8, 9.3 Hz, 1H), 2.05 – 1.92 (m, 7H), 1.84 (t, *J* = 12.2 Hz, 1H).

Example 31

2-(6-((4'-(((2*R*,4*R*,5*S*)-4,5-Dihydroxytetrahydro-2*H*-pyran-2-yl)methoxy)-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



Step 1) methyl 2-(6-((4'-(((2*R*,4*R*,5*S*)-4,5-dihydroxytetrahydro-2*H*-pyran-2-yl)methoxy)-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetate

[00269] The title compound was prepared according to the procedure described in step 11 of Example 30. The reaction yielded the product as colorless oil (200 mg, 27%).

MS (ESI, pos. ion) *m/z*: 549.2 $[M+H]^+$.

Step 2) 2-(6-((4'-(((2*R*,4*R*,5*S*)-4,5-dihydroxytetrahydro-2*H*-pyran-2-yl)methoxy)-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetic acid

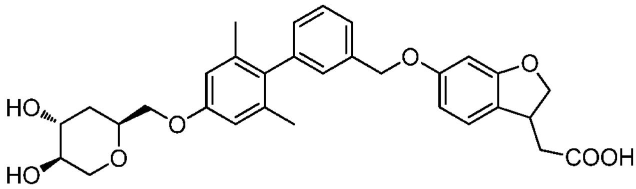
[00270] The title compound was prepared according to the procedure described in step 12 of Example 26 using methyl 2-(6-((4'-(((2*R*,4*R*,5*S*)-4,5-dihydroxytetrahydro-2*H*-pyran-2-yl)methoxy)-2',6'-dimethyl-[1,1'-biphenyl] -3-yl) methoxy)-2,3-dihydrobenzofuran-3-yl)acetate (200 mg, 0.36 mmol). The reaction yielded the product as a white solid (133 mg, 68.2%).

MS (ESI, pos. Ion) *m/z*: 535.2 $[M+H]^+$; and

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.48 – 7.36 (m, 2H), 7.17 (s, 1H), 7.08 (dd, *J* = 15.8, 7.8 Hz, 2H), 6.69 (s, 2H), 6.57 – 6.41 (m, 2H), 5.07 (s, 2H), 4.77 (t, *J* = 9.0 Hz, 1H), 4.30 (dd, *J* = 9.1, 6.1 Hz, 1H), 4.19 – 4.14 (m, 1H), 4.09 (dd, *J* = 10.0, 6.1 Hz, 1H), 3.99 (dd, *J* = 10.1, 3.9 Hz, 1H), 3.89 – 3.74 (m, 4H), 3.64 (d, *J* = 12.6 Hz, 1H), 2.81 (dd, *J* = 16.8, 5.3 Hz, 1H), 2.62 (dd, *J* = 16.8, 9.3 Hz, 1H), 1.99 (d, *J* = 16.3 Hz, 7H), 1.76 (dd, *J* = 23.8, 11.9 Hz, 1H).

Example 32

2-(6-((4'-(((2*S*,4*R*,5*R*)-4,5-Dihydroxytetrahydro-2*H*-pyran-2-yl)methoxy)-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



Step 1) (1*S*,4*S*,6*R*)-4-(((3'-(chloromethyl)-2,6-dimethyl-[1,1'-biphenyl]-4-yl)oxy)methyl)-3,7-dioxabicyclo [4.1.0]heptane

[00271] To a solution of (*S*)-2-(((3'-(chloromethyl)-2,6-dimethyl-[1,1'-biphenyl]-4-yl)oxy)methyl)-3,6-dihydro-2*H*-pyran (1.5 g, 4.4 mmol) in DCM (80 mL) at 0 °C was added 3-chloroperoxybenzoic acid (2.6 g, 11 mmol). The resulting mixture was stirred at 0 °C for 1 h. The reaction mixture was quenched with dimethyl sulfide (2 mL) and extracted with EtOAc (20 mL × 2). The combined organic phases were washed with brine (20 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PET/ EtOAc (v/v) = 3/1) to give the title compound as yellow oil (390 mg, 24.6%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.42 (t, *J* = 7.7 Hz, 1H), 7.37 (d, *J* = 7.7 Hz, 1H), 7.17 (s, 1H), 7.10 (d, *J* = 7.4 Hz, 1H), 6.69 (s, 2H), 4.64 (s, 2H), 4.34 (dd, *J* = 13.6, 4.1 Hz, 1H), 4.05 (d, *J* = 13.6 Hz, 1H), 3.97 (d, *J* = 4.5 Hz, 2H), 3.82 (ddd, *J* = 11.9, 7.6, 4.6 Hz, 1H), 3.49 (d, *J* = 3.5 Hz, 1H), 3.34 (t, *J* = 4.2 Hz, 1H), 2.16 (d, *J* = 14.5 Hz, 1H), 2.02 – 2.00 (m, 7H).

Step 2) (3*R*,4*R*,6*S*)-6-(((3'-(chloromethyl)-2,6-dimethyl-[1,1'-biphenyl]-4-yl)oxy)methyl)tetrahydro-2*H*-pyran-3,4-diol

[00272] To a solution of (1*S*,4*S*,6*R*)-4-(((3'-(chloromethyl)-2,6-dimethyl-[1,1'-biphenyl]-4-yl)oxy)methyl)-3,7-

dioxabicyclo[4.1.0]heptane (340 mg, 0.95mmol) in water (20 mL) and acetonitrile (20 mL) was added bismuth trichloride (60 mg, 0.19 mmol) at room temperature. The resulting mixture was stirred at room temperature for 2 days and filtered. The filtrate was extracted with EtOAc (20 mL × 2). The combined organic phases were washed with brine (20 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PET/EtOAc (v/v) = 1/1) to give the title compound as yellow oil (170 mg, 47.6%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 – 7.34 (m, 2H), 7.18 (s, 1H), 7.13 – 7.08 (m, 1H), 6.71 (s, 2H), 4.64 (s, 2H), 4.20 – 4.02 (m, 4H), 3.99 (dd, *J* = 10.0, 4.2 Hz, 1H), 3.88 (d, *J* = 12.3 Hz, 1H), 3.59 (s, 1H), 2.12 (ddd, *J* = 14.4, 11.5, 3.1 Hz, 1H), 2.02 (s, 6H), 1.74 (d, *J* = 14.3 Hz, 1H).

Step 3) methyl 2-(6-((4'-(((2*S*,4*R*,5*R*)-4,5-dihydroxytetrahydro-2*H*-pyran-2-yl)methoxy)-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetate

[00273] A mixture of (3*R*,4*R*,6*S*)-6-(((3'-(chloromethyl)-2,6-dimethyl-[1,1'-biphenyl]-4-yl)oxy)methyl) tetrahydro-2*H*-pyran-3,4-diol (170 mg, 0.45 mmol), methyl 2-(6-hydroxy-2,3- dihydrobenzofuran-3-yl)acetate (100 mg, 0.48 mmol) and potassium phosphate (150 mg, 0.71 mmol) in DMF (10 mL) was stirred at 60 °C for 3 h under nitrogen atmosphere. The reaction mixture was quenched with water (5 mL) and extracted with EtOAc (20 mL × 2). The combined organic phases were washed with brine (5 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PET/EtOAc (v/v) = 1/2) to give the title compound as light yellow oil (180 mg, 72.7%).

MS (ESI, pos. Ion) *m/z*: 549.2 $[M+H]^+$.

Step 4) 2-(6-((4'-(((2*S*,4*R*,5*R*)-4,5-dihydroxytetrahydro-2*H*-pyran-2-yl)methoxy)-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetic acid

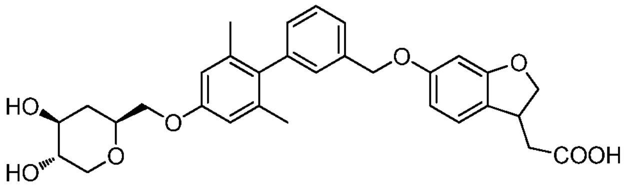
[00274] To a solution of methyl 2-(6-((4'-(((2*S*,4*R*,5*R*)-4,5-dihydroxytetrahydro-2*H*-pyran-2-yl)methoxy)-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetate (180 mg, 0.33 mmol) in tetrahydrofuran (4 mL) was added aqueous lithium hydroxide solution (4 mL, 1 M). The mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with water (5 mL), acidifed with aqueous hydrochloric acid (10 mL, 1 M), and extracted with EtOAc (20 mL × 2). The combined organic phases were washed with brine (3 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give the title compound as a white solid (53 mg, 30.2%).

MS (ESI, pos. Ion) *m/z*: 535.3 $[M+H]^+$; and

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 (dt, *J* = 15.0, 7.6 Hz, 2H), 7.18 (s, 1H), 7.08 (dd, *J* = 10.9, 7.8 Hz, 2H), 6.70 (s, 2H), 6.55 – 6.44 (m, 2H), 5.08 (s, 2H), 4.77 (t, *J* = 9.0 Hz, 1H), 4.30 (dd, *J* = 9.2, 6.0 Hz, 1H), 4.13 (ddd, *J* = 18.1, 12.1, 4.2 Hz, 3H), 4.04 (dd, *J* = 10.1, 5.7 Hz, 1H), 3.99 (dd, *J* = 10.1, 4.1 Hz, 1H), 3.88 (d, *J* = 12.7 Hz, 1H), 3.85 – 3.78 (m, 1H), 3.59 (s, 1H), 2.81 (dd, *J* = 16.8, 5.4 Hz, 1H), 2.62 (dd, *J* = 16.8, 9.2 Hz, 1H), 2.05 – 1.97 (m, 7H), 1.74 (d, *J* = 14.6 Hz, 1H).

Example 33

2-(6-((4'-(((2*S*,4*S*,5*S*)-4,5-Dihydroxytetrahydro-2*H*-pyran-2-yl)methoxy)-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



Step 1) (1*R*,4*S*,6*S*)-4-(((3'-(chloromethyl)-2,6-dimethyl-[1,1'-biphenyl]-4-yl)oxy)methyl)-3,7-dioxabicyclo [4.1.0]heptane

[00275] The title compound was prepared according to the procedure described in step 1 of Example 32. The reaction yielded the product as pale yellow oil (290 mg, 18.3%).

Step 2) (3*S*,4*S*,6*S*)-6-(((3'-(chloromethyl)-2,6-dimethyl-[1,1'-biphenyl]-4-yl)oxy)methyl)tetrahydro-2*H*-pyran-3,4-diol

[00276] The title compound was prepared according to the procedure described in step 2 of Example 32 using (1*R*,4*S*,6*S*)-4-(((3'-(chloromethyl)-2,6-dimethyl-[1,1'-biphenyl]-4-yl)oxy)methyl)-3,7-dioxabicyclo [4.1.0]heptane (290 mg, 0.81 mmol). The reaction yielded the product as pale yellow oil (110 mg, 36.1%).

Step 3) methyl 2-(6-((4'-(((2*S*,4*S*,5*S*)-4,5-dihydroxytetrahydro-2*H*-pyran-2-yl)methoxy)-2',6'-dimethyl -[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetate

[00277] The title compound was prepared according to the procedure described in step 3 of Example 32 using (3*S*,4*S*,6*S*)-6-(((3'-(chloromethyl)-2,6-dimethyl-[1,1'-biphenyl]-4-yl)oxy)methyl)tetrahydro-2*H*-pyran-3,4-diol (290 mg, 0.81 mmol) and methyl 2-(6-hydroxy-2,3-dihydrobenzofuran-3-yl)acetate (60 mg, 0.28 mmol). The reaction yielded the product as pale yellow oil (120 mg, 75.0%).

Step 4) 2-(6-((4'-(((2S,4S,5S)-4,5-dihydroxytetrahydro-2H-pyran-2-yl)methoxy)-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetic acid

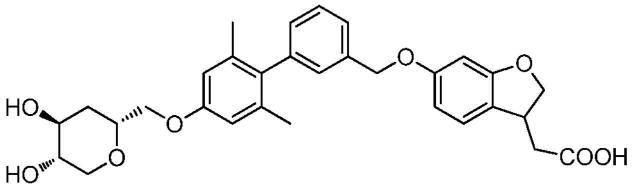
[00278] The title compound was prepared according to the procedure described in step 4 of Example 32 using methyl 2-(6-((4'-(((2*S*,4*S*,5*S*)-4,5-dihydroxytetrahydro-2*H*-pyran-2-yl)methoxy)-2',6'-dimethyl-[1,1'-biphenyl]-3-yl) methoxy)-2,3-dihydrobenzofuran-3-yl)acetate (120 mg, 0.22 mmol). The reaction yielded the product as a white solid (73 mg, 62.4%).

MS (ESI, pos. Ion) *m/z*: 535.3 $[M+H]^+$; and

^{1}H NMR (400 MHz, DMSO-d_6): δ 12.32 (s, 1H), 7.49 – 7.33 (m, 2H), 7.20 – 7.02 (m, 3H), 6.69 (s, 2H), 6.47 (dd, *J* = 10.9, 2.7 Hz, 2H), 5.09 (s, 2H), 4.93 (d, *J* = 2.9 Hz, 1H), 4.80 (d, *J* = 4.1 Hz, 1H), 4.68 (t, *J* = 9.0 Hz, 1H), 4.19 (dd, *J* = 8.9, 6.8 Hz, 1H), 3.90 (ddd, *J* = 12.4, 9.9, 5.4 Hz, 3H), 3.81 – 3.55 (m, 4H), 3.29 (s, 1H), 2.69 (dd, *J* = 16.6, 5.6 Hz, 1H), 2.46 (d, *J* = 9.0 Hz, 1H), 1.96 – 1.81 (m, 7H), 1.49 (d, *J* = 12.7 Hz, 1H).

Example 34

2-(6-((4'-(((2*R*,4*S*,5*S*)-4,5-Dihydroxytetrahydro-2*H*-pyran-2-yl)methoxy)-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



Step 1) (1*S*,4*R*,6*R*)-4-(((3'-(chloromethyl)-2,6-dimethyl-[1,1'-biphenyl]-4-yl)oxy)methyl)-3,7-dioxabicyclo [4.1.0]heptane

[00279] The title compound was prepared according to the procedure described in step 1 of Example 32 using (*R*)-2-(((3'-(chloromethyl)-2,6-dimethyl-[1,1'-biphenyl]-4-yl)oxy)methyl)-3,6-dihydro-2*H*-pyran (1.5 g, 4.4 mmol) and metachloroperbenzoic acid (2.6 g, 11 mmol). The reaction yielded the product as pale yellow oil (310 mg, 20.0%).

Step 2) (3*S*,4*S*,6*R*)-6-(((3'-(chloromethyl)-2,6-dimethyl-[1,1'-biphenyl]-4-yl)oxy)methyl)tetrahydro-2*H*-pyran-3,4-diol

[00280] The title compound was prepared according to the procedure described in step 2 of Example 32 using (1*S*,4*R*,6*R*)-4-(((3'-(chloromethyl)-2,6-dimethyl-[1,1'-biphenyl]-4-yl)oxy)methyl)-3,7-dioxabicyclo[4.1.0]heptane (310 mg, 0.86 mmol). The reaction yielded the product as pale yellow oil (130 mg, 39.9%).

Step 3) methyl 2-(6-((4'-(((2*R*,4*S*,5*S*)-4,5-dihydroxytetrahydro-2*H*-pyran-2-yl)methoxy)-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetate

[00281] The title compound was prepared according to the procedure described in step 3 of Example 32 using (3*S*,4*S*,6*R*)-6-(((3'-(chloromethyl)-2,6-dimethyl-[1,1'-biphenyl]-4-yl)oxy)methyl)tetrahydro-2*H*-pyran-3,4-diol (130 mg, 0.34 mmol) and methyl 2-(6-hydroxy-2,3-dihydrobenzofuran-3-yl)acetate (72 mg, 0.34 mmol). The reaction yielded the product as pale yellow oil (123 mg, 65.0%).

Step 4) 2-(6-((4'-(((2*R*,4*S*,5*S*)-4,5-dihydroxytetrahydro-2*H*-pyran-2-yl)methoxy)-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetic acid

[00282] The title compound was prepared according to the procedure described in step 4 of Example 32 using methyl 2-(6-((4'-(((2*R*,4*S*,5*S*)-4,5-dihydroxytetrahydro-2*H*-pyran-2-yl)methoxy)-2',6'-dimethyl-[1,1'-biphenyl]-3-yl) methoxy)-2,3-dihydrobenzofuran-3-yl)acetate (123 mg, 0.22 mmol). The reaction yielded the product as a white solid (73 mg, 60.9%).

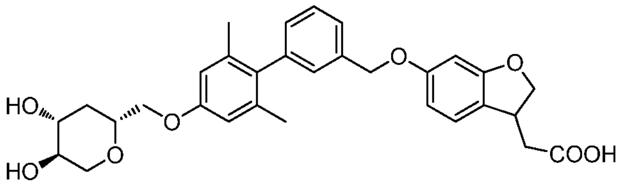
MS (ESI, pos. Ion) *m/z*: 535.3 $[M+H]^+$; and

^{1}H NMR (400 MHz, CD_3OD): δ 7.48 – 7.36 (m, 2H), 7.14 (s, 1H), 7.07 (dd, *J* = 15.0, 7.7 Hz, 2H), 6.69 (s, 2H), 6.49 (dd, *J* = 8.2, 2.2 Hz, 1H), 6.42 (d, *J* = 2.1 Hz, 1H), 5.08 (s, 2H), 4.70 (t, *J* = 9.0 Hz, 1H), 4.23 (dd, *J* = 9.1, 6.3 Hz, 1H), 4.14 – 4.06 (m, 1H), 4.04 – 3.85 (m, 4H), 3.76 (dd, *J* = 16.0, 9.3 Hz, 2H), 3.49 (s, 1H), 2.72 (dd, *J* = 16.4, 5.8 Hz, 1H), 2.52 (dd, *J* = 16.4, 8.9 Hz, 1H), 2.09 – 1.99 (m, 1H), 1.95 (s, 6H), 1.67 (d, *J* = 13.8 Hz, 1H).

Example 35

2-(6-((4'-(((2*R*,4*R*,5*R*)-4,5-Dihydroxytetrahydro-2*H*-pyran-2-yl)methoxy)-2',6'-dimethyl-[1,1'-biphenyl]-3-

yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



Step 1) (1*R*,4*R*,6*S*)-4-(((3'-(chloromethyl)-2,6-dimethyl-[1,1'-biphenyl]-4-yl)oxy)methyl)-3,7-dioxabicyclo [4.1.0]heptane

[00283] The title compound was prepared according to the procedure described in step 1 of Example 32. The reaction yielded the product as pale yellow oil (240 mg, 15.2%).

Step 2) (3*R*,4*R*,6*R*)-6-(((3'-(chloromethyl)-2,6-dimethyl-[1,1'-biphenyl]-4-yl)oxy)methyl)tetrahydro-2*H*-pyran-3,4-diol

[00284] The title compound was prepared according to the procedure described in step 2 of Example 32 using (1*R*,4*R*,6*S*)-4-(((3'-(chloromethyl)-2,6-dimethyl-[1,1'-biphenyl]-4-yl)oxy)methyl)-3,7-dioxabicyclo[4.1.0] heptane (240 mg, 0.67 mmol). The reaction yielded the product as pale yellow oil (53 mg, 21%).

Step 3) methyl 2-(6-((4'-(((2*R*,4*R*,5*R*)-4,5-dihydroxytetrahydro-2*H*-pyran-2-yl)methoxy)-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetate

[00285] The title compound was prepared according to the procedure described in step 3 of Example 32 using (3*R*,4*R*,6*R*)-6-(((3'-(chloromethyl)-2,6-dimethyl-[1,1'-biphenyl]-4-yl)oxy)methyl)tetrahydro-2*H*-pyran-3,4-diol (130 mg, 0.34 mmol) and methyl 2-(6-hydroxy-2,3-dihydrobenzofuran-3-yl)acetate (35 mg, 0.16 mmol). The reaction yielded the product as pale yellow oil (40 mg, 51.8%).

