Description

Title of Invention: PIPERIDINE- AND MORPHOLINE-CARBOXYLATE COMPOUNDS AS SORT1 INHIBITORS

Technical Field

[0001] This invention relates to novel compounds, pharmaceutical compositions containing them and their use as medicaments, in particular in the prophylaxis or treatment of disorders benefiting from inhibition of sortilin.

Background Art

[0002] Sortilin is a multifunctional receptor predominantly expressed in neurons of the central and peripheral nervous systems, but also in metabolic tissues including liver. This type I receptor, belonging to the Vps10 domain family, plays multiple roles in the cellular transport and signaling of a variety of ligands which interact with its luminal/extracellular VPS10 domain. The C-terminal cytoplasmic tail of sortilin is known to associate with adaptor molecules which can determine whether sortilin trafficking occurs via the anterograde or retrograde pathway. Sortilin has been demonstrated to be responsible for trafficking ligands between secretory and lysosomal protein pathways (NPL1). At the cell surface sortilin acts as a receptor of neurotrophic factors and neuropeptides. Following endocytosis of bound ligands sortilin releases its cargo upon entering acidic endosomal compartments. Fusion of these compartments with lysosomes ultimately degrades the endocytosed ligand, however sortilin can, possibly through dimerization (NPL2), be recycled to the Golgi by the retromer pathway and back to the plasma membrane.

[0003] The interaction between progranulin (PGRN) and sortilin (SORT1) was originally identified in a ligand binding screen of an expression library (NPL3). Lysosomal trafficking of PGRN was found to be mediated through the binding of its C-terminal domain to sortilin in a similar fashion as previously described for neurotensin (NTS). Unsurprisingly NTS interferes with PGRN binding of sortilin (NPL3). Likewise, a small molecular weight sortilin inhibitor, AF38496, was also shown to interfere with NTS binding, indicating that small molecular weight compounds could be developed to similarly inhibit PGRN-sortilin binding as a potential means to elevate PGRN levels (NPL4). The ability of sortilin to regulate PGRN levels by impacting lysosomal trafficking and thereby PGRN turnover, has been demonstrated in cellular and mouse sortilin deficient models. Mice lacking sortilin demonstrated elevations of brain and serum PGRN levels by 2.5- to 5-fold. PGRN decreases observed in GRN+/- mice were normalized by genetic ablation of the gene encoding sortilin, Sort1 (NPL3). In vivo administration of sortilin targeting antibodies have also been described which deplete

sortilin giving rise to a similar elevation in PGRN as observed with genetic ablation (NPL5). The ability of sortilin to act as a regulator of PGRN levels has furthermore been observed through genome-wide association studies where genetic variants, single nucleotide polymorphisms (SNPs) rs646776 and rs611917, were associated with increased SORT1 mRNA levels and decreased plasma PGRN (NPL6).

[0004] PGRN is a secreted pleiotropic growth factor associated with multiple biological processes including regulation of cell growth, survival inflammation, and wound healing (NPL9). Within the central nervous system (CNS) PGRN is attributed with neurotrophic and anti-inflammatory properties (NPL10; NPL11). The clinical significance of PGRN to neurodegenerative disease was made clear in 2006 with the discovery that missense mutations in one allele of the PGRN encoding gene, GRN, resulting in GRN haploinsufficiency, are causal for the development of frontotemporal lobar degeneration (FTLD) (NPL12; NPL13). Mutations in both GRN alleles result in neuronal ceroid lipofuscinosis (NCL), a lysosomal storage disease (NPL15). These PGRN insufficiency diseases are both associated with neuroinflammation and lysosomal dysfunction. Markers of inflammation and lysosomal functions were both improved in a GRN deficient mouse model by lentiviral expression of GRN (NPL14). Neither GRN+/- or Sort1-/- mouse models exhibit the pathological phenotypes observed in the GRN deficient mouse. While sortilin appears to be the major lysosomal trafficking receptor for PGRN, other sortilin independent trafficking routes have been identified (NPL15). Overall, the evidence suggests pharmacological interference of PGRN-sortilin interaction, by brain penetrant small molecular weight inhibitors, has the potential to deliver clinical benefit in FTLD and other diseases characterised by PGRN insufficiency.

[0005] In addition to FTLD, SORT1 polymorphisms have also been linked to altered Alzheimer's disease (AD) susceptibility (NPL16). Potentially pathogenic GRN missense mutations have also been identified in neurodegenerative diseases, including Alzheimer's disease (AD) (NPL17; NPL18; NPL19; NPL20; NPL21; NPL22), Parkinson's disease (PD) (NPL23), and amyotrophic lateral sclerosis (ALS) (NPL24). A beneficial impact from progranulin modulation has been further validated in animal models of neurodegenerative disease. Direct injection of PGRN into the brains of 5xFAD mice leads to a reduction of Aβ plaques, downregulation of beta-secretase 1 (BACE1), and enhanced microglia Aβ phagocytosis (NPL25). Lentiviral introduction of PGRN in the APP AD mouse model was demonstrated to be beneficial to reduce plaque load, enhance survival of hippocampal neurons and prevent memory deficits (NPL26). Lentiviral mediated GRN expression also protected dopaminergic (DA) neurons from the parkinsonian toxin MPTP (NPL27). A key histopathological hallmark of FTLD with GRN mutations is the presence of ubiquitinated TDP-43 in-

clusions. This pathology is shared with ALS and suggests potential common pathological mechanism across the two diseases (NPL28). In zebrafish models, overexpression of human PGRN mRNA is protective against mutant TDP-43 induced axonopathy (NPL29). PGRN overexpression has also been shown to reduce insoluble TDP-43 levels in TDP-43(A315T) mice (NPL30). Inversely PGRN insufficiency has been associated with the increased generation of pathological forms of TDP-43 (NPL31). Reduction of TDP-43 may be benifit in CNS pathologies including spinocerebellar ataxia 3 (SCA3) (NPL69), Huntington's diseases (HD) (NPL64) and limbic-predominant age-related TDP-43 encephalopathy (LATE) (NPL9) which show the cytoplasmic accumulations of TDP-43. GWAS studies have also implicated GRN as a risk factor for LATE (NPL32).