Step 4) 2-(6-((4'-(((2*R*,4*R*,5*R*)-4,5-dihydroxytetrahydro-2*H*-pyran-2-yl)methoxy)-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetic acid

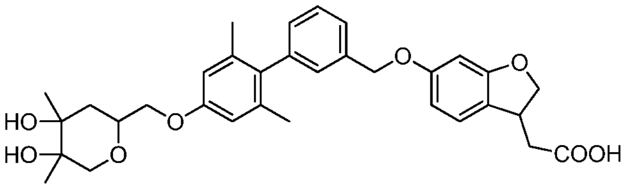
[00286] The title compound was prepared according to the procedure described in step 4 of Example 32 using methyl 2-(6-((4'-(((2*R*,4*R*,5*R*)-4,5-dihydroxytetrahydro-2*H*-pyran-2-yl)methoxy)-2',6'-dimethyl-[1,1'-biphenyl]-3-yl) methoxy)-2,3-dihydrobenzofuran-3-yl)acetate (40 mg, 0.073 mmol). The reaction yielded the product as a white solid (28 mg, 71.8%).

MS (ESI, pos. Ion) *m/z*: 535.3 $[M+H]^+$; and

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 (dt, J = 15.1, 7.6 Hz, 2H), 7.18 (s, 1H), 7.08 (dd, J = 11.2, 7.8 Hz, 2H), 6.70 (s, 2H), 6.54 – 6.44 (m, 2H), 5.08 (s, 2H), 4.77 (t, J = 9.0 Hz, 1H), 4.30 (dd, J = 9.1, 6.1 Hz, 1H), 4.19 – 3.98 (m, 5H), 3.88 (d, J = 12.4 Hz, 1H), 3.83 (d, J = 5.8 Hz, 1H), 3.59 (s, 1H), 2.81 (dd, J = 16.8, 5.4 Hz, 1H), 2.62 (dd, J = 16.7, 9.2 Hz, 1H), 2.04 – 2.00 (m, 7H), 1.74 (d, J = 14.3 Hz, 1H).

Example 36

2-(6-((4'-((4,5-Dihydroxy-4,5-dimethyltetrahydro-2*H*-pyran-2-yl)methoxy)-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



Step1) ethyl 4,5-dimethyl-3,6-dihydro-2*H*-pyran-2-carboxylate

[00287] A solution of ethyl 2-oxoacetate (6.3 mL, 30 mmol) and bismuth(III) chloride (0.5 g, 1.58 mmol) in choroform (150 mL) was stirred at room temperature for 20 min, then a solution of 2,3-dimethylbuta-1,3-diene (20 g, 153 mmol) in choroform (50 mL) was added dropwise at room temperature. The mixture was stirred at 60 °C for 2 h. The reaction mixture was quenched with saturated solium bicarbonate solution (20 mL) and extracted with DCM (80 mL × 2). The combined organic phases were washed with brine (30 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PET/EtOAc (v/v) = 50/1) to give the title compound as colorless liquid (2.3 g, 41 %).

Step2) (4,5-dimethyl-3,6-dihydro-2*H*-pyran-2-yl)methanol

[00288] To a suspension of Lithium aluminium hydride (93 mg, 2.45 mmol) in tetrahydrofuran (5 mL) at 0 °C was added a solution of ethyl 4,5-dimethyl-3,6-dihydro-2*H*-pyran-2-carboxylate (300 mg, 1.6 mmol) in tetrahydrofuran (5 mL) dropwise. The formed mixture was stirred at room temperature overnight. To the reaction mixture was added successively water (5 mL) and 10% sodium hydroxide solution (25 mL). The resulting mixture was extracted with EtOAc (100 mL × 2). The combined organic phases were washed with brine (50 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PET/EtOAc (v/v) = 3/1) to give the title compound as yellow oil (220 mg, 95 %).

^1H NMR (600 MHz, $CDCl_3$): δ 4.07 (d, J = 15.4 Hz, 1H), 3.99 (d, J = 15.4 Hz, 1H), 3.70 – 3.62 (m, 2H), 3.57 (dd, J = 11.4, 7.3 Hz, 1H), 2.36 (s, 1H), 2.08 – 2.00 (m, 1H), 1.73 (d, J = 16.6 Hz, 1H), 1.66 (s, 3H), 1.55 (s, 3H).

Step 3) (4,5-dimethyl-3,6-dihydro-2*H*-pyran-2-yl)methyl 4-methylbenzenesulfonate

[00289] To a solution of (4,5-dimethyl-3,6-dihydro-2*H*-pyran-2-yl)methanol (1.33 g, 9.36 mmol) triethylamine (2.0 mL, 14.2 mmol) and *N,N,N',N'*-tetramethyl-1,6-hexanediamine (0.21 mL, 0.96 mmol) in toluene (30 mL) was added tosyl chloride (2.7 g, 14 mmol) at 0 °C. The formed mixture was stirred at 0 °C for 3 h. The reaction mixture was quenched with water (10 mL) and extracted with EtOAc (30 mL × 2). The combined organic phases were washed with brine (30 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PET/EtOAc (v/v) = 10/1) to give the title compound as light yellow oil (2.4 g, 86%).

^1H NMR (600 MHz, $CDCl_3$): δ 7.83 (d, J = 8.3 Hz, 2H), 7.36 (d, J = 8.0 Hz, 2H), 4.06 – 4.02 (m, 2H), 3.98 (d, J = 15.6 Hz, 1H), 3.91 (d, J = 15.5 Hz, 1H), 3.79 (ddd, J = 10.5, 9.2, 5.1 Hz, 1H), 2.47 (s, 3H), 2.02 – 1.94 (m, 1H), 1.79 (d, J = 16.4 Hz, 1H), 1.64 (s, 3H), 1.53 (s, 3H).

Step 4) methyl 2-(6-((4'-((4,5-dimethyl-3,6-dihydro-2*H*-pyran-2-yl)methoxy)-2',6'-dimethyl-[1,1'-biphenyl]

-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetate

[00290] A mixture of (4,5-dimethyl-3,6-dihydro-2*H*-pyran-2-yl)methyl 4-methylbenzene-sulfonate (425 mg, 1.43 mmol), methyl 2-(6-((4'-hydroxy-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl) acetate (400 mg, 0.96 mmol) and potassium carbonate (401 mg, 2.88 mmol) in DMF (10 mL) was stirred at 90 °C overnight. The reaction mixture was quenched with water (30 mL) and extracted with EtOAc (30 mL). The organic phase was washed with brine (30 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PET/ EtOAc (v/v) = 12/1) to give the title compound as pale yellow oil (282 mg, 54.4 %).

MS (ESI, pos. ion) *m/z*: 543.3 $[M + H]^+$.

Step 5) methyl 2-(6-((4'-((4,5-dihydroxy-4,5-dimethyltetrahydro-2*H*-pyran-2-yl)methoxy)-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetate

[00291] To a solution of methyl 2-(6-((4'-((4,5-dimethyl-3,6-dihydro-2*H*-pyran-2-yl)methoxy)-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetate (204 mg, 0.38 mmol) and 4-nethylmorpholine *N*-oxide monohydrate (158 mg, 1.13 mmol) in acetone (3 mL) and H_2O (0.5 mL) was added osmium(VIII) oxide (7 mg) at room temperature. The formed mixture was stirred at room temperature for 48 h. The reaction mixture was quenched with sodium sulfite and extracted with EtOAc (20 mL × 2). The combined organic phases were washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PET/ EtOAc (v/v) = 4/1) to give the title compound as a light yellow solid (131 mg, 60.4 %).

MS (ESI, pos. ion) *m/z*: 599.3 $[M + Na]^+$.

Step 6) 2-(6-((4'-((4,5-dihydroxy-4,5-dimethyltetrahydro-2*H*-pyran-2-yl)methoxy)-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetic acid

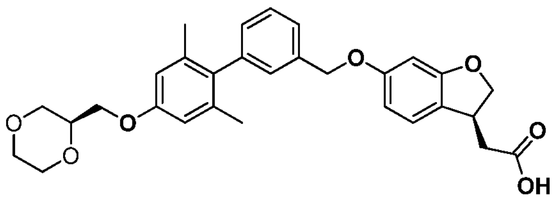
[00292] To a solution of methyl 2-(6-((4'-((4,5-dihydroxy-4,5-dimethyltetrahydro-2*H*-pyran-2-yl) methoxy)-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetate (83 mg, 0.14 mmol) in tetrahydrofuran (2 mL) was added aqueous lithium hydroxide solution (2 mL, 1 M). The mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with water (5 mL), acidifed with hydrochloric acid (3 mL, 1 M), and extracted with EtOAc (10 mL × 2). The combined organic phases were washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give the title compound as a white solid (40 mg, 49.4%).

MS (ESI, neg. ion) *m/z*: 561.3 $[M - H]^-$; and

^1H NMR (400 MHz, $CDCl_3$): δ 7.41 (dt, *J* = 14.9, 7.6 Hz, 2H), 7.18 (s, 1H), 7.08 (dd, *J* = 10.0, 7.9 Hz, 2H), 6.69 (s, 2H), 6.54 – 6.44 (m, 2H), 5.08 (s, 2H), 4.77 (t, *J* = 9.0 Hz, 1H), 4.30 (dd, *J* = 9.2, 6.1 Hz, 1H), 4.22 – 4.11 (m, 1H), 4.03 (dd, *J* = 9.9, 5.8 Hz, 1H), 3.96 (dd, *J* = 9.9, 4.3 Hz, 1H), 3.87 – 3.75 (m, 2H), 3.49 (d, *J* = 10.7 Hz, 1H), 2.82 (dd, *J* = 16.8, 5.2 Hz, 1H), 2.62 (dd, *J* = 16.8, 9.3 Hz, 1H), 2.00 (s, 6H), 1.79 (dd, *J* = 6.8, 5.3 Hz, 2H), 1.39 (s, 3H), 1.31 (s, 3H).

Example 37

2-((*S*)-6-((4'-(((*S*)-1,4-Dioxan-2-yl)methoxy)-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



Step1) 4'-(allyloxy)-2',6'-dimethyl-[1,1'-biphenyl]-3-carbaldehyde

[00293] To the solution of 4'-hydroxy-2',6'-dimethyl-[1,1'-biphenyl]-3-carbaldehyde (10 g, 44.19 mmol) and potassium phosphate (15.4 g, 71.1 mmol) in DMF (200 mL) was added 3-bromo-prop-1-ene (6 mL, 67.95 mmol) at room temperature. The mixture was stirred at 60 °C overnight. The reaction mixture was washed with water (200 mL) and extracted with EtOAc (200 mL × 2). The combined organic phases were washed with brine (50 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PET/EtOAc (v/v) = 25/1) to give the title compound as yellow oil (11.46 g, 97.4 %).

^1H NMR (600 MHz, $CDCl_3$): δ 10.07 (s, 1H), 7.88 (d, J = 7.7 Hz, 1H), 7.69 (s, 1H), 7.61 (t, J = 7.6 Hz, 1H), 7.45 (d, J = 7.5 Hz, 1H), 6.72 (s, 2H), 6.11 (ddd, J = 22.4, 10.5, 5.3 Hz, 1H), 5.47 (dd, J = 17.3, 1.3 Hz, 1H), 5.32 (s, 1H), 4.59 (d, J = 5.2 Hz, 2H), 2.02 (s, 6H).

Step2) (*S*)-4'-(2,3-dihydroxypropoxy)-2',6'-dimethyl-[1,1'-biphenyl]-3-carbaldehyde

[00294] To the solution of 4'-(allyloxy)-2',6'-dimethyl-[1,1'-biphenyl]-3-carbaldehyde (600 mg, 2.25 mmol) in *tert*-butanol (15 mL) and H_2O (15 mL) was added AD-Mix-α (3.2 g) at room temperature. The mixture was stirred at room temperature overnight. The reaction mixture was quenched with sodium sulfite (500 mg) and extracted with EtOAc (100 mL × 2). The combined organic phases were washed with brine (30 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PET/EtOAc (v/v) = 1/1) to give the title compound as colorless oil (675 mg, 99.7 %).

Step3) (*S*)-4'-((1,4-dioxan-2-yl)methoxy)-2',6'-dimethyl-[1,1'-biphenyl]-3-carbaldehyde

[00295] To the solution of (*S*)-4'-(2,3-dihydroxypropoxy)-2',6'-dimethyl-[1,1'-biphenyl]-3-carbaldehyde (677 mg, 2.25 mmol) and tetrabutylammonium bromide (148 mg, 0.45 mmol) in 1,2-dichloroethane (15 mL) was added aqueous sodium hydroxide solution (10 mL) at room temperature. The mixture was stirred at 50 °C for 18 h. Then additional 1,2-dichloro- ethane (15 mL) and aqueous sodium hydroxide solution (10 mL) were added and the mixture was stirred at 50 °C for 8 h. The reaction mixture was diluted with water (50 mL) and extracted with DCM (100 mL × 2). The combined organic phases were washed with 30 mL of brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PET/ EtOAc (v/v) = 8/1) to give the title compound as light yellow oil (424 mg, 57.6 %).

^1H NMR (400 MHz, $CDCl_3$): δ 10.07 (s, 1H), 7.88 (d, J = 7.7 Hz, 1H), 7.68 (s, 1H), 7.61 (t, J = 7.6 Hz, 1H), 7.43 (d, J = 7.5 Hz, 1H), 6.71 (s, 2H), 4.03 (ddd, J = 12.0, 6.6, 3.3 Hz, 2H), 3.99 – 3.91 (m, 2H), 3.86 (dd, *J* = 10.6, 2.9 Hz, 2H), 3.78 – 3.67 (m, 2H), 3.58 (dd, *J* = 11.3, 9.7 Hz, 1H), 2.01 (s, 6H).

Step4) (*S*)-(4'-((1,4-dioxan-2-yl)methoxy)-2',6'-dimethyl-[1,1'- biphenyl]-3-yl)methanol

[00296] To a solution of (*S*)-4'-((1,4-dioxan-2-yl)methoxy)-2',6'-dimethyl-[1,1'-biphenyl]-3- carbaldehyde (424 mg, 1.3 mmol) in THF (10 mL) and MeOH (5 mL) was added sodium borohydride (76 mg, 1.97 mmol) portionwise at 0 °C. The mixture was stirred at 0 °C overnight. The reaction mixture was diluted with water (30 mL) and extracted with EtOAc (30 mL). The organic phase was washed with brine (30 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PET/EtOAc (v/v) = 4/1) to give the title compound as light yellow oil (395 mg, 92.3 %).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.43 (t, *J* = 7.6 Hz, 1H), 7.36 (d, *J* = 7.7 Hz, 1H), 7.14 (s, 1H), 7.08 (d, *J* = 7.5 Hz, 1H), 6.69 (s, 2H), 4.75 (s, 2H), 4.08 – 4.01 (m, 2H), 3.99 – 3.92 (m, 2H), 3.86 (dtd, *J* = 14.4, 11.7, 2.6 Hz, 2H), 3.73 (ddd, *J* = 24.2, 14.7, 7.5 Hz, 2H), 3.58 (dd, *J* = 11.4, 9.8 Hz, 1H), 2.02 (s, 6H).

Step5) methyl 2-((*S*)-6-((4'-(((*S*)-1,4-dioxan-2-yl)methoxy)-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetate

[00297] To the solution of (*S*)-(4'-((1,4-dioxan-2-yl)methoxy)-2',6'-dimethyl-[1,1'-biphenyl] -3-yl)methanol (174 mg, 0.53 mmol) and (*S*)-methyl 2-(6-hydroxy-2,3-dihydrobenzofuran-3-yl)acetate (100 mg, 0.48 mmol) in toluene (10 mL) were added tributylphosphane (0.2 mL, 0.8 mmol) and 1,1'-(azodicarbonyl)-dipiperidine (200 mg, 0.78 mmol). The formed mixture was stirred at room temperature for 3 h. The reaction mixture was quenched with water (15 mL) and extracted with EtOAc (20 mL × 2). The combined organic phases were washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PET/EtOAc (v/v) = 4/1) to give the title compound as light yellow oil (211 mg, 84.7 %).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.44 (t, *J* = 7.5 Hz, 1H), 7.39 (d, *J* = 7.7 Hz, 1H), 7.18 (s, 1H), 7.09 (d, *J* = 7.4 Hz, 1H), 7.04 (d, *J* = 8.2 Hz, 1H), 6.69 (s, 2H), 6.50 (dd, *J* = 8.2, 2.2 Hz, 1H), 6.48 (d, *J* = 2.1 Hz, 1H), 5.07 (s, 2H), 4.77 (t, *J* = 9.0 Hz, 1H), 4.28 (dd, *J* = 9.1, 6.1 Hz, 1H), 4.07 – 4.00 (m, 2H), 3.97 – 3.93 (m, 2H), 3.89 (dd, *J* = 11.6, 2.2 Hz, 1H), 3.84 (ddd, *J* = 14.7, 9.3, 3.0 Hz, 2H), 3.80 – 3.76 (m, 1H), 3.74 (s, 3H), 3.73 – 3.68 (m, 1H), 3.57 (dd, *J* = 11.4, 9.8 Hz, 1H), 2.77 (dd, *J* = 16.4, 5.4 Hz, 1H), 2.58 (dd, *J* = 16.4, 9.3 Hz, 1H), 2.01 (s, 6H).

Step 6) 2-((*S*)-6-((4'-(((*S*)-1,4-dioxan-2-yl)methoxy)-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetic acid

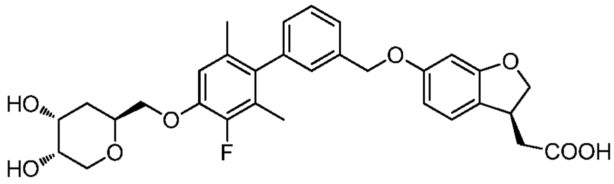
[00298] To a solution of methyl 2-((*S*)-6-((4'-(((*S*)-1,4-dioxan-2-yl)methoxy)-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetate (210 mg, 0.40 mmol) in tetrahydrofuran (4 mL) was added aqueous lithium hydroxide solution (4 mL, 1 M). The mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with water (5 mL), acidifed with hydrochloric acid (6 mL, 1 M), and extracted with EtOAc (10 mL × 2). The combined organic phases were washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give the title compound as a white solid (116 mg, 56.7%).

MS (ESI, pos. ion) m/z: 505.2 $[M + H]^+$; and

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.46 – 7.38 (m, 2H), 7.18 (s, 1H), 7.08 (dd, J = 15.3, 7.8 Hz, 2H), 6.69 (s, 2H), 6.54 – 6.47 (m, 2H), 5.08 (s, 2H), 4.78 (t, J = 9.0 Hz, 1H), 4.31 (dd, J = 9.1, 6.1 Hz, 1H), 4.08 – 4.00 (m, 2H), 3.99-3.94 (m, 2H), 3.92 – 3.76 (m, 4H), 3.75-3.69 (m, 1H), 3.61 – 3.55 (m, 1H), 2.83 (dd, J = 16.8, 5.2 Hz, 1H), 2.64 (dd, J = 16.8, 9.4 Hz, 1H), 2.01 (s, 6H).

Example 38

2-((*S*)-6-((4'-(((2*S*,4*R*,5*S*)-4,5-Dihydroxytetrahydro-2*H*-pyran-2-yl)methoxy)-3'-fluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



Step1) 4-bromo-2-fluoro-3,5-dimethylphenol

[00299] A mixture of 4-bromo-3,5-dimethylphenol (3 g, 14.9 mmol) and *N*-fluoropyridinium trifluoromethanesulphonate (9 g, 36.4 mmol) in 1,2-dichloroethane (40 mL) was refluxed for 8 h. After cooling to room temperature, the mixture was quenched with saturated sodium thiosulfate solution (50 mL) and extracted with EtOAc (100 mL × 2). The combined organic phases were washed with brine (30 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PET/EtOAc (v/v) = 100/1) to give the title compound as a white solid (800 mg, 24.5 %).

MS (ESI, neg.ion) m/z: 217.1 $[M - H]^-$.

Step2) 3'-fluoro-4'-hydroxy-2',6'-dimethyl-[1,1'-biphenyl]-3-carbaldehyde

[00300] A mixture of 4-bromo-2-fluoro-3,5-dimethylphenol (1.5 g, 6.8 mmol), (3-formylphenyl)boronic acid (1.1 g, 7.3 mmol), sodium carbonate (2.23 g, 21 mmol) and tetrakis(triphenylphosphine)palladium (0.4 g, 0.3 mmol) in etanol (10 mL), H_2O (21 mL) and toluene (30 mL) was stirred at 80 °C overnight. The mixture was filtered through a Celite pad. The filtrate was extracted with EtOAc (20 mL × 2). The combined organic phases were washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PET/EtOAc (v/v) = 10/1) to give the title compound as yellow oil (910 mg, 54 %).

MS (ESI, neg.ion) m/z: 243.1$[M - H]^-$.

Step3) 3-fluoro-3'-(hydroxymethyl)-2,6-dimethyl-[1,1'-biphenyl]-4-ol

[00301] To a solution of 3'-fluoro-4'-hydroxy-2',6'-dimethyl-[1,1'-biphenyl]-3-carbaldehyde (0.91 g, 3.7 mmol) in THF (20 mL) and MeOH (10 mL) was added sodium borohydride (0.15 g, 3.9 mmol) at 0 °C. The mixture was stirred at 0 °C overnight. After removing of the solvent, the residue was purified by silica gel column chromatography (PET/EtOAc (v/v) = 5/1) to give the title compound as a white solid (710 mg, 77 %).

MS (ESI, neg.ion) m/z: 245.2$[M - H]^-$.

Step4) (*S*)-(4'-((3,6-dihydro-2*H*-pyran-2-yl)methoxy)-3'-fluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl) methanol

[00302] A mixture of (*S*)-(3,6-dihydro-2*H*-pyran-2-yl)methyl 4-methylbenzenesulfonate (600 mg, 2.24 mmol), 3-fluoro-3'-(hydroxymethyl)-2,6-dimethyl-[1,1'-biphenyl]-4-ol (600 mg, 2.44 mmol), and potassium carbonate (1 g, 7.24 mmol) in *N,N*-dimethylformamide (30 mL) was heated at 100 °C overnight. After cooling to room temperature, the mixture was dilutedwith water (50 mL) and extracted with EtOAc (100 mL × 2). The combined organic phases were washed with brine (30 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PET/EtOAc (v/v) = 5/1) to give the title compound as light yellow oil (760 mg, 99 %).

Step5) (*S*)-2-(((3'-(chloromethyl)-3-fluoro-2,6-dimethyl-[1,1'-biphenyl]-4-yl)oxy)methyl)-3,6-dihydro-2*H*-pyran

[00303] To a solution of (*S*)-(4'-((3,6-dihydro-2H-pyran-2-yl)methoxy)-3'-fluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methanol (760 mg, 2.22 mmol) in DMF (20 mL) was added phosphorus oxychloride (0.25 mL, 2.7 mmol) at room temperature. The mixture was stirred at room temperature for 3 h. The reaction mixture was quenched with water (20 mL) and extracted with EtOAc (40 mL × 2). The combined organic phases were washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PET/EtOAc (v/v) = 5/1) to give the title compound as light yellow oil (628 mg, 78.4 %).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.44 (t, J = 7.6 Hz, 1H), 7.39 (d, J = 7.7 Hz, 1H), 7.16 (d, J = 1.2 Hz, 1H), 7.09 (d, J = 6.6 Hz, 1H), 6.78 (d, J = 8.3 Hz, 1H), 5.90 (ddd, J = 9.9, 5.2, 2.2 Hz, 1H), 5.81 (d, J = 10.2 Hz, 1H), 4.64 (s, 2H), 4.35 – 4.27 (m, 2H), 4.21 – 4.14 (m, 1H), 4.09 – 4.01 (m, 2H), 2.29 – 2.22 (m, 1H), 2.15 (dd, J = 17.2, 1.8 Hz, 1H), 2.00 (s, 3H), 1.95 (d, J = 2.7 Hz, 3H).

Step 6) methyl 2-((*S*)-6-((4'-(((*S*)-3,6-dihydro-2*H*-pyran-2-yl)methoxy)-3'-fluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetate

[00304] A mixture of (*S*)-2-(((3'-(chloromethyl)-3-fluoro-2,6-dimethyl-[1,1'-biphenyl]-4-yl)oxy)methyl)-3,6-dihydro-2*H*-pyran (628 mg, 1.74 mmol), (*S*)-methyl 2-(6-hydroxy-2,3-dihydrobenzofuran-3-yl) acetate (350 mg, 1.68 mmol) and potassium phosphate (530 mg, 2.5 mmol) in DMF (20 mL) were stirred at 60 °C for 3 h. The reaction mixture was quenched with water (20 mL) and extracted with EtOAc (40 mL × 2). The combined organic phases were washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PET/EtOAc (v/v) = 5/1) to give the title compound as light yellow oil (750 mg, 83.8 %).

MS (ES-API, pos. ion) *m/z*: 533.3 $[M + H]^+$.

Step 7) methyl 2-((*S*)-6-((4'-(((2*S*,4*R*,5*S*)-4,5-dihydroxytetrahydro-2*H*-pyran-2-yl)methoxy)-3'-fluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetate

[00305] A mixture of methyl 2-((*S*)-6-((4'-(((*S*)-3,6-dihydro-2*H*-pyran-2-yl)methoxy)-3'-fluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetate (750 mg, 1.41mmol), OsO_4 (170 mg, 0.676 mmol), *N*-methylmorpholine *N*-oxide (500 mg, 4.27 mmol) in acetone (40 mL) and H_2O (8 mL) was stirred at room temperature overnight. The reaction mixture was quenched with saturated sodium thiosulfate solution (20 mL) and extracted with EtOAc (40 mL × 2). The combined organic phases were washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PET/EtOAc (v/v) = 1/1) to give the title compound as light yellow oil (340 mg, 42%).

Step 8) 2-((*S*)-6-((4'-(((2*S*,4*R*,5*S*)-4,5-dihydroxytetrahydro-2*H*-pyran-2-yl)methoxy)-3'-fluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetic acid

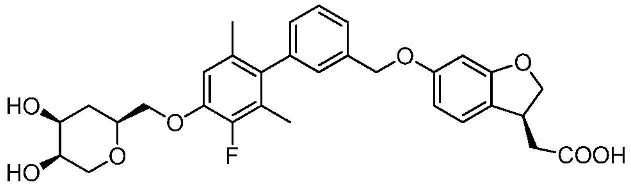
[00306] To a solution of methyl 2-((*S*)-6-((4'-(((2*S*,4*R*,5*S*)-4,5-dihydroxytetrahydro-2*H*-pyran-2-yl)methoxy)-3'-fluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetate (340 mg, 0.60 mmol) in tetrahydrofuran (6 mL) was added aqueous lithium hydroxide solution (6 mL, 1 M), and the mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with water (5 mL), acidifed with hydrochloric acid (10 mL, 1 M), and extracted with EtOAc (20 mL × 2). The combined organic phases were washed with 10 mL of brine, dried over Na_2SO_4 and concentrated *in vacuo* to give the title compound as a white solid (258 mg, 77.8%).

MS (ESI, pos. ion) *m/z*: 553.2 $[M + H]^+$; and

^1H NMR (600 MHz, $CDCl_3$): δ 7.48 – 7.39 (m, 2H), 7.15 (s, 1H), 7.07 (d, J = 7.9 Hz, 2H), 6.74 (d, J = 8.2 Hz, 1H), 6.49 (dd, J = 18.2, 5.1 Hz, 2H), 5.08 (s, 2H), 4.78 (t, J = 9.0 Hz, 1H), 4.31 (dd, J = 9.2, 6.1 Hz, 1H), 4.25 (d, J = 2.4 Hz, 1H), 4.14 (s, 1H), 4.11 – 4.02 (m, 2H), 3.91 – 3.80 (m, 3H), 3.72 – 3.64 (m, 1H), 2.82 (dd, J = 16.8, 5.4 Hz, 1H), 2.63 (dd, J = 16.8, 9.3 Hz, 1H), 2.07 – 2.02 (m, 1H), 1.97 (s, 3H), 1.93 (d, J = 2.3 Hz, 3H), 1.88 – 1.84 (m, 1H).

Example 39

2-((*S*)-6-((4'-(((2*S*,4*S*,5*R*)-4,5-Dihydroxytetrahydro-2*H*-pyran-2-yl)methoxy)-3'-fluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



Step 1) methyl 2-((*S*)-6-((4'-(((2*S*,4*S*,5*R*)-4,5-dihydroxytetrahydro-2*H*-pyran-2-yl)methoxy)-3'-fluoro -2',6'- dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetate

[00307] The title compound was prepared according to the procedure described in step 7 of Example 38. The reaction yielded the product as light yellow oil (240 mg, 30%).

Step 2) 2-((*S*)-6-((4'-(((2*S*,4*S*,5*R*)-4,5-dihydroxytetrahydro-2*H*-pyran-2-yl)methoxy)-3'-fluoro-2',6'-

dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetic acid

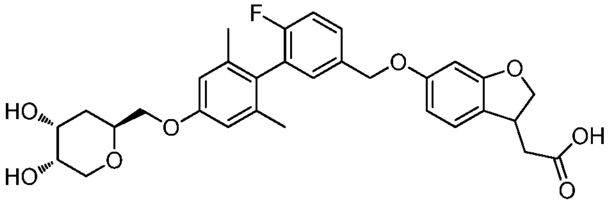
[00308] The title compound was prepared according to the procedure described in step 8 of Example 38 using methyl 2-((*S*)-6-((4'-(((2*S*,4*S*,5*R*)-4,5-dihydroxytetrahydro-2*H*-pyran-2-yl)methoxy)-3'-fluoro-2',6'-dimethyl-[1,1' -biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetate (240 mg, 0.43 mmol). The reaction yielded the product as a white solid (178 mg, 76.1%).

MS (ESI, neg. ion) *m/z*: 551.3 [M − H]$^-$; and

^{1}H NMR (600 MHz, CDCl$_3$): δ 7.46 – 7.39 (m, 2H), 7.15 (s, 1H), 7.06 (d, *J* = 8.1 Hz, 2H), 6.73 (d, *J* = 8.2 Hz, 1H), 6.54 – 6.45 (m, 2H), 5.07 (s, 2H), 4.77 (t, *J* = 9.0 Hz, 1H), 4.30 (dd, *J* = 8.9, 6.2 Hz, 1H), 4.15 (s, 2H), 4.06 (dd, *J* = 10.1, 3.9 Hz, 1H), 3.86 (d, *J* = 7.3 Hz, 2H), 3.83 – 3.79 (m, 2H), 3.65 (d, *J* = 12.7 Hz, 1H), 2.81 (dd, *J* = 16.8, 5.3 Hz, 1H), 2.62 (dd, *J* = 16.8, 9.3 Hz, 1H), 1.99 (d, *J* = 13.0 Hz, 1H), 1.97 (s, 3H), 1.93 (s, 3H), 1.79 (d, *J* = 12.1 Hz, 1H).

Example 40

2-((*S*)-6-((4'-(((2*S*,4*S*,5*R*)-4,5-Dihydroxytetrahydro-2*H*-pyran-2-yl)methoxy)-3'-fluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



Step 1) 6-fluoro-4'-hydroxy-2',6'-dimethyl-[1,1'-biphenyl]-3-carbaldehyde

[00309] The title compound was prepared according to the procedure described in step 2 of Example 38 using methyl 4-bromo-3,5-dimethylphenol (3.50 g, 17.4 mmol) and (2-fluoro-5-formylphenyl)boronic acid (3.22 g, 19.2 mmol). The reaction yielded the product as yellow oil (1.3 g, 31%).

Step 2) 2'-fluoro-5'-(hydroxymethyl)-2,6-dimethyl-[1,1'-biphenyl]-4-ol

[00310] The title compound was prepared according to the procedure described in step 3 of Example 38 using 6-fluoro-4'-hydroxy-2',6'-dimethyl-[1,1'-biphenyl]-3-carbaldehyde (1.3 g, 5.3 mmol). The reaction yielded the product as yellow oil (1.1 g, 84%).

Step 3) (*S*)-(4'-((3,6-dihydro-2*H*-pyran-2-yl)methoxy)-6-fluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl) methanol

[00311] The title compound was prepared according to the procedure described in step 4 of Example 38 using 2'-fluoro-5'-(hydroxymethyl)-2,6-dimethyl-[1,1'-biphenyl]-4-ol (1.1 g, 4.47 mmol) and (*S*)-(3,6-dihydro-2*H* -pyran-2-yl)methyl 4-methylbenzenesulfonate (1.2 g, 4.47 mmol). The reaction yielded the product as yellow oil (1.5 g, 98%).

Step 4) (*S*)-2-(((5'-(chloromethyl)-2'-fluoro-2,6-dimethyl-[1,1'-biphenyl]-4-yl)oxy)methyl)-3,6-dihydro-2*H*-pyran

[00312] The title compound was prepared according to the procedure described in step 5 of Example 38 using

(*S*)-(4'-((3,6-dihydro-2*H*-pyran-2-yl)methoxy)-6-fluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl) methanol (1.5 g, 4.38 mmol) and phosphorus oxychloride (0.5 mL, 5.33 mmol). The reaction yielded the product as yellow oil (1.4 g, 88.6%).

Step 5) methyl 2-((*S*)-6-((4'-(((*S*)-3,6-dihydro-2*H*-pyran-2-yl)methoxy)-6-fluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetate

[00313] The title compound was prepared according to the procedure described in step 6 of Example 38 using (*S*)-2-(((5'-(chloromethyl)-2'-fluoro-2,6-dimethyl-[1,1'-biphenyl]-4-yl)oxy)methyl)-3,6-dihydro-2*H*-pyran (1.4 g, 3.88 mmol) and (*S*)-ethyl 2-(6-hydroxy-2,3-dihydrobenzofuran-3-yl)acetate (808 mg, 3.88 mmol). The reaction yielded the product as yellow oil (1.8 g, 87%).

Step 6) methyl 2-(6-((4'-(((2*S*,4*R*,5*S*)-4,5-dihydroxytetrahydro-2*H*-pyran-2-yl)methoxy)-6-fluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetate

[00314] The title compound was prepared according to the procedure described in step 7 of Example 38 using methyl 2-((*S*)-6-((4'-(((*S*)-3,6-dihydro-2*H*-pyran-2-yl)methoxy)-6-fluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl) methoxy) -2,3-dihydrobenzofuran-3-yl)acetate (400 mg, 0.75 mmol). The reaction yielded the product as yellow oil (145 mg, 41.1%).

Step 7) 2-(6-((4'-(((2*S*,4*R*,5*S*)-4,5-dihydroxytetrahydro-2*H*-pyran-2-yl)methoxy)-6-fluoro-2',6'-dimethyl -[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetic acid

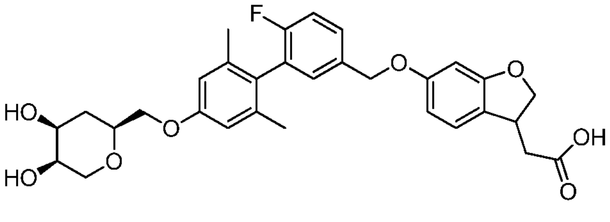
[00315] The title compound was prepared according to the procedure described in step 8 of Example 38 using methyl 2-(6-((4'-(((2*S*,4*R*,5*S*)-4,5-dihydroxytetrahydro-2*H*-pyran-2-yl)methoxy)-6-fluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetate (132 mg, 0.23 mmol). The reaction yielded the product as a white soild (90 mg, 70%).

MS (ESI, pos. ion) *m/z*: 553.25 $[M + H]^+$; and

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.39 (s, 1H), 7.16 (dd, *J* = 10.7, 7.1 Hz, 2H), 7.07 (d, *J* = 8.1 Hz, 1H), 6.71 (s, 2H), 6.49 (d, *J* = 8.2 Hz, 1H), 6.46 (s, 1H), 5.03 (s, 2H), 4.77 (t, *J* = 9.0 Hz, 1H), 4.30 (dd, *J* = 9.0, 6.2 Hz, 1H), 4.24 (s, 1H), 4.17 – 4.07 (m, 1H), 4.00 (d, *J* = 4.5 Hz, 2H), 3.86 (dd, *J* = 9.8, 5.2 Hz, 2H), 3.80 (dd, *J* = 11.0, 7.9 Hz, 1H), 3.68 (t, *J* = 12.8 Hz, 1H), 2.81 (dd, *J* = 16.8, 5.1 Hz, 1H), 2.62 (dd, *J* = 16.8, 9.2 Hz, 1H), 2.02 (s, 6H), 1.83 (t, *J* = 12.2 Hz, 1H), 1.28 – 1.18 (m, 1H).

Example 41

2-(6-((4'-(((2*S*,4*S*,5*R*)-4,5-Dihydroxytetrahydro-2*H*-pyran-2-yl)methoxy)-6-fluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



Step 1) methyl 2-(6-((4'-(((2*S*,4*S*,5*R*)-4,5-dihydroxytetrahydro-2*H*-pyran-2-yl)methoxy)-6-fluoro-2',6'-

dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetate

[00316] The title compound was prepared according to the procedure described in step 6 of Example 40. The reaction yielded the product as yellow oil (175 mg, 41.1%).

Step 2) 2-(6-((4'-(((2*S*,4*S*,5*R*)-4,5-dihydroxytetrahydro-2*H*-pyran-2-yl)methoxy)-6-fluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetic acid

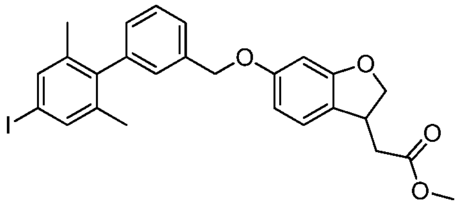
[00317] The title compound was prepared according to the procedure described in step 8 of Example 38 using methyl 2-(6-((4'-(((2*S*,4*S*,5*R*)-4,5-dihydroxytetrahydro-2*H*-pyran-2-yl)methoxy)-6-fluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetate (162 mg, 0.29 mmol). The reaction yielded the product as yellow oil (100 mg, 63.3%).

MS (ESI, pos. ion) *m/z*: 553.2 $[M + H]^+$; and

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.43 – 7.37 (m, 1H), 7.15 (t, *J* = 8.7 Hz, 2H), 7.06 (d, *J* = 8.2 Hz, 1H), 6.70 (s, 2H), 6.48 (dd, *J* = 8.2, 1.9 Hz, 1H), 6.46 (d, *J* = 1.8 Hz, 1H), 5.01 (s, 2H), 4.76 (t, *J* = 9.0 Hz, 1H), 4.29 (dd, *J* = 9.1, 6.2 Hz, 1H), 4.16 (d, *J* = 12.3 Hz, 1H), 4.08 (dd, *J* = 10.0, 6.1 Hz, 1H), 3.99 (dd, *J* = 9.9, 3.8 Hz, 1H), 3.89 – 3.83 (m, 2H), 3.82 – 3.77 (m, 2H), 3.63 (d, *J* = 12.6 Hz, 1H), 2.79 (dd, *J* = 16.8, 5.3 Hz, 1H), 2.61 (dd, *J* = 16.8, 9.3 Hz, 1H), 2.02 (s, 6H), 1.98 – 1.93 (m, 1H), 1.78 (dd, *J* = 23.8, 12.0 Hz, 1H).

Example 42

Methyl 2-(6-((4'-iodo-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetate



Step 1) methyl 4'-amino-2',6'-dimethyl-[1,1'-biphenyl]-3-carboxylate

[00318] A solution of 4-bromo-3,5-dimethylaniline (1 g, 10 mmol), (3-(methoxycarbonyl)phenyl)boronic acid (2.7 g, 15 mmol), potassium carbonate (4.14 g, 30 mmol) and 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (0.37 g, 0.5 mmol) in *N*,*N*-dimethylformamide (30 mL) and water (10 mL) was stirred at 90 °C under nitrogen atmosphere for 1 h. The reaction mixture was cooled to room temperature, and partitioned between EtOAc (200 mL) and water (30 mL). The organic phase was washed with brine (50 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PET/ EtOAc (v/v) = 4/1) to give the title compound as a light yellow solid (2.1 g, 82%).