[0006] PGRN has been demonstrated to exert a protective effect against photoreceptor cell damage in mouse models (NPL33). PGRN attenuated neuronal injury induced by cerebral ischemia (NPL11). PGRN also protected axonal loss and astrogliosis following traumatic brain injury which was exaggerated in GRN-/- mice (NPL34).

[0007] Possible pathological overlap between FTLD with other CNS diseases has also been suggested. Schizophrenia-like psychosis was observed in patients, years before a dementia diagnosis consistent with TDP-43 positive FTD was made (NPL35). A study of siblings presenting with either FTD or schizophrenia while both carried a loss of function GRN mutation has been reported (NPL36). Schizophrenia has previously been linked to mutations on a region of chromosome 17q21 shared by the GRN gene (NPL37). There is additional evidence of a clinical overlap between FTD and bipolar disorder (BPD). Plasma PGRN levels were observed to be significantly decreased relative to controls in a small study of patients with BPD (NPL38).

[0008] PGRN overexpression in sensory neurons of transgenic mice attenuates neuropathic pain after sciatic nerve injury (NPL39). PGRN-deficient mice models were demonstrated to develop more intense nociceptive hypersensitivity after nerve injury. Recombinant PGRN rescued primary dorsal root ganglia neurons from cell death induced by nerve growth factor withdrawal suggesting raised PGRN levels have the potential for therapeutic use in the treatment of injury associated chronic pain (NPL40). The sortilin ligand neurotensin, has also been demonstrated to effect peripheral neuropathic pain. Sortilin inhibition by antibodies or the small molecular weight inhibitor AF38469 blocked BDNF-induced pain and alleviated injury-induced neuropathic pain mechanical allodynia in a spared nerve injury model (NPL5).

[0009] Progranulin modulation could protect against acute focal cerebral ischaemia by a variety of mechanisms including attenuation of blood-brain barrier disruption, neuroinflammation suppression, and neuroprotection. Progranulin could regulate vascular permeability via vascular endothelial growth factor, suppress neuroinflammation after

ischaemia via anti-inflammatory interleukin 10 in the microglia, and render neuro-protection in part by inhibition of cytoplasmic redistribution of TAR DNA-binding protein-43. Administered recombinant progranulin has been shown to reduce cerebral infarct and oedema, suppress haemorrhagic transformation, and improved motor outcomes (NPL41). Decreased progranulin levels, potentially associated with suppressed neutrophil recruitment, has been observed in patients, and rats, with sub-arachnoid hemorrhage (NPL42). The ability of sortilin to impact neuroinflammation is not restricted however to its influence on PGRN alone. Neurotensin has also been demonstrated to affect chemotaxis of microglia which could be blocked in cell models through the addition of the sortilin pro-peptide which competes for neurotensin binding on sortilin (NPL43). Cells carrying the GRN rs5848 variant, obtained from idiopathic normal pressure hydrocephalus (iNPH) patients also demonstrate an increased proin-flammatory response. Suggesting that modulation of PGRN may have a beneficial effect for iNPH (NPL44).

[0010] In addition to the numerous neurological effects already listed, modulation of sortilin ligands has the potential to impact a variety of systemic diseases as well.

[0011] Retinal degeneration has been demonstrated in GRN deficient mice resulting in thinner retinas and increased lipofuscin deposits relative to controls which could be rescued through intravitreal injection of PGRN (NPL45). PGRN has also demonstrated protective effects on photoreceptors against excessive light exposure (NPL33; NPL46), suggesting that PGRN modulation may be therapeutic for age-related macular de-generation and other neurodegenerative disease of the eye.

[0012] PGRN levels have been reported to impact TNFR signalling and other immune function regulated pathways with suggested beneficial effects of modulating PGRN levels in a number of inflammatory diseases including but not restricted to rheumatoid arthritis (RA), osteoarthritis (OA), systemic lupus erythematosus (SLE), systemic sclerosis (SSc), inflammatory bowel disease (IBD), psoriasis, type 1 diabetes mellitus (T1DM) and MS (NPL47).

[0013] ProNGF and proBDNF are known apoptotic ligands that bind to the receptor complex of p75NTR and sortilin. Thus, inhibition of sortilin is believed to be beneficial in preventing neurodegeneration (NPL5).

[0014] Modulation of sortilin also has the potential to influence other inflammatory cytokines. Sortilin has been demonstrated to aid the intracellular trafficking of IFN-g and IL-6, but not IL-5 or MCP-1 (NPL48). In addition to reducing systemic markers of inflammation, the transfer of sortilin-deficient bone marrow into irradiated atherosclerotic mice also reduced atherosclerosis. Agents which impact the ability of sortilin to effectively transport IFN-g also have the potential to regulate autoimmune functions and could be of therapeutic benefit in the treatment of autoimmune disorders

such as inflammatory bowel disease.

[0015] PGRN modulation may also be therapeutically relevant for inflammation-related osteoporosis. PGRN inhibited TNF-α-induced osteoclastogenesis from spleen cells of PGRN-KO mice. Moreover, PGRN significantly promoted ALP activity, osteoblast-related mRNA (ALP, osteocalcin) expression in a dose-dependent manner and up-regulated osteoblastic differentiation by down-regulating phosphorylation of ERK