Step 2) methyl 4'-amino-2',6'-dimethyl-[1,1'-biphenyl]-3-carboxylate

[00319] To a suspension of methyl 4'-amino-2',6'-dimethyl-[1,1'-biphenyl]-3-carboxylate (1.5 g, 5.9 mmol) in concentrated hydrochloric acid (6 mL) was added a aqueous sodium nitrite solution (811 mg, 11.8 mmol, 5 mL) dropwise at 0 °C. The mixture was stirred at 0 °C for 15 min. To a solution of potassium iodide (9.75 g, 59.0 mmol) in water (20 mL) was added the above mixture dropwise at 0 °C. The reaction mixture was stirred at room temperature for 2 h and quenched with saturated aqueous sodium thiosulfate (20 mL). The resulting

mixture was extracted with EtOAc (50 mL × 2). The combined organic phases were washed with brine (50 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PET/EtOAc (v/v) = 10/1) to give the title compound as a pale yellow solid (1.6 g, 74%).

Step 3) (4'-iodo-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methanol

[00320] To a solution of methyl 4'-amino-2',6'-dimethyl-[1,1'-biphenyl]-3-carboxylate (3 g, 8.2 mmol) in toluene (100 mL) was slowly added diisobutylaluminium hydride (33 mL, 1M in toluene) at −10°C. The mixture was stirred at room temperature overnight. The mixture was quenched with hydrochloric acid (50 mL, 1 M), and extracted with EtOAc (50 mL). The organic phase was washed with brine (30 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PET/EtOAc (v/v) = 4/1) to give the title compound as pale yellow oil (2.5 g, 90%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.49 (s, 2H), 7.45 (t, J = 7.6 Hz, 1H), 7.38 (d, J = 7.7 Hz, 1H), 7.13 (s, 1H), 7.06 (d, J = 7.5 Hz, 1H), 4.76 (s, 2H), 1.99 (s, 6H).

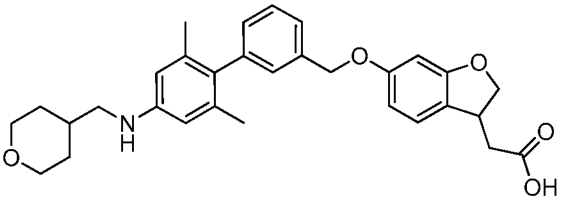
Step 4) methyl 2-(6-((4'-iodo-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl) acetate

[00321] To a solution of (4'-iodo-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methanol (2.5 g, 7.4 mmol) and methyl 2-(6-hydroxy-2,3-dihydrobenzofuran-3-yl)acetate (1.5 g, 7.2 mmol) in toluene (120 mL) were added tributylphosphine (3 mL, 12 mmol) and 1,1'-(azodicarbonyl)-dipiperidine (3 g, 12 mmol) in turn under nitrogen atmosphere. The formed mixture was stirred at room temperature for 3 h under nitrogen atmosphere. The reaction mixture was quenched with water (50 mL) and extracted with EtOAc (30 mL). The organic phase was washed with brine (30 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PET/EtOAc (v/v) = 10/1) to give the title compound as a white solid (3.2 g, 82%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.49 (s, 2H), 7.45 (d, J = 7.5 Hz, 1H), 7.42 (s, 1H), 7.16 (s, 1H), 7.06 (dd, J = 20.2, 7.8 Hz, 2H), 6.49 (m, 2H), 5.08 (s, 2H), 4.77 (t, J = 9.0 Hz, 1H), 4.28 (dd, J = 9.2, 6.1 Hz, 1H), 3.85-3.80 (m, 1H), 3.74 (s, 3H), 2.77 (dd, J = 16.4, 5.5 Hz, 1H), 2.58 (dd, J = 16.4, 9.3 Hz, 1H), 1.98 (s, 6H).

Example 43

2-(6-((2',6'-Dimethyl-4'-(((tetrahydro-2*H*-pyran-4-yl)methyl)amino)-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



Step1) methyl 2-(6-((2',6'-dimethyl-4'-(((tetrahydro-2*H*-pyran-4-yl)methyl)amino)-[1,1'-biphenyl]-3-yl) methoxy)-2,3-dihydrobenzofuran-3-yl)acetate

[00322] A mixture of (tetrahydro-2*H*-pyran-4-yl)methanamine (90 mg, 0.76 mmol), potassium carbonate (106 mg, 0.76 mmol), cuprous iodide (8 mg, 0.04 mmol), *L*-proline (9 mg, 0.08 mmol) and methyl

2-(6-((4'-iodo-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetate (200 mg, 0.38 mmol) in dimethyl sulfoxide (4 mL) was stirred at 100 °C overnight. The reaction mixture was quenched with water (20 mL) and extracted with EtOAc (80 mL × 2). The combined organic phases were washed with brine (30 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PET/ EtOAc (v/v) = 10/1) to give the title compound as yellow oil (44 mg, 23 %).

MS (ESI, pos. ion) *m/z*: 516.3 $[M + H]^+$.

Step2) 2-(6-((2',6'-dimethyl-4'-(((tetrahydro-2*H*-pyran-4-yl)methyl)amino)-[1,1'-biphenyl]-3-yl)methoxy) -2,3-dihydrobenzofuran-3-yl)acetic acid

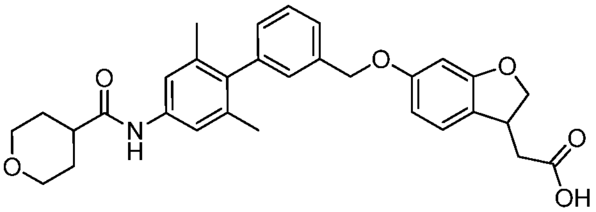
[00323] To a solution of methyl 2-(6-((2',6'-dimethyl-4'-(((tetrahydro-2*H*-pyran-4-yl)methyl)amino)-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetate (44 mg, 0.08 mmol) in tetrahydrofuran (2 mL) was added aqueous lithium hydroxide solution (2 mL, 1 M). The mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with water (5 mL), acidifed with hydrochloric acid (4 mL, 1 M), and extracted with EtOAc (10 mL × 2). The combined organic phases were washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give the title compound as a light yellow solid (16 mg, 37.4%).

MS (ESI, pos. ion) *m/z*: 502.2 $[M + H]^+$; and

^1H NMR (600 MHz, $CDCl_3$): δ 7.45 – 7.35 (m, 2H), 7.20 (s, 1H), 7.09 (dd, *J* = 30.1, 7.5 Hz, 2H), 6.55 – 6.46 (m, 2H), 6.40 (s, 2H), 5.07 (s, 2H), 4.78 (t, *J* = 8.9 Hz, 1H), 4.34 – 4.27 (m, 1H), 4.04 (d, *J* = 9.2 Hz, 2H), 3.83 (s, 1H), 3.45 (t, *J* = 11.6 Hz, 2H), 3.07 (d, *J* = 6.5 Hz, 2H), 2.82 (dd, *J* = 16.8, 4.5 Hz, 1H), 2.63 (dd, *J* = 16.6, 9.4 Hz, 1H), 1.98 (s, 6H), 1.90 (s, 1H), 1.76 (d, *J* = 12.7 Hz, 2H), 1.46 – 1.36 (m, 2H).

Example 44

2-(6-((2',6'-Dimethyl-4'-(tetrahydro-2*H*-pyran-4-carboxamido)-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydro benzofuran-3-yl)acetic acid



Step 1) methyl tetrahydro-2*H*-pyran-4-carboxylate

[00324] The solution of tetrahydro-2*H*-pyran-4-carboxylic acid (2 g, 15 mmol) in methanol (10 mL) was added thionyl chloride (1.7 mL, 23 mmol) at 0 °C. The mixture stirred at 90 °C overnight. After evaporating the solvent, the residue was quenched with water (20 mL) and extracted with EtOAc (80 mL × 2). The combined organic phases were washed with brine (30 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give the title compound as yellow oil (1.65 g, 75.8 %).

Step 2) tetrahydro-2*H*-pyran-4-carboxamide

[00325] A solution of methyl tetrahydro-2*H*-pyran-4-carboxylate (450 mg, 3.12 mmol) in ammonium

hydroxide (10 mL, 25% solution in water) was stirred at room temperature overnight in sealed tube. After evaporating the solvent, the residue was purified by silica gel column chromatography (DCM/MeOH (v/v) = 20/1) to give the title compound as a white soild (353 mg, 87.5 %).

^{1}H NMR (600 MHz, DMSO-d_6): δ 7.24 (s, 1H), 6.76 (s, 1H), 3.87 – 3.80 (m, 2H), 3.35 – 3.25 (m, 2H), 2.33 – 2.28 (m, 1H), 1.57 – 1.53 (m, 4H).

Step3) methyl 2-(6-((2',6'-dimethyl-4'-(tetrahydro-2*H*-pyran-4-carboxamido)-[1,1'-biphenyl]-3-yl)methoxy) -2,3-dihydrobenzofuran-3-yl)acetate

[00326] A mixture of tetrahydro-2*H*-pyran-4-carboxamide (59 mg, 0.46 mmol), cesium carbonate (252 mg, 0.76 mmol), cuprous iodide (4 mg, 0.02 mmol), trans-*N*,*N'*-dimethylcyclohexane-1,2-diamine (6 mg, 0.04 mmol) and methyl 2-(6-((4'-iodo-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetate (200 mg, 0.38 mmol) in 1,4-dioxane (2 mL) was stirred at 110 °C overnight. The reaction mixture was allowed to cool to room temperature and quenched with water (20 mL). The resulting mixture was extracted with EtOAc (80 mL × 2). The combined organic phases were washed with brine (30 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PET/EtOAc (v/v) = 2/1) to give the title compound as a white soild (84 mg, 42 %).

MS (ESI, pos. ion) *m/z*: 530.3 $[M + H]^+$.

Step 4) 2-(6-((2',6'-dimethyl-4'-(tetrahydro-2*H*-pyran-4-carboxamido)-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetic acid

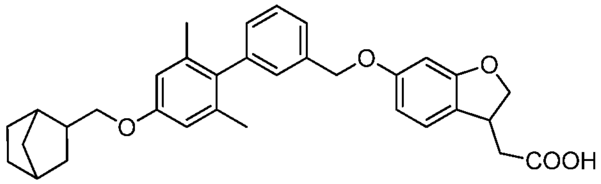
[00327] To a solution of methyl 2-(6-((2',6'-dimethyl-4'-(tetrahydro-2*H*-pyran-4-carboxamido)-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetate (84 mg, 0.16 mmol) in tetrahydrofuran (3 mL) was added aqueous lithium hydroxide solution (3 mL, 1 M). The mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with water (5 mL), acidifed with hydrochloric acid (5 mL, 1 M), and extracted with EtOAc (10 mL × 2). The combined organic phases were washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give the title compound as a white solid (72 mg, 87.4%).

MS (ESI, pos. ion) *m/z*: 516.3 $[M + H]^+$; and

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.49 – 7.38 (m, 2H), 7.30 (s, 3H), 7.16 (s, 1H), 7.07 (s, 2H), 6.61 – 6.38 (m, 2H), 5.08 (s, 2H), 4.78 (t, J = 8.7 Hz, 1H), 4.35 – 4.25 (m, 1H), 4.10 (d, J = 8.6 Hz, 2H), 3.82 (s, 1H), 3.49 (t, J = 10.6 Hz, 2H), 2.81 (dd, J = 16.6, 4.8 Hz, 1H), 2.63 (dd, J = 16.5, 9.2 Hz, 1H), 2.53 (s, 1H), 2.01 (s, 6H), 1.92 (dd, J = 50.8, 11.7 Hz, 4H).

Example 45

2-(6-((4'-(Bicyclo[2.2.1]heptan-2-ylmethoxy)-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



Step1) bicyclo[2.2.1]heptan-2-ylmethyl methanesulfonate

[00328] To a solution of bicyclo[2.2.1]heptan-2-ylmethanol (2 g, 15.8 mmol) and triethylamine (2.7 mL, 19 mmol) in DCM (50 mL) was added methanesulfonyl chloride (1.5 mL, 19 mmol) dropwise at 0 °C. The mixture was stirred at room temperature for 1 h and quenched with water (20 mL). The reaction mixture was extracted with DCM (80 mL × 2). The combined organic phases were washed with brine (30 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PET/EtOAc (v/v) = 50/1) to give the title compound as yellow oil (2.3 g, 71 %).

^{1}H NMR (600 MHz, $CDCl_3$): δ 4.27 (dd, J = 9.6, 7.0 Hz, 1H), 4.13 (t, J = 9.5 Hz, 1H), 3.02 (s, 3H), 1.80 – 1.73 (m, 1H), 1.60 – 1.53 (m, 2H), 1.51 – 1.41 (m, 3H), 1.32 – 1.05 (m, 4H), 0.72 (ddd, J = 12.5, 5.1, 2.1 Hz, 1H).

Step2) methyl 2-(6-((4'-(bicyclo[2.2.1]heptan-2-ylmethoxy)-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetate

[00329] A mixture of bicyclo[2.2.1]heptan-2-ylmethyl methanesulfonate (370 mg, 1.81 mmol), methyl 2-(6-((4'-hydroxy-2',6'-dimethyl-[1,1'-bi-phenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetate (500 mg, 1.2 mmol) and potassium carbonate (500 mg, 3.62 mmol) in DMF (10 mL) was stirred at 100 °C overnight. The reaction mixture was quenched with water (30 mL) and extracted with EtOAc (30 mL × 2). The combined organic phases were washed with brine (30 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PET/EtOAc (v/v) = 50/1) to give the title compound as yellow oil (200 mg, 31.8 %).

Step 3) 2-(6-((4'-(bicyclo[2.2.1]heptan-2-ylmethoxy)-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetic acid

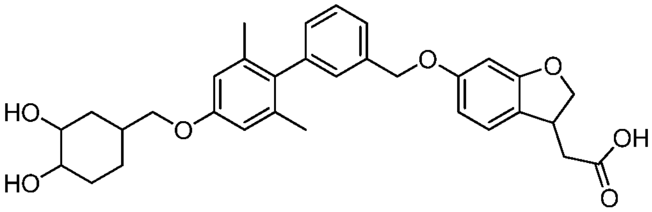
[00330] To a solution of methyl 2-(6-((4'-(bicyclo[2.2.1]heptan-2-ylmethoxy)-2',6'-dimethyl-[1,1'-biphenyl] -3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetate (200 mg, 0.38 mmol) in tetrahydrofuran (3.8 mL) was added aqueous lithium hydroxide solution (3.8 mL, 1 M). The mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with water (5 mL), acidifed with hydrochloric acid (7 mL, 1 M), and extracted with EtOAc (10 mL × 2). The combined organic phases were washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give the title compound as a white solid (130 mg, 66.8%).

MS (ESI, pos. ion) m/z: 513.3 $[M + H]^+$; and

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 (dd, J = 14.8, 7.3 Hz, 2H), 7.20 (s, 1H), 7.09 (dd, J = 14.9, 7.5 Hz, 2H), 6.69 (d, J = 5.7 Hz, 2H), 6.56 – 6.45 (m, 2H), 5.08 (s, 2H), 4.78 (t, J = 8.9 Hz, 1H), 4.32 – 4.24 (m, 2H), 4.15 (t, J = 9.4 Hz, 1H), 3.84 (d, J = 8.9 Hz, 1H), 2.83 (dd, J = 16.8, 5.0 Hz, 1H), 2.64 (dd, J = 16.8, 9.3 Hz, 1H), 2.02 (s, 8H), 1.50 - 1.36 (m, 11H).

Example 46

2-(6-((4'-((3,4-Dihydroxycyclohexyl)methoxy)-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



Step1) cyclohex-3-en-1-ylmethyl 4-methylbenzenesulfonate

[00331] To a solution of cyclohex-3-en-1-ylmethanol (2.32 g, 20.7 mmol), triethylamine (4.36 mL, 31.1 mmol) and *N,N,N',N'*-tetramethyl-1,6-hexanediamine (0.45 mL, 2.0 mmol) in toluene (50 mL) was added tosyl chloride (5.97 g, 31 mmol) at 0 °C. The formed mixture was stirred at 0 °C overnight. The reaction mixture was quenched with water (10 mL) and extracted with EtOAc (30 mL × 2). The combined organic phases were washed with brine (30 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PET/EtOAc (v/v) = 50/1) to give the title compound as light yellow oil (4.64 g, 84.2%).

Step 2) methyl 2-(6-((4'-(cyclohex-3-en-1-ylmethoxy)-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetate

[00332] A mixture of cyclohex-3-en-1-ylmethyl 4-methylbenzenesulfonate (287 mg, 1.08 mmol), methyl 2-(6-((4'-hydroxy-2',6'-dimethyl-[1,1'-bi-phenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetate (300 mg, 0.72 mmol) and potassium carbonate (301 mg, 2.16 mmol) in DMF (8 mL) was stirred at 90 °C overnight. The reaction mixture was diluted with water (30 mL) and extracted with EtOAc (30 mL). The combined organic phases were washed with brine (30 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PET/EtOAc (v/v) = 20/1) to give the title compound as light yellow oil (234 mg, 63.7 %).

MS (ESI, pos. ion) *m/z*: 513.3 $[M + H]^+$.

Step3) methyl 2-(6-((4'-((3,4-dihydroxycyclohexyl)methoxy)-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetate

[00333] To a solution of methyl 2-(6-((4'-(cyclohex-3-en-1-ylmethoxy)-2',6'-dimethyl-[1,1'-biphenyl]-3-yl) methoxy)-2,3-dihydrobenzofuran-3-yl)acetate (234 mg, 0.46 mmol) in *tert*-butanol (7 mL) and water (75 mL) was added AD-Mix-α (917 mg) at room temperature. The mixture was stirred at room temperature overnight. The reaction mixture was quenched with sodium sulfite (500 mg) and extracted with EtOAc (100 mL × 2). The combined organic phases were washed with brine (30 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (DCM/MeOH (v/v) = 60/1) to give the title

compound as a white solid (214 mg, 85.8 %).

Step 4) 2-(6-((4'-((3,4-dihydroxycyclohexyl)methoxy)-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetic acid

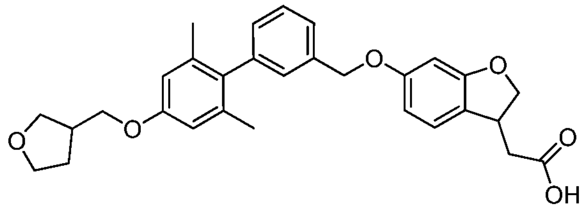
[00334] To a solution of methyl 2-(6-((4'-((3,4-dihydroxycyclohexyl)methoxy)-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetate (214 mg, 0.39 mmol) in tetrahydrofuran (4 mL) was added aqueous lithium hydroxide solution (4 mL, 1 M). The mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with water (5 mL), acidifed with hydrochloric acid (8 mL, 1 M), and extracted with EtOAc (10 mL × 2). The combined organic phases were washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give the title compound as a white solid (150 mg, 71.9%).

MS (ESI, pos. ion) *m/z*: 533.3 $[M + H]^+$; and

^1H NMR (600 MHz, DMSO-d_6): δ 7.48 – 7.34 (m, 2H), 7.14 (s, 1H), 7.10 (d, J = 8.1 Hz, 1H), 7.05 (d, J = 7.4 Hz, 1H), 6.68 (d, J = 6.2 Hz, 2H), 6.47 (dd, J = 12.8, 4.6 Hz, 2H), 5.10 (s, 2H), 4.68 (t, J = 9.0 Hz, 1H), 4.38 (d, J = 26.3 Hz, 1H), 4.23 – 4.06 (m, 2H), 3.83 – 3.73 (m, 3H), 3.71 – 3.63 (m, 1H), 3.43 (d, J = 8.7 Hz, 1H), 2.69 (dd, J = 16.6, 5.5 Hz, 1H), 1.91 (d, J = 1.6 Hz, 6H), 1.87 – 1.71 (m, 2H), 1.68 – 1.28 (m, 5H).

Example 47

2-(6-((2',6'-Dimethyl-4'-((tetrahydrofuran-3-yl)methoxy)-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



Step1) methyl 2-(6-((2',6'-dimethyl-4'-((tetrahydrofuran-3-yl)methoxy)-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetate

[00335] To a solution of (tetrahydrofuran-3-yl)methanol (56 mg, 0.54 mmol) and methyl 2-(6-((4'-hydroxy-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetate (150 mg, 0.36 mmol) in toluene (10 mL) were added tributylphosphine (0.15 mL, 0.57 mmol) and 1,1'-(azodicarbonyl)-dipiperidine (146 mg, 0.57 mmol). The formed mixture was stirred at room temperature for 1 h under nitrogen atmosphere. The reaction mixture was quenched with water (20 mL) and extracted with EtOAc (40 mL × 2). The combined organic phases were washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PET/EtOAc (v/v) = 4/1) to give the title compound as a white solid (144 mg, 80%).

MS (ESI, pos. ion) *m/z*: 503.2 $[M + H]^+$.

Step 2) 2-(6-((2',6'-dimethyl-4'-((tetrahydrofuran-3-yl)methoxy)-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetic acid

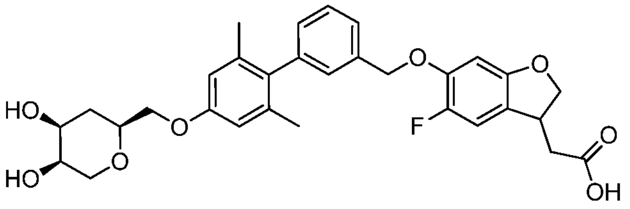
[00336] To a solution of methyl 2-(6-((2',6'-dimethyl-4'-((tetrahydrofuran-3-yl)methoxy)-[1,1'-biphenyl]-3-yl) methoxy)-2,3-dihydrobenzofuran-3-yl)acetate (144 mg, 0.28 mmol) in tetrahydrofuran (3 mL) was added aqueous lithium hydroxide solution (3 mL, 1 M). The mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with water (5 mL), acidifed with hydrochloric acid (6 mL, 1 M), and extracted with EtOAc (10 mL × 2). The combined organic phases were washed with 10 mL of brine, dried over Na_2SO_4 and concentrated *in vacuo* to give the title compound as a white solid (76 mg, 54.3%).

MS (ESI, pos. ion) *m/z*: 489.2 $[M + H]^+$; and

^1H NMR (400 MHz, $CDCl_3$): δ 7.48 – 7.36 (m, 2H), 7.19 (s, 1H), 7.13 – 7.03 (m, 2H), 6.68 (s, 2H), 6.54 –6.46 (m, 2H), 5.08 (s, 2H), 4.78 (t, J = 9.0 Hz, 1H), 4.34 – 4.26 (m, 1H), 4.01 – 3.88 (m, 4H), 3.87 – 3.78(m, 2H), 3.78 – 3.70 (m, 1H), 2.87 – 2.70 (m, 2H), 2.63 (dd, J = 16.8, 9.4 Hz, 1H), 2.21 – 2.09 (m, 1H),2.01 (s, 6H), 1.85 – 1.72 (m, 1H).

Example 48

2-(6-((4'-(((2*S*,4*S*,5*R*)-4,5-Dihydroxytetrahydro-2*H*-pyran-2-yl)methoxy)-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-5-fluoro-2,3-dihydrobenzofuran-3-yl)acetic acid



Step 1) methyl 2-(6-((4'-(((*S*)-3,6-dihydro-2*H*-pyran-2-yl)methoxy)-2',6'-dimethyl-[1,1'-biphenyl]-3-yl) methoxy)-5-fluoro-2,3-dihydrobenzofuran-3-yl)acetate

[00337] The title compound was prepared according to the procedure described in step 10 of Example 26 using (*S*)-2-(((3'-(chloromethyl)-2,6-dimethyl-[1,1'-biphenyl]-4-yl)oxy)methyl)-3,6-dihydro-2*H*-pyran (712 mg, 2.1 mmol) and methyl 2-(5-fluoro-6-hydroxy-2,3-dihydrobenzofuran-3-yl)acetate (470 mg, 2.1 mmol). The reaction yielded the product as pale yellow oil (845 mg, 76.4%).

MS (ESI, pos. ion) *m/z*: 533.3 $[M + H]^+$.

Step 2) methyl 2-(6-((4'-(((2*S*,4*S*,5*R*)-4,5-dihydroxytetrahydro-2*H*-pyran-2-yl)methoxy)-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-5-fluoro-2,3-dihydrobenzofuran-3-yl)acetate

[00338] The title compound was prepared according to the procedure described in step 11 of Example 26 using methyl 2-(6-((4'-(((*S*)-3,6-dihydro-2*H*-pyran-2-yl)methoxy)-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-5-fluoro-2,3-dihydrobenzofuran-3-yl)acetate (854 mg, 1.6 mmol). The reaction yielded the product as pale yellow oil (326 mg, 36%).

Step 3) 2-(6-((4'-(((2*S*,4*S*,5*R*)-4,5-dihydroxytetrahydro-2*H*-pyran-2-yl)methoxy)-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-5-fluoro-2,3-dihydrobenzofuran-3-yl)acetic acid

[00339] The title compound was prepared according to the procedure described in step 12 of Example 26 using methyl 2-(6-((4'-(((2*S*,4*S*,5*R*)-4,5-dihydroxytetrahydro-2*H*-pyran-2-yl)methoxy)-2',6'-dimethyl-[1,1'-biphenyl]-

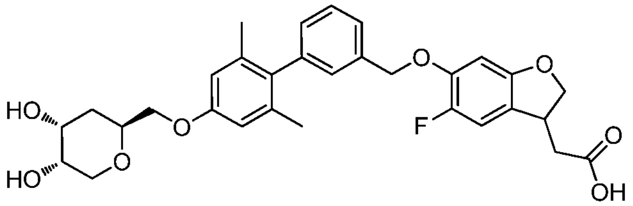
3-yl)methoxy)-5-fluoro-2,3-dihydrobenzofuran-3-yl)acetate (326 mg, 0.57 mmol). The reaction yielded the product as a white solid (250 mg, 78.6%).

MS (ESI, pos. ion) *m/z*: 553.3 $[M + H]^+$; and

^{1}H NMR (600 MHz, $CDCl_3$): *δ* 7.48 – 7.38 (m, 2H), 7.17 (s, 1H), 7.10 (d, *J* = 7.3 Hz, 1H), 6.94 (d, *J* = 10.2 Hz, 1H), 6.69 (s, 2H), 6.50 (d, *J* = 6.6 Hz, 1H), 5.14 (s, 2H), 4.74 (t, *J* = 9.0 Hz, 1H), 4.27 (dd, *J* = 9.1, 6.1 Hz, 1H), 4.17 (d, *J* = 14.2 Hz, 1H), 4.10 (dd, *J* = 10.0, 6.1 Hz, 1H), 3.99 (dd, *J* = 10.1, 4.0 Hz, 1H), 3.84 – 3.81 (m, 2H), 3.80-3.76 (m, 1H), 3.65 (d, *J* = 12.6 Hz, 1H), 2.78 (dd, *J* = 16.9, 5.8 Hz, 1H), 2.63 (dd, *J* = 16.9, 8.9 Hz, 1H), 2.31 – 2.19 (m, 1H), 2.03 (d, *J* = 6.2 Hz, 1H), 1.99 (d, *J* = 3.6 Hz, 6H), 1.74 (d, *J* = 12.3 Hz, 1H).

Example 49

2-(6-((4'-(((2*S*,4*R*,5*S*)-4,5-dihydroxytetrahydro-2*H*-pyran-2-yl)methoxy)-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-5-fluoro-2,3-dihydrobenzofuran-3-yl)acetic acid



Step 1) methyl 2-(6-((4'-(((2*S*,4*R*,5*S*)-4,5-dihydroxytetrahydro-2*H*-pyran-2-yl)methoxy)-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-5-fluoro-2,3-dihydrobenzofuran-3-yl)acetate

[00340] The title compound was prepared according to the procedure described in step 2 of Example 48. The reaction yielded the product as pale yellow oil (356 mg, 39.3%).

Step 2) 2-(6-((4'-(((2*S*,4*R*,5*S*)-4,5-dihydroxytetrahydro-2*H*-pyran-2-yl)methoxy)-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-5-fluoro-2,3-dihydrobenzofuran-3-yl)acetic acid

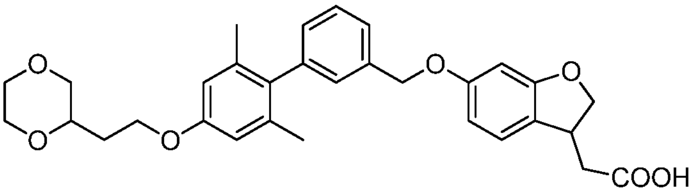
[00341] The title compound was prepared according to the procedure described in step 12 of Example 26 using methyl 2-(6-((4'-(((2*S*,4*R*,5*S*)-4,5-dihydroxytetrahydro-2*H*-pyran-2-yl)methoxy)-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-5-fluoro-2,3-dihydrobenzofuran-3-yl)acetate (356 mg, 0.63 mmol). The reaction yielded the product as a white solid (290 mg, 83.5%).

MS (ESI, pos. ion) *m/z*: 553.3 $[M + H]^+$; and

^{1}H NMR (600 MHz, $CDCl_3$): *δ* 7.46 – 7.38 (m, 2H), 7.16 (d, *J* = 4.5 Hz, 1H), 7.10 (d, *J* = 7.1 Hz, 1H), 6.94 (d, *J* = 9.3 Hz, 1H), 6.69 (d, *J* = 5.8 Hz, 2H), 6.51 – 6.47 (m, 1H), 5.15 (d, *J* = 4.0 Hz, 2H), 4.76 – 4.72 (m, 1H), 4.30 – 4.22 (m, 2H), 4.12 – 4.11 (m, 1H), 4.00 – 3.98(m, 1H), 3.91 – 3.85 (m, 2H), 3.83 – 3.79 (m, 1H), 3.70 – 3.66 (m, 1H), 2.79 – 2.75 (m, 1H), 2.62 (dd, *J* = 16.9, 8.9 Hz, 1H), 2.25 (t, *J* = 7.6 Hz, 1H), 2.04 – 1.98 (m, 7H),1.87 – 1.84 (m, 1H).

Example 50

2-(6-((4'-(2-(1,4-Dioxan-2-yl)ethoxy)-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



Step 1) methyl 2-(6-((4'-(but-3-en-1-yloxy)-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetate

[00342] The title compound was prepared according to the procedure described in step 1 of Example 37 using methyl 2-(6-((4'-hydroxy-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetate (500 mg, 1.20 mmol) and 4-bromobut-1-ene (0.25 mL, 2.4 mmol). The reaction yielded the product as pale yellow oil (419 mg, 74.2%).

Step 2) methyl 2-(6-((4'-(3,4-dihydroxybutoxy)-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetate

[00343] To a solution of methyl 2-(6-((4'-(but-3-en-1-yloxy)-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetate (507 mg, 1.07 mmol) in acetone (9 mL) and water (1.5 mL) were added osmium tetroxide (5 mg, 0.02 mmol) and *N*-methylmorpholine *N*-oxide (398 mg, 3.4 mmol) at room temperature. The mixture was stirred at room temperature overnight and filtered. The filtrate was diluted with water (5 mL). The resulting mixture was extracted with EtOAc (20 mL × 2). The combined organic layers were washed with saturated aqueous sodium chloride (10 mL), dried over Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PET/EtOAc (v/v) = 1/1) to give the title compound as pale yellow oil (476 mg, 87.6%).

Step 3) methyl 2-(6-((4'-(2-(1,4-dioxan-2-yl)ethoxy)-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetate

[00344] The title compound was prepared according to the procedure described in step 3 of Example 37 using methyl 2-(6-((4'-(3,4-dihydroxybutoxy)-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetate (476 mg, 0.94 mmol). The reaction yielded the product as pale yellow oil (80 mg, 16.0%).

MS (ESI, pos. ion) *m/z*: 533.3 $[M + H]^+$.

Step 4) 2-(6-((4'-(2-(1,4-dioxan-2-yl)ethoxy)-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetic acid

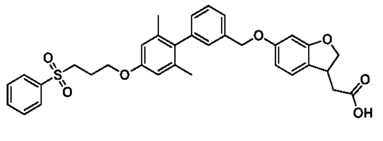
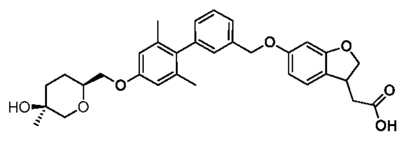
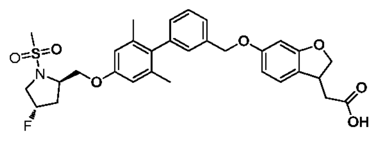
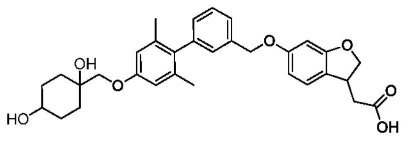
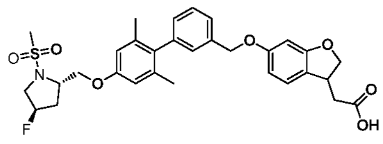
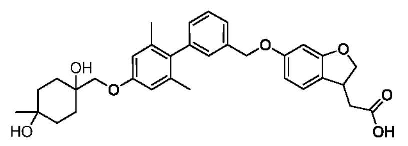
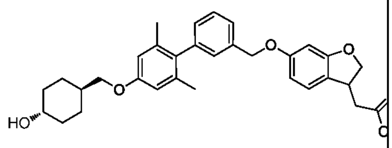
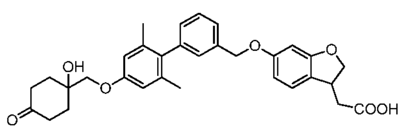
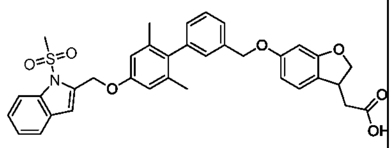
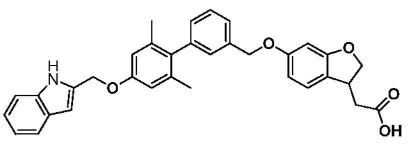
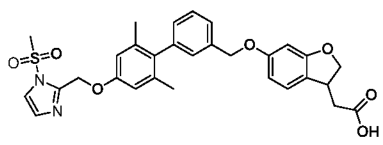
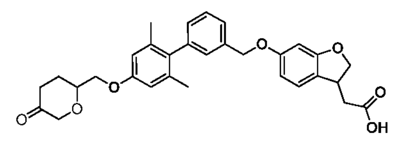
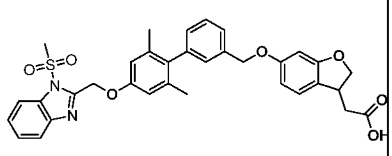
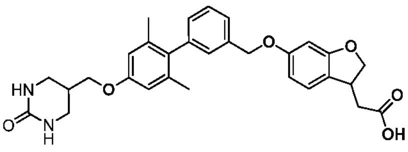
[00345] The title compound was prepared according to the procedure described in step 6 of Example 37 using methyl 2-(6-((4'-(2-(1,4-dioxan-2-yl)ethoxy)-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetate (77 mg, 0.15 mmol). The reaction yielded the product as a pale yellow soild (35 mg, 46.7%).

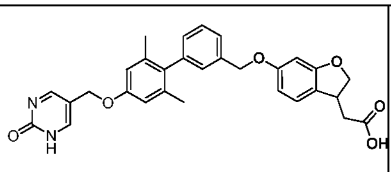
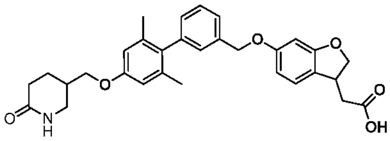
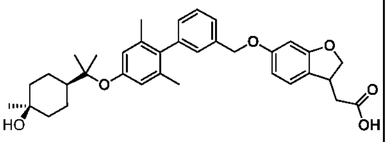
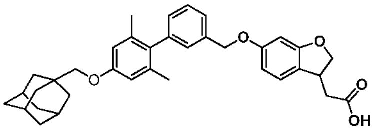
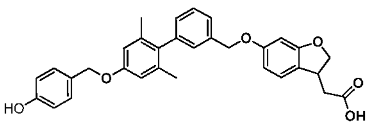
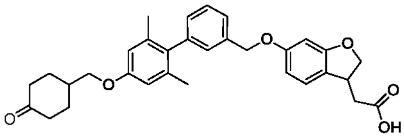
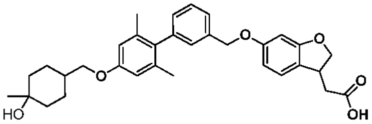
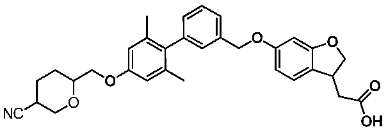
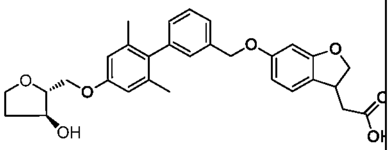
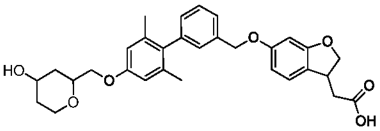
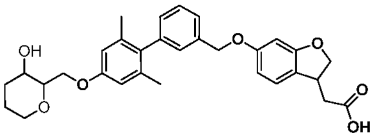
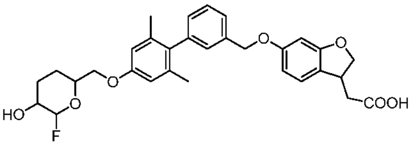
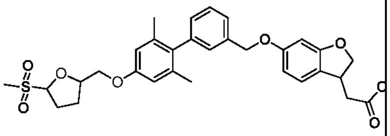
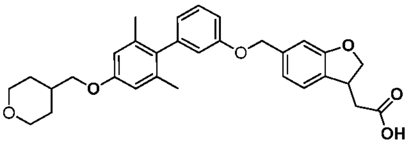
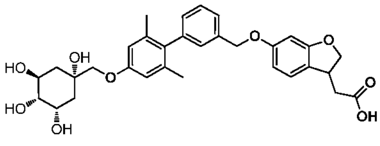
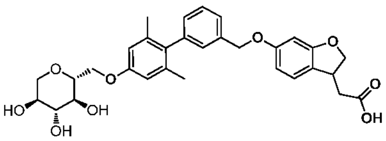
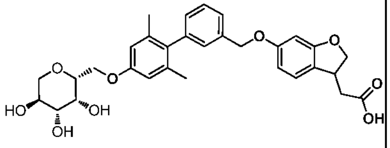
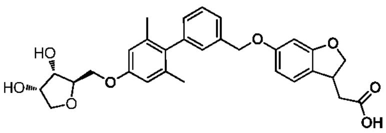
MS (ESI, pos. ion) *m/z*: 519.2 $[M + H]^+$; and

^1H NMR (600 MHz, $CDCl_3$): δ 7.48 – 7.37 (m, 2H), 7.19 (s, 1H), 7.09 (dd, J = 19.8, 7.6 Hz, 2H), 6.69 (s, 2H), 6.55 – 6.47 (m, 2H), 5.08 (s, 2H), 4.78 (t, J = 8.9 Hz, 1H), 4.35 – 4.27 (m, 1H), 4.15-4.06(m, 2H), 3.89 – 3.72 (m, 6H), 3.69-3.62 (m, 1H), 3.41 (t, J = 10.9 Hz, 1H), 2.83 (dd, J = 16.8, 4.8 Hz, 1H), 2.64 (dd, J = 16.7, 9.4 Hz, 1H), 2.02 (s, 6H), 1.92-1.74(m, 2H).

Example 51-82

[00346] The compounds of Examples 51 to 82 were prepared according to the procedure described in Example 4.

No.	Structure	MS [M+H]$^+$	No.	Structure	MS [M+H]$^+$
51		587.2	67		533.3
52		584.2	68		533.3
53		584.2	69		546.7
54		516.2	70		530.2
55		612.2	71		534.2
56		563.2	72		517.2
57		613.2	73		517.2

58		513.2	74		516.2
59		559.3	75		553.3
60		511.2	76		515.2
61		531.2	77		528.2
62		505.2	78		519.2
63		519.2	79		537.2
64		567.2	80		503.2
65		565.2	81		551.2
66		551.2	82		521.2

Example 83-89

[00347] The compounds of Examples 83 to 84 were prepared according to the procedure described in Example 38.

[00348] The compound of Example 85 was prepared according to the procedure described in Example 36.

[00349] The compound of Example 86 was prepared according to the procedure described in Example 16.

[00350] The compound of Example 87 was prepared according to the procedure described in Example 37.

[00351] The compounds of Examples 88 to 89 were prepared according to the procedure described in Example 26.

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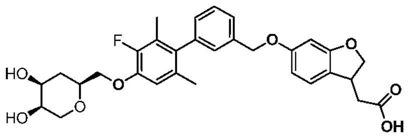
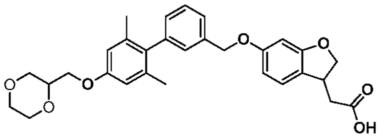
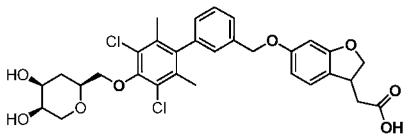
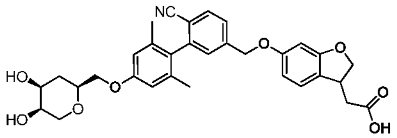
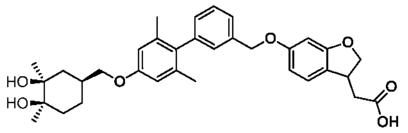
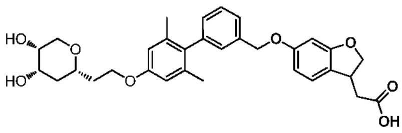
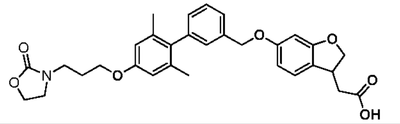
83		553.2	87		504.3
84		603.2	88		560.2
85		561.3	89		549.2
86		532.2			

Example 90

Testing the activation activity of the compounds of the present invention against GPR40 cell

[00352] hGPR40 overexpression cells (HEK293 cell lines stably expressing hGPR40 stable) were seeded into a 384-well plate at a inoculation density of 8000 cells per well. The cells were incubated for 24 h at 37 °C in a 5% CO_2 and air environment. At the beginning of the assay, the 384-well plate seeded with the cells was taken out of the incubator, after removal of medium from cells, Calcium dye (the compoistion of the Calcium dye: 20 mL HBSS (20 mM HEPES) + 2 tube dye +200 μL 10% BSA, Calcium 4 assay kit, Molecular Device) was added at a volume of 40 μL per well. The cells were further incubated for 1 h. Experimental procedure was run on a FLIPR (fluorescence image plate reader), the compounds of the invention diluted to a desired concentration by means of 3-fold serial dilution were added into the wells at a volume of 10 μL per well, the increased Ca^{2+} levels in cells were readed by FLIPR. The EC_{50} values of the compounds were obtained from a fitted curve based on the original data by using XLfit software.

Table 2: The activation activity of the compounds of the present invention

No.	EC_{50} (nM)	No.	EC_{50} (nM)	No.	EC_{50} (nM)
Example 3	121	Example 18	53	Example 32	52

Example 4	108	Example 19	201	Example 33	44
Example 5	93	Example 20	100	Example 34	65
Example 6	25	Example 21	119	Example 35	62
Example 7	93	Example 22	59	Example 36	20
Example 8	95	Example 23	100	Example 37	15
Example 9	43	Example 24	105	Example 40	15
Example 10	62	Example 25	38	Example 41	20
Example 11	117	Example 26	55	Example 43	94
Example 12	72	Example 27	53	Example 44	38
Example 13	158	Example 28	25	Example 45	104
Example 14	76	Example 29	24	Example 46	48
Example 15	147	Example 30	28	Example 47	66
Example 16	129	Example 31	29		

[00353] Conlusions: Each of the compounds disclosed herein has obvious GPR40 activation activity.

Example 91

Testing pharmacokinetics features

[00354] Experimental animal: 6 healthy adult male SD rats were divided into two groups, which purchased from Hunan Si Lai Ke Jing Da laboratory animal co., LTD. One group (3 rats) was administered by intravenous infusion and another group (3 rats) was administered by gavage.

[00355] Preparation of drugs: a certain amount of the compound disclosed herein were dissolved in a mixture containing 5% DMSO, 10% Kolliphor HS15 and 85% Saline.

[00356] Drug delivery and sample collection: These rats were administered the drugs after 12-hour fast. During the fasting period, these rats drank water freely. 3 Hours after the administration of the drugs, these rats took diet. The drugs were administered to these SD rats by intravenous infusion through the hind legs vein at a dose of 2 mg/kg and by gavage at a dose of 5 mg/kg. Blood samples with a volume of about 200-400 μL per at each time point were collected from the caudal vein immediately at 0, 0.083, 0.25, 0.5, 1, 2, 4, 6, 8 and 24 h after administration of the drugs. The whole blood samples collected at each time were put into K2EDTA anticoagulant tube and preserved in incubator with ice packs. All blood samples were centrifuged at 4600 r/min and 4 °C for 5 min within 15 min after collection and then plasma was separated. The blood samples (plasma) were stored at −80 °C for the following test. The reserve samples were stored for further 1 week after analyzing.

[00357] Analytical method: The contents of the test compounds in plasma after administration of diffirent compounds were tested by using a LC-MS/MS analysis method.

Results:

Table 3: The pharmacokinetics features of the compounds of the present invention

Rats PK	Route of administration	Dose	F(%)	AUC$_{INF}$	AUC$_{last}$	Cl	C$_{max}$	MRT$_{INF}$	T$_{1/2}$	T$_{max}$	V$_{ss}$
No.		(mg/kg)		h*ng/ml	h*ng/ml	l/h/kg	ng/ml	h	h	h	l/kg

Example 6	*iv*	2	122.63	5019.62	4978.24	0.42	3103.33	2.07	1.96	0.08	0.82
	po	5		15389.43	15240.47	N/A	3833.33	3.10	2.77	0.67	N/A
Example 9	*iv*	2	93.50	8367.19	8299.44	0.24	4176.67	1.92	1.00	0.08	0.46
	po	5		19557.97	19384.27	N/A	6370.00	2.34	0.94	0.67	N/A
Example 28	*iv*	2	89.90	57918.67	53013.64	0.03	10236.39	8.49	7.15	0.08	0.30
	po	5		130186.25	123337.66	N/A	18112.72	7.28	5.92	0.58	N/A
Example 29	*iv*	2	147.90	29291.18	26889.50	0.07	9580.60	7.82	7.56	0.08	0.53
	po	5		108318.87	104476.83	N/A	15527.63	6.38	5.68	1.00	N/A

"N/A" is none.

[00358] Conclusions: Each of the compounds disclosed herein has high blood concentration in rats and AUC (area under the concentration versus time curve) levels after orally administration, low clearance rate, long half-life period, and good pharmacokinetic features.

Example 92

Testing in vivo pharmacodynamics

1. Test purpose

[00359] Observed the effects of the test compounds on intraperitoneal glucose tolerance.

2. Experimental animal:

[00360] 24 Healthy adult male SD rats were divided into four groups (number of each group is 6), which purchased from Hunan Si Lai Ke Jing Da laboratory animal co., LTD..

3. Preparation of drugs:

[00361] A certain amount of the drugs were dissolved in a mixture containing 5% DMSO, 10% Kolliphor HS15 and 85% Saline.

[00362] 4. Exaperimental method:

4.1 Grouping

[00363] The rats were divided into blank control group and test drugs groups based on their weights and fasting blood glucose levels after a 16-hour overnight fast.

4.2 Dose

[00364] The drugs were administered at a dose of 20 mg/kg or 30 mg/kg, the blank control group was administered solvent (5% DMSO, 10% Kolliphor HS15 and 85% Saline)

4.3 Methods of administration

[00365] The rats were administered dugs by gavage, after 30 min, a glucose solution (2 g/kg, 20%) was injected into the abdominal cavity.

4.4 Blood glucose assay

[00366] Each group was administered at a dose immediately after measurement of the blood glucose level (*i.e.* −30 min point blood glucose), after 30 min, a glucose solution (2 g/kg, 20%) was injected into the abdominal cavity and the blood was drawn at 0, 15, 30, 45, 60 and 120 min. The blood glucose levels of the rats were

measured by using ROCHE blood-glucose meter.

4.5 Data statistics

[00367] By using Excel statistical software, average value was calculated by AVG function, SD value was calculated by STDEV function and differences between groups P value was calvulated by TTEST function.

[00368] The computational equation of AUC:

$$AUC=1/2\times(BG0+BG1)\times T1+1/2\times(BG1+BG2)\times T2+1/2\times(BG2+BG3)\times T3+\ldots\ldots+1/2\times(BGn-1+BGn)\times Tn$$

[00369] In the above equation, Tn is the time difference of the n^{th} measurement of blood glucose since the previous one, BGn is the blood glucose value in the n^{th} measurement.

5. Results:

Table 4: In vivo pharmacodynamics activity of the compounds of the present invention

No.	Dose (mg/kg)	Blood glucose decline after administration of drug 30 min			AUC decline
		15 min	30 min	45 min	
Example 6	20	25.79%	32.73%	28.37%	25.41%
Example 9	20	28.27%	43.88%	24.62%	23.57%
Example 28	30	-4.75%	32.02%	44.63%	26.25%
Example 29	30	-11.40%	25.45%	37.19%	19.43%

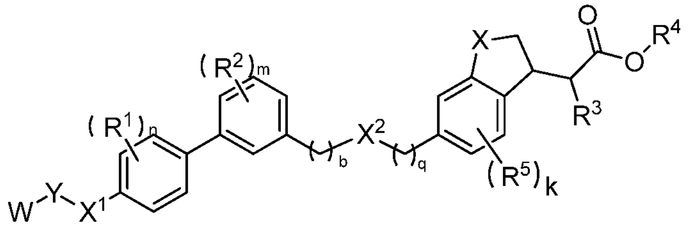
[00370] Conclusions: Each of the compounds disclosed herein has obvious hypoglycemic effect for SD rats, which were orally administered at a dose of 20 mg/kg or 30 mg/kg and injected into the abdominal cavity with glucose tolerance.

[00371] Reference throughout this specification to "an embodiment," "some embodiments," "one embodiment", "another example," "an example," "a specific examples," or "some examples," means that a particular feature, structure, material, or characteristic described in connection with the embodiment or example is included in at least one embodiment or example of the present disclosure. Thus, the appearances of the phrases such as "in some embodiments," "in one embodiment", "in an embodiment", "in another example, "in an example," "in a specific examples," or "in some examples," in various places throughout this specification are not necessarily referring to the same embodiment or example of the present disclosure. Furthermore, the particular features, structures, materials, or characteristics may be combined in any suitable manner in one or more embodiments or examples.

Although explanatory embodiments have been shown and described, it would be appreciated by those skilled in the art that the above embodiments cannot be construed to limit the present disclosure, and changes, alternatives, and modifications can be made in the embodiments without departing from spirit, principles and scope of the present disclosure.

WHAT IS CLAIMED IS:

1. A compound having Formula (I):



(I)

or a stereoisomer, a geometric isomer, a tautomer, a mesomer, a racemate, an enantiomer, a diastereoisomer, an *N*-oxide, a hydrate, a solvate, a metabolite, a hydrolysate, a pharmaceutically acceptable salt or a prodrug thereof, wherein

each of X and X^1 is independently O, NH, CH_2 or S;

X^2 is O, S or NH;

Y is alkylene or alkenylene, wherein one or more methylene groups of the alkylene or alkenylene are optionally independently replaced with NR^a, S, $S(=O)_2$ or S(=O), and wherein each of the alkylene and alkenylene is optionally independently substituted by one or more substituents independently selected from hydroxy, F, Cl, Br, I, cyano, amino, mercapto, nitro, oxo (=O), alkyl or hereoalkyl;

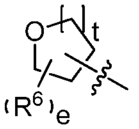
each R^1, R^2 and R^3 is independently H, F, Cl, Br, I, hydroxy, cyano, amino, mercapto, nitro, alkyl, heteroalkyl, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, alkoxy, alkylamino, cycloalkyl, heterocyclyl, aryl, heteroaryl or haloalkyl;

R^4 is H or alkyl;

each R^5 is independently H, F, Cl, Br, I, hydroxy, cyano, amino, mercapto, nitro, alkyl, alkoxy, alkylamino or heteroalkyl;

each of k, n, m, b and q is independently 0, 1, 2, 3 or 4;

W is adamantyl, bridged cyclyl, bridged heterocyclyl, spiro cyclyl, spiro heterocyclyl, fused cyclyl or fused heterocyclyl, wherein each of the damantyl, bridged cyclyl, bridged heterocyclyl, spiro cyclyl, spiro heterocyclyl, fused cyclyl and fused heterocyclyl is optionally independently substituted by one or more R^6 groups; or W is



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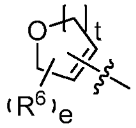

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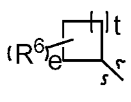

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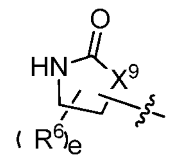

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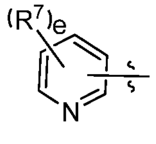

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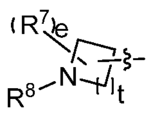

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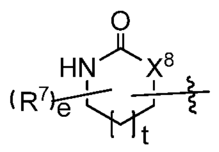

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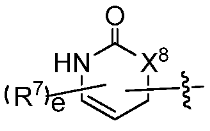

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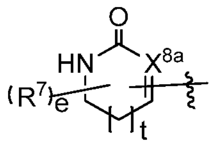

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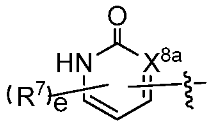

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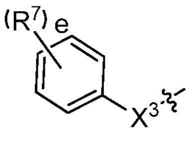

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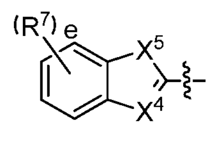

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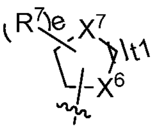
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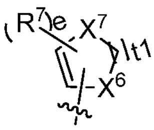
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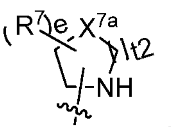
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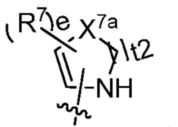
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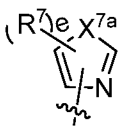
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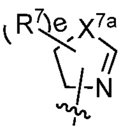
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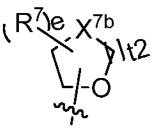
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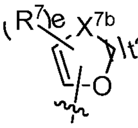
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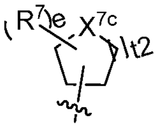
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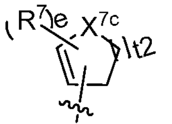
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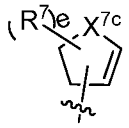
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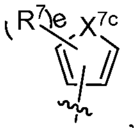
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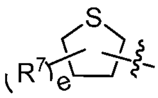
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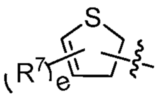
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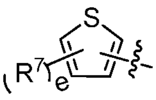
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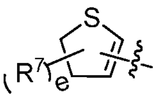
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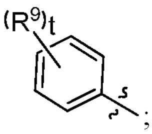
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wherein each R^6 is independently H, F, Cl, Br, I, hydroxy, cyano, amino, mercapto, nitro, oxo(=O), alkyl, heteroalkyl, haloalkyl, hydroxyalkyl, aminoalkyl, alkoxy, alkylamino, alkyl-$S(=O)_2$- or alkyl-S(=O)-;

each R^7 is independently H, F, Cl, Br, I, hydroxy, cyano, amino, mercapto, nitro, alkyl, heteroalkyl, haloalkyl, hydroxyalkyl, aminoalkyl, alkoxy, alkylamino, alkyl-$S(=O)_2$- or alkyl-S(=O)-;

R^8 is H, C_{2-10} alkyl, heteroalkyl, haloalkyl, hydroxyalkyl, aminoalkyl, alkyl-$S(=O)_2$- or alkyl-S(=O)-;

each R^9 is independently F, Cl, Br, I, hydroxy, cyano, amino, mercapto, nitro, alkyl, heteroalkyl, haloalkyl, hydroxyalkyl, aminoalkyl, alkoxy, alkylamino, alkyl-$S(=O)_2$- or alkyl-S(=O)-;

X^3 is NR^a, O, S, $S(=O)_2$ or S(=O);

each of X^4 and X^{8a} is independently CH or N;

each of X^5 and X^{7a} is independently CH_2 or NR^a;

X^7 is CH_2, S, O or NR^a;

X^{7b} is CH_2, O or S;

X^{7c} is CH_2, O or NR^a;

each of X^6 and X^8 is independently CH_2, O or NH;

X^9 is O or NH;

each R^a is independently alkyl-$S(=O)_2$- or H;

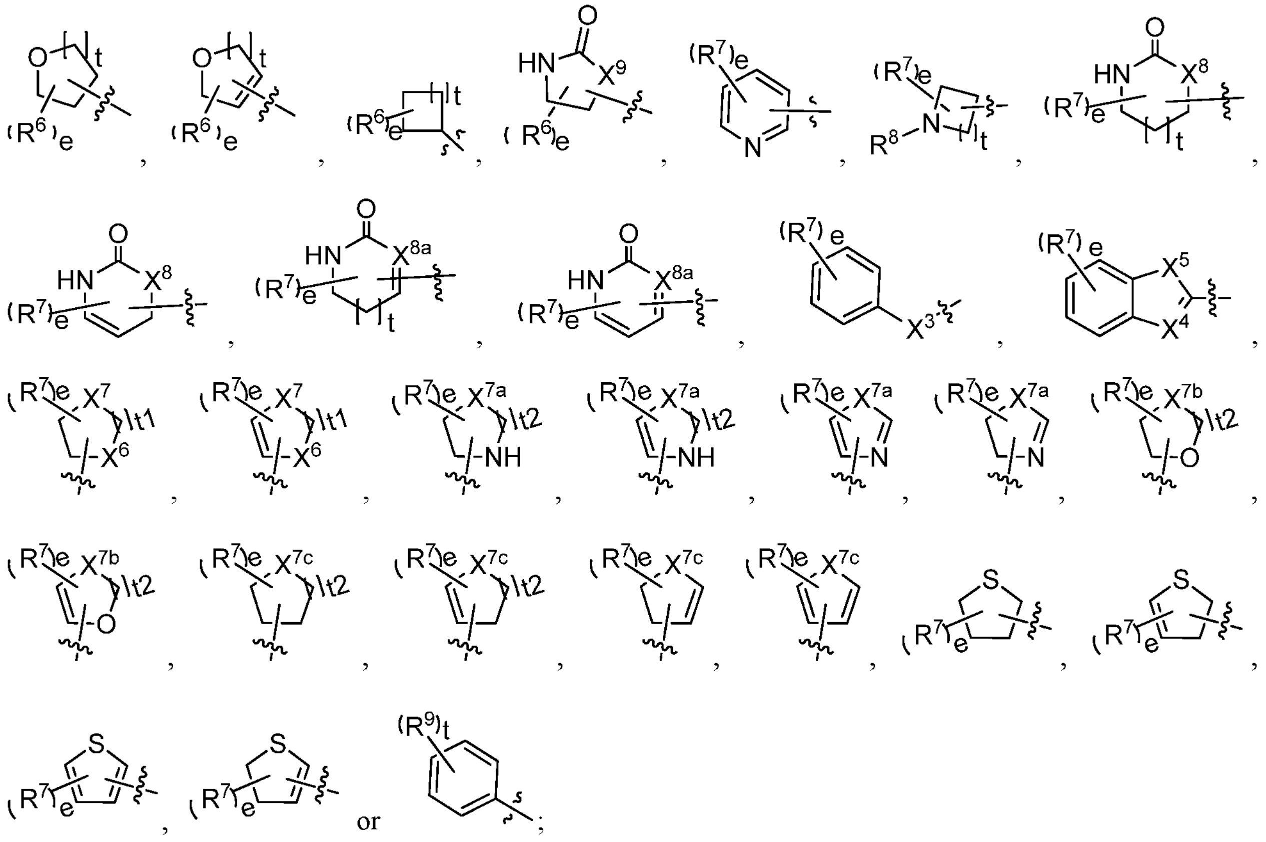
each e is independently 0, 1, 2, 3, 4, 5, 6, 7 or 8;

each t is independently 1, 2, 3, 4 or 5;

t1 is 3, 4 or 5; and

each t2 is independently 1 or 2.

2. The compound of claim 1, wherein W is adamantyl, C_{5-12} bridged cyclyl, C_{5-12} bridged heterocyclyl, C_{5-12} spiro cyclyl, C_{5-12} spiro heterocyclyl, C_{4-12} fused cyclyl or C_{4-12} fused heterocyclyl, and wherein each of damantyl, C_{5-12} bridged cyclyl, C_{5-12} bridged heterocyclyl, C_{5-12} spiro cyclyl, C_{5-12} spiro heterocyclyl, C_{4-12} fused cyclyl and C_{4-12} fused heterocyclyl is optionally independently substituted by one or more R^6 groups; or W is



and wherein each R^6 is independently H, F, Cl, Br, I, hydroxy, cyano, amino, mercapto, nitro, oxo (=O), C_{1-6} alkyl, C_{2-6} heteroalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} aminoalkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{1-6} alkyl-S(=O)$_2$- or C_{1-6} alkyl-S(=O)-;

each R^7 is independently H, F, Cl, Br, I, hydroxy, cyano, amino, mercapto, nitro, C_{1-6} alkyl, C_{2-6} heteroalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} aminoalkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{1-6} alkyl-S(=O)$_2$- or C_{1-6} alkyl-S(=O)-;

R^8 is H, C_{2-6} alkyl, C_{2-6} heteroalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} aminoalkyl, C_{1-6} alkyl-S(=O)$_2$- or C_{1-6} alkyl-S(=O)-;

each R^9 is independently F, Cl, Br, I, hydroxy, cyano, amino, mercapto, nitro, C_{1-6} alkyl, C_{2-6} heteroalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} aminoalkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{1-6} alkyl-S(=O)$_2$- or C_{1-6} alkyl-S(=O)-; and

each R^a is independently C_{1-6} alkyl-S(=O)$_2$- or H.

3. The compound of claim 2, wherein each R^6 is independently H, F, Cl, Br, I, hydroxy, cyano, amino, mercapto, nitro, oxo(=O), methyl, ethyl, propyl, isopropyl, butyl, trifluoromethyl, hydroxymethyl, aminomethyl, methoxy, ethoxy, methylamino, ethylamino, CH_3-S(=O)$_2$- or CH_3-S(=O)-;

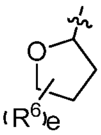
each R^7 is independently H, F, Cl, Br, I, hydroxy, cyano, amino, mercapto, nitro, methyl, ethyl, propyl, isopropyl, butyl, trifluoromethyl, hydroxymethyl, aminomethyl, methoxy, ethoxy, methylamino, ethylamino, CH_3-S(=O)$_2$- or CH_3-S(=O)-;

R^8 is H, ethyl, trifluoromethyl, hydroxymethyl, aminomethyl, CH_3-S(=O)$_2$- or CH_3-S(=O)-;

each R^9 is independently F, Cl, Br, I, hydroxy, cyano, amino, mercapto, nitro, methyl, ethyl, propyl, isopropyl, butyl, trifluoromethyl, hydroxymethyl, aminomethyl, methoxy, ethoxy, methylamino, ethylamino, CH_3-S(=O)$_2$- or CH_3-S(=O)-; and

each R^a is independently CH_3-S(=O)$_2$- or H.

4. The compound of claim 1, wherein W is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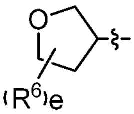
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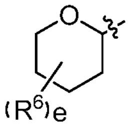
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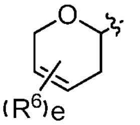
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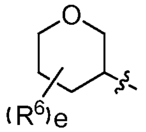
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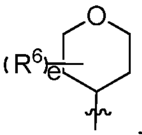
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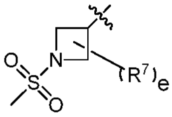
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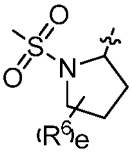
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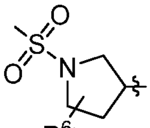
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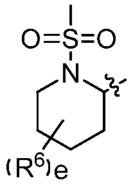
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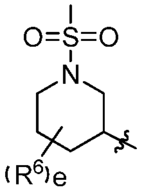
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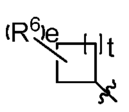
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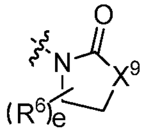
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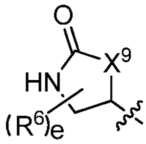
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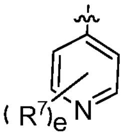
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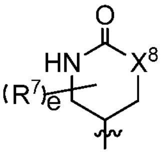
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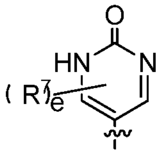
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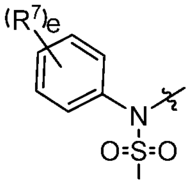
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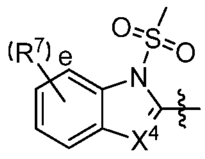
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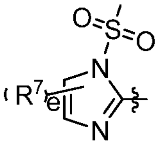
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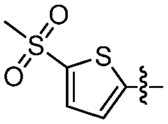
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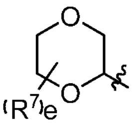
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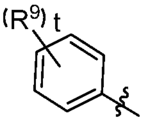
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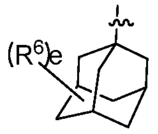
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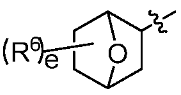
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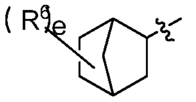
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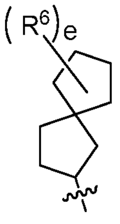
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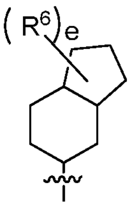
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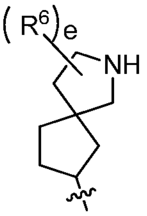
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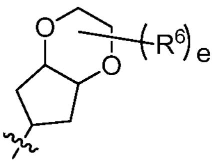
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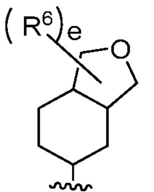
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wherein each R^6 is independently H, F, Cl, Br, I, hydroxy, cyano, amino, mercapto, nitro, oxo(=O), methyl, ethyl, propyl, isopropyl, butyl, trifluoromethyl, hydroxymethyl, aminomethyl, methoxy, ethoxy, methylamino, ethylamino, CH_3-S(=O)$_2$- or CH_3-S(=O)-;

each R^7 is independently H, F, Cl, Br, I, hydroxy, cyano, amino, mercapto, nitro, methyl, ethyl, propyl, isopropyl, butyl, trifluoromethyl, hydroxymethyl, aminomethyl, methoxy, ethoxy, methylamino, ethylamino, CH_3-S(=O)$_2$- or CH_3-S(=O)-; and

each R^9 is independently F, Cl, Br, I, hydroxy, cyano, amino, mercapto, nitro, methyl, ethyl, propyl, isopropyl, butyl, trifluoromethyl, hydroxymethyl, aminomethyl, methoxy, ethoxy, methylamino, ethylamino,

CH_3-S(=O)$_2$- or CH_3-S(=O)-.

5. The compound of claim 1, wherein Y is C_{2-6} alkylene or C_{2-6} alkenylene, and wherein one or more methylene groups of the C_{2-6} alkylene or C_{2-6} alkenylene are optionally replaced with NR^a, S, S(=O)$_2$ or S(=O), each of the C_{2-6} alkylene and C_{2-6} alkenylene is optionally independently substituted by one or more substituents independently selected from hydroxy, F, Cl, Br, I, cyano, amino, mercapto, nitro, oxo (=O), C_{1-6} alkyl or C_{2-6} hereoalkyl; and

R^a is CH_3-S(=O)$_2$- or H.

6. The compound of claim 1, wherein each R^1, R^2 and R^3 is independently H, F, Cl, Br, I, hydroxy, cyano, amino, mercapto, nitro, C_{1-6} alkyl, C_{2-6} heteroalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} hydroxyalkyl, C_{1-6} aminoalkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{3-10} cycloalkyl, C_{2-10} heterocyclyl, C_{6-10} aryl, C_{1-9} heteroaryl or C_{1-6} haloalkyl;

R^4 is H or C_{1-6} alkyl; and

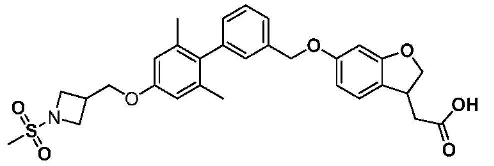
each R^5 is independently H, F, Cl, Br, I, hydroxy, cyano, amino, mercapto, nitro, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino or C_{2-6} heteroalkyl.

7. The compound of claim 1, wherein each R^1, R^2 and R^3 is independently H, F, Cl, Br, I, hydroxy, cyano, amino, mercapto, nitro, methyl, ethyl, propyl, isopropyl, butyl, vinyl, ethynyl, hydroxymethyl, aminomethyl, methoxy, methylamino, cyclopropyl, tetrahydrofuranyl, phenyl, pyrrolyl or trifluoromethyl;

R^4 is H, methyl or ethyl; and

each R^5 is independently H, F, Cl, Br, I, hydroxy, cyano, amino, mercapto, nitro, methyl, ethyl, methoxy, ethoxy, isopropoxy, methylamino, ethylamino or propylamino.

8. The compound of claim 1 having one of the following structures:



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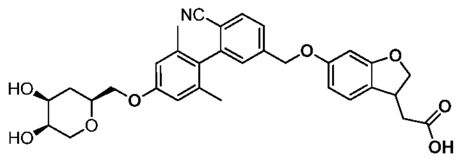

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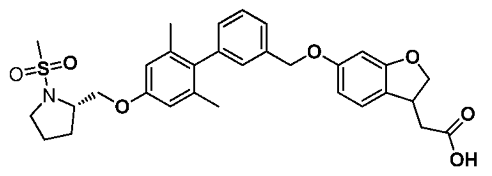

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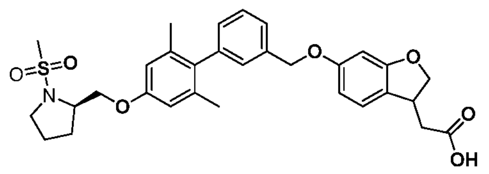

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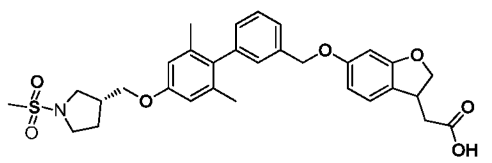

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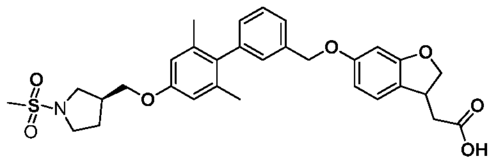

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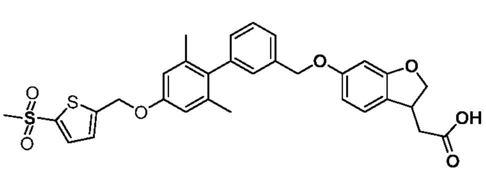
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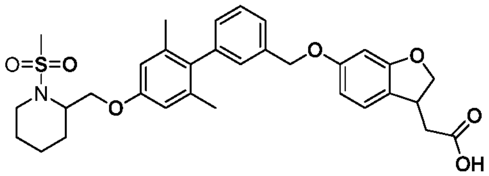
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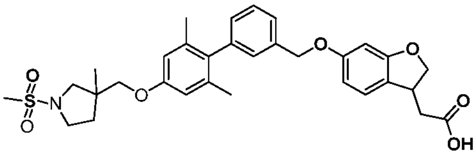
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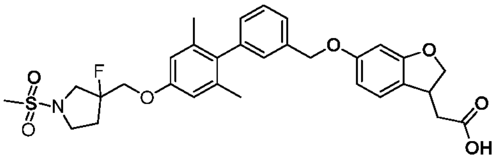
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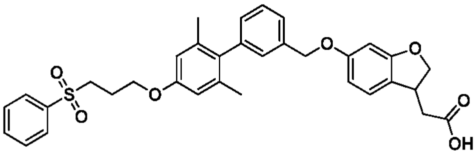
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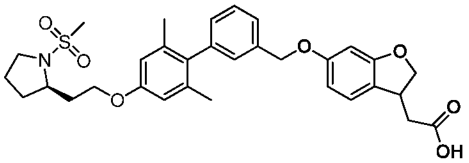
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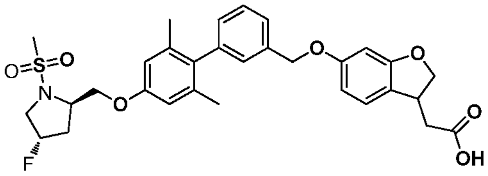
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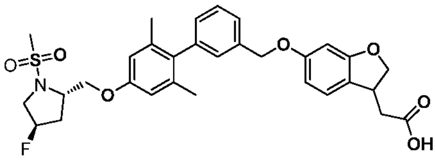
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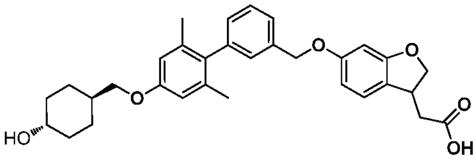
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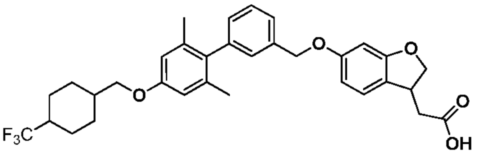
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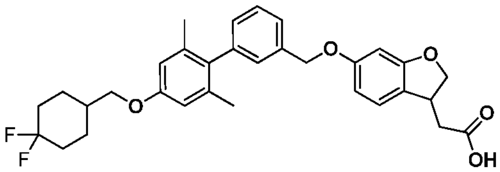
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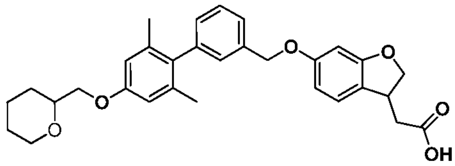
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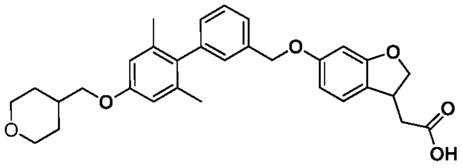
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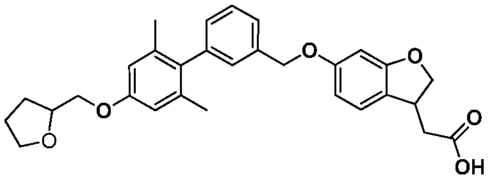
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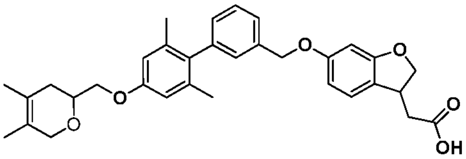
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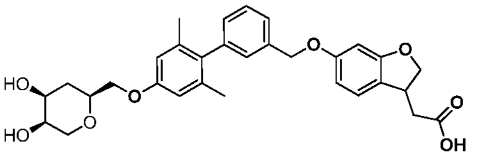
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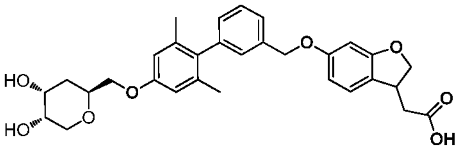
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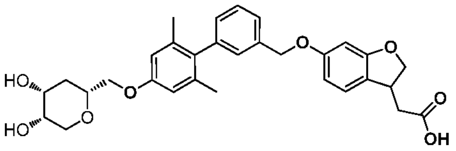
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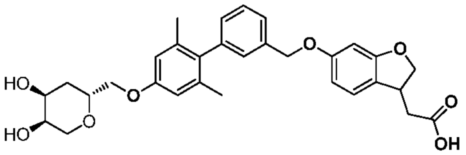
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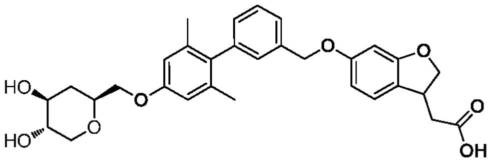
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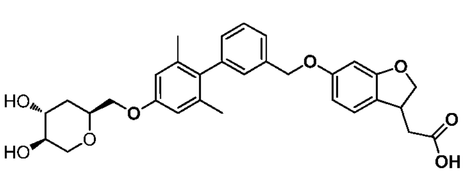
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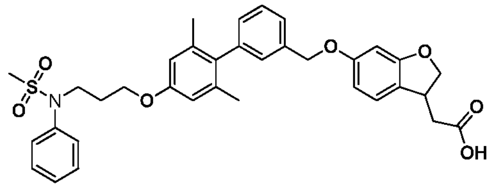
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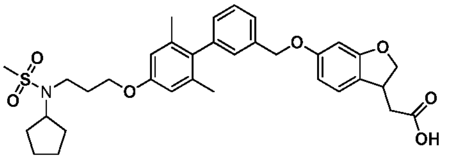
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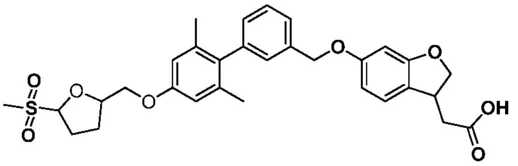
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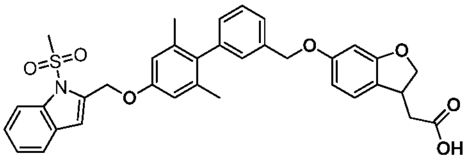
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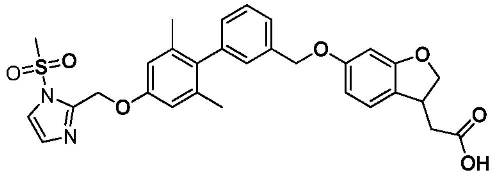
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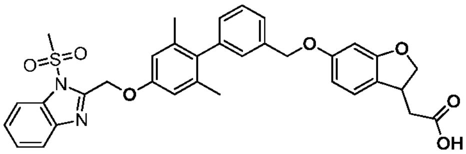
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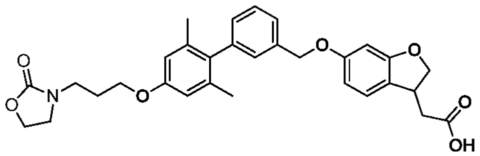
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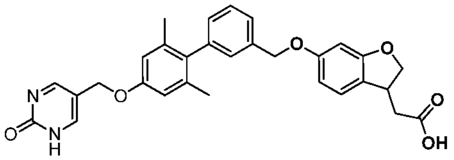
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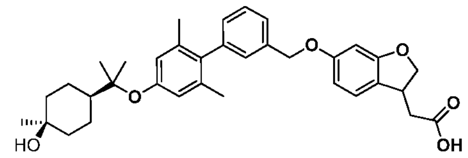
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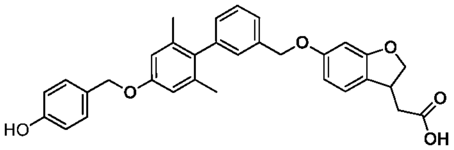
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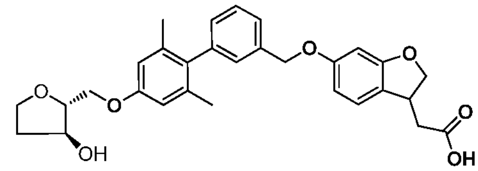
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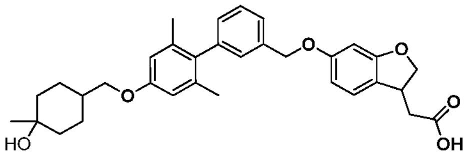
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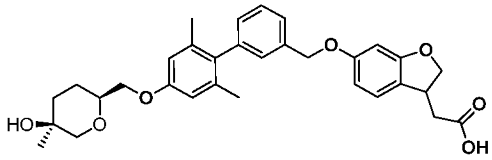
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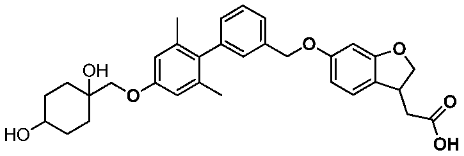
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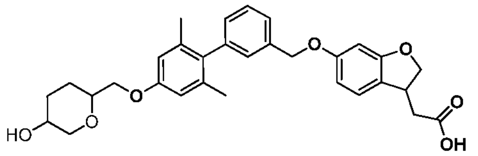
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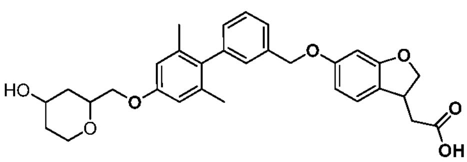
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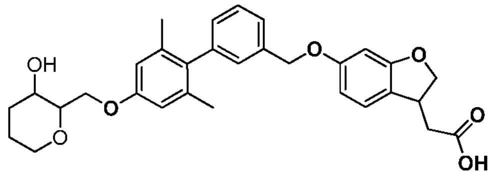
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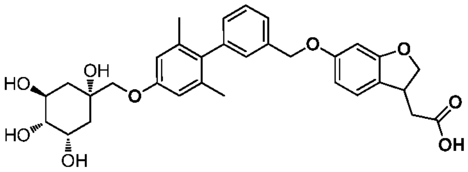
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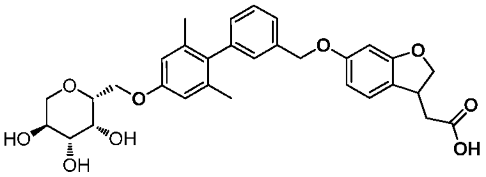
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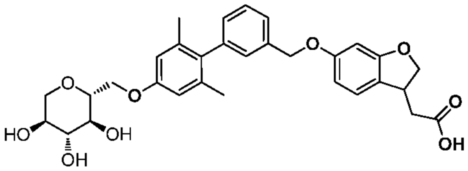
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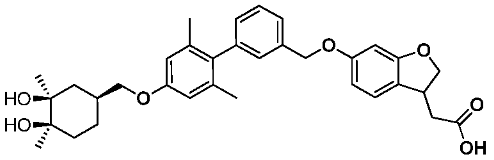
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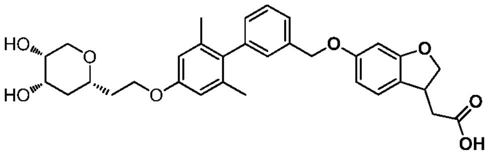
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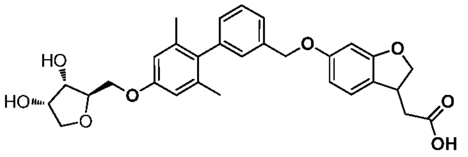
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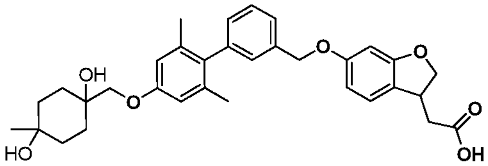
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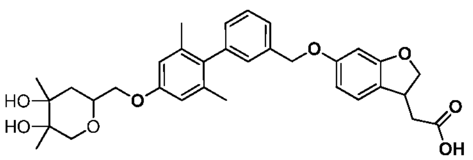
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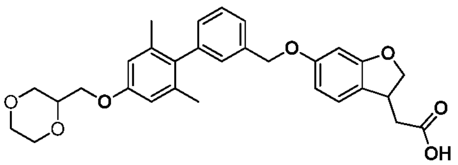
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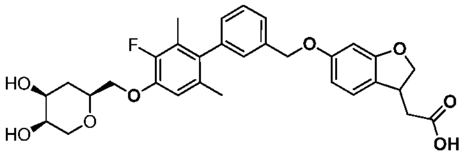
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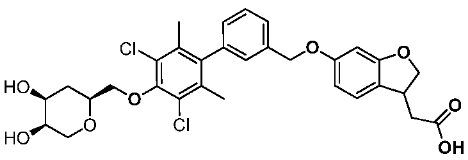
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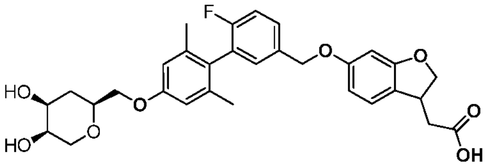
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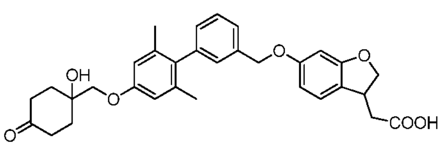
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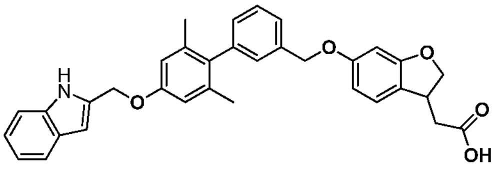
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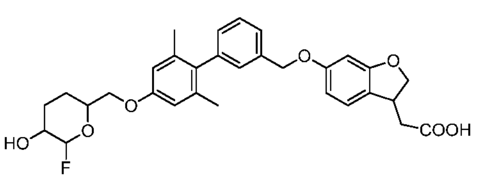
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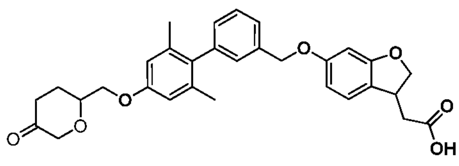
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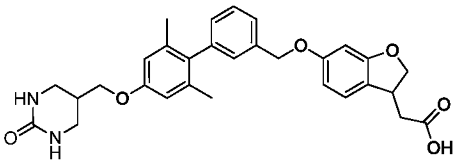
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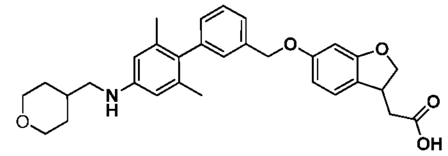
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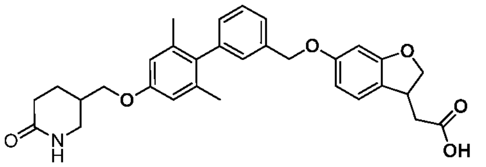
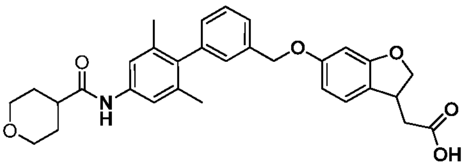
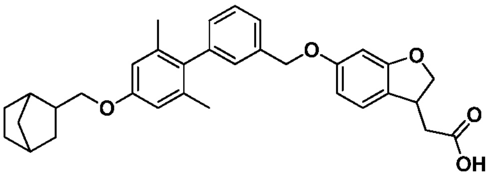
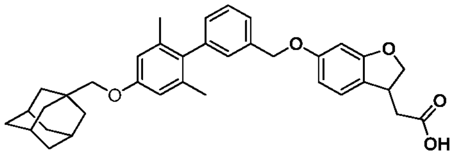
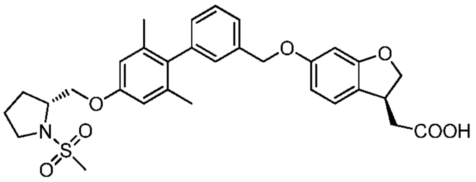
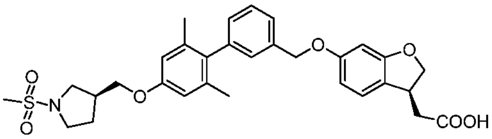
 (63),

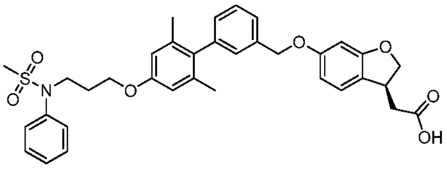
 (64),

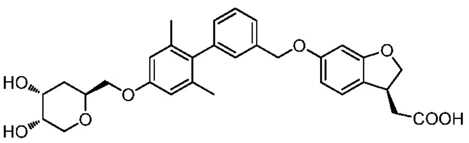
 (65),

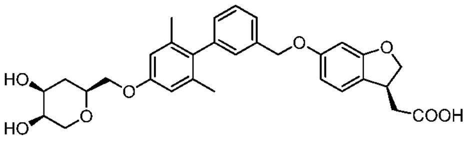
 (66),

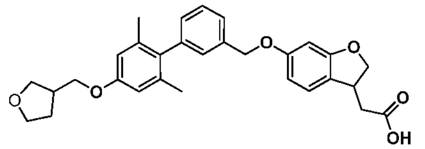
 (67),

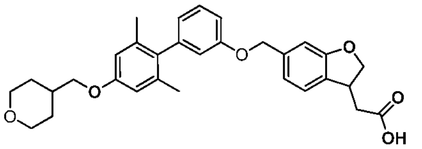
 (68),

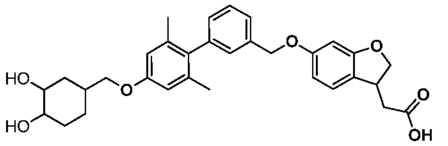
 (69),

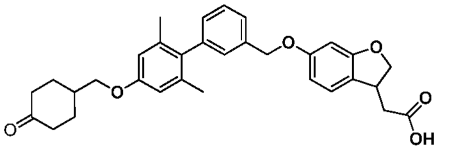
 (70),

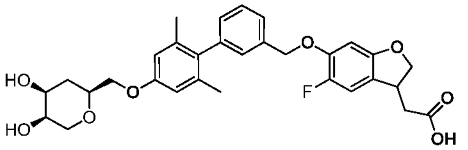
 (71),

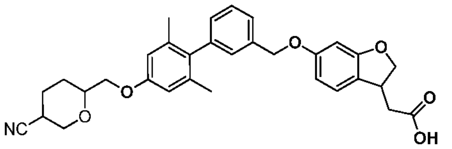
 (72),

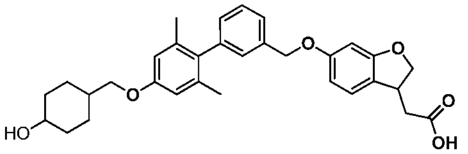
 (73),

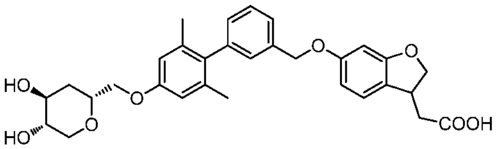
 (74),

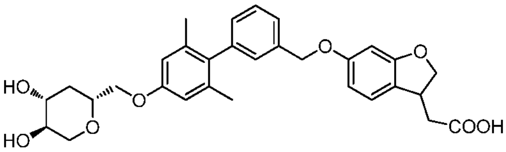
 (75),

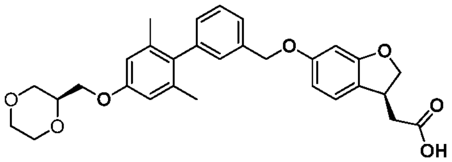
 (76),

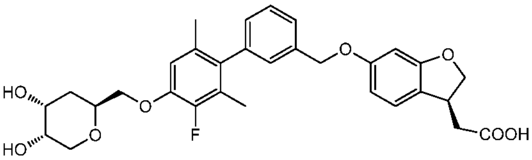
 (77),

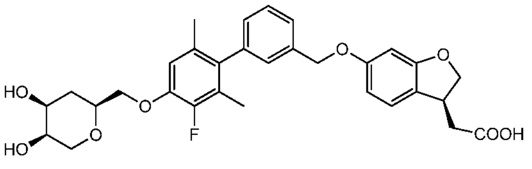
 (78),

 (79),

 (80),

 (81),

 (82),



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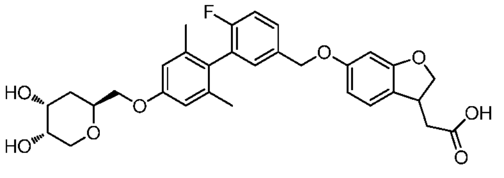
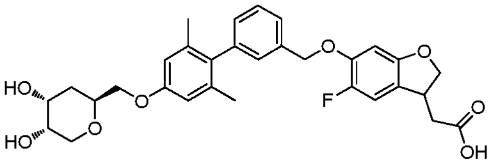
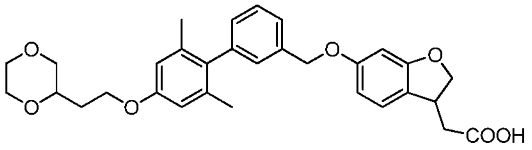


(84),



(85) or



(86).

9. A pharmaceutical composition comprising the compound according to any one of claims 1 to 8.

10. The pharmaceutical composition according to claim 9 further comprising at least one of pharmaceutically acceptable carriers, excipients, diluents, adjuvants and vehicles.

11. The pharmaceutical composition according to claim 9 further comprising at least one of antidiabetic agents, antihyperglycemic agents, antiadipositas drugs, antihypertensive agents, antiplatelet agents, antiatherosclerotic drugs, lipid-lowering agents and anti-inflammatories.

12. The pharmaceutical composition according to claim 11, wherein the antidiabetic agent is at least one of SGLT-2 inhibitors, biguanides, sulfonylureas, glucosidase inhibitors, PPAR agonists, αP2 inhibitors, PPARα/γ dual agonists, dipeptidyl peptidase inhibitors, ndinedglinides, insulin, glucagon like peptide-1 inhibitors, PTP1B inhibitors, glycogen phosphorylase inhibitors and glucose-6-phosphatase inhibitors.

13. The pharmaceutical composition according to any one of claims 9 to 12 further comprising at least one of GPR40 receptor agonists.

14. Use of the compound according to any one of claims 1 to 8 or the pharmaceutical composition according to any one of claims 9 to 13 in the manufacture of a medicament for preventing, treating, lessening or delaying diabetes, diabetic retinopathy, diabetic neuropathy, diabetic nephropathy, insulin resistance, hyperglycemia, hyperinsulinemia, elevated blood levels of fatty acids or glycerol, hyperlipidemia, obesity, hypertriglyceridemia, syndrome X, ketosis acidosis, glucose intolerance, hypercholesterolemia, dyslipidemia, metabolic syndrome, cardiovascular disease, renal disease, thrombotic disorders, nephropathy, sexual dysfunction, skin disease, indigestion, hypoglycemia, cancer, edema, diabetes complications, atherosclerosis or hypertension, or increasing high density lipoprotein level.

15. Use of the compound according to any one of claims 1 to 8 or the pharmaceutical composition according to any one of claims 9 to 13 in the manufacture of a medicament for exciting G-protein coupled receptor.

16. The use according to claim 15, wherein the G-protein coupled receptor is GPR40 receptor.

17. A method for preventing, treating, lessening or delaying diabetes, diabetic retinopathy, diabetic neuropathy, diabetic nephropathy, insulin resistance, hyperglycemia, hyperinsulinemia, elevated blood levels of fatty acids or glycerol, hyperlipidemia, obesity, hypertriglyceridemia, syndrome X, ketosis acidosis, glucose

intolerance, hypercholesterolemia, dyslipidemia, metabolic syndrome, cardiovascular disease, renal disease, thrombotic disorders, nephropathy, sexual dysfunction, skin disease, indigestion, hypoglycemia, cancer, edema, diabetes complications, atherosclerosis or hypertension, or increasing high density lipoprotein level, comprising administering to a subject in need thereof a therapeutically effective amount of the compound according to any one of claims 1 to 8 or the pharmaceutical composition according to any one of claims 9 to 13.

18. A method for exciting G-protein coupled receptor, comprising administering to a subject a therapeutically effective amount of the compound according to any one of claims 1 to 8 or the pharmaceutical composition according to any one of claims 9 to 13.

19. The method according to claim 18, wherein the G-protein coupled receptor is GPR40 receptor.

20. The compound according to any one of claims 1 to 8 or the pharmaceutical composition according to any one of claims 9 to 13 for use in preventing, treating, lessening or delaying diabetes, diabetic retinopathy, diabetic neuropathy, diabetic nephropathy, insulin resistance, hyperglycemia, hyperinsulinemia, elevated blood levels of fatty acids or glycerol, hyperlipidemia, obesity, hypertriglyceridemia, syndrome X, ketosis acidosis, glucose intolerance, hypercholesterolemia, dyslipidemia, metabolic syndrome, cardiovascular disease, renal disease, thrombotic disorders, nephropathy, sexual dysfunction, skin disease, indigestion, hypoglycemia, cancer, edema, diabetes complications, atherosclerosis or hypertension, or increasing high density lipoprotein level.

21. The compound according to any one of claims 1 to 8 or the pharmaceutical composition according to any one of claims 9 to 13 for use in exciting G-protein coupled receptor.

22. The compound according to any one of claims 1 to 8 or the pharmaceutical composition according to any one of claims 9 to 13, wherein the G-protein coupled receptor is GPR40 receptor.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN2014/089725

A. CLASSIFICATION OF SUBJECT MATTER

C07D 405/12(2006.01)i; C07D 407/12(2006.01)i; C07D 409/12(2006.01)i; C07D 307/80(2006.01)i; C07D 413/12(2006.01)i; A61K 31/397(2006.01)i; A61P 3/10(2006.01)i

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 405/-, C07D 407/-, C07D 409/-, C07D 307/-, C07D 413/-, A61K, A61P

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CNABS, DWPI, CNKI, REGISTRY, CAPLUS: substructure search according to Formula (I), GPR40

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CN 103145663 A (SHANGHAI GAOHUAI PHARM CO LTD) 12 June 2013 (2013-06-12) claim 4	1-16, 20-22
A	WO 2008001931 A2 (TAKEDA PHARMACEUTICAL) 03 January 2008 (2008-01-03) the whole document	1-16, 20-22
A	WO 2005087710 A1 (TAKEDA PHARMACEUTICAL) 22 September 2005 (2005-09-22) the whole document	1-16, 20-22
A	WO 2004106276 A1 (TAKEDA CHEMICAL INDUSTRIES LTD) 09 December 2004 (2004-12-09) the whole document	1-16, 20-22
X	Nobuyuki Negoro et al. "Optimization of (2, 3-Dihydro-1-benzofuran-3-yl)acetic Acids: Discovery of a Non-Free Fatty Acid-Like, Highly Bioavailable G Protein-Coupled Receptor 40/Free Fatty Acid Receptor 1 Agonist as a Glucose-Dependent Insulinotropic Agent" *J. Med. Chem.*, Vol. Vol. 55, No. No. 8, 10 April 2012 (2012-04-10), page 3965, compound 21	1-16, 20-22

☐ 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 **26 January 2015**	Date of mailing of the international search report **03 February 2015**
Name and mailing address of the ISA/CN **STATE INTELLECTUAL PROPERTY OFFICE OF THE P.R.CHINA(ISA/CN)** **6,Xitucheng Rd., Jimen Bridge, Haidian District, Beijing 100088 China** Facsimile No. **(86-10)62019451**	Authorized officer **ZHAO,Zhenzhen** Telephone No. **(86-10)62086358**

Box No. II **Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☑ Claims Nos.: **17-19**
because they relate to subject matter not required to be searched by this Authority, namely:

[1] Claims 17-19 are directed to a method of treatment of the human/animal body (PCT Rule 39.1(iv)).

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.

PCT/CN2014/089725

Patent document cited in search report	Publication date (day/month/year)	Patent family member(s)	Publication date (day/month/year)
WO 2004106276 A1	09 December 2004	EP 1630152 A4	23 September 2009
		CA 2527691 A1	09 December 2004
		EP 1630152 A1	01 March 2006
		CA 2527691 C	22 January 2013
		US 2006258722 A1	16 November 2006
		US 7820837 B2	26 October 2010
CN 103145663 A	12 June 2013	None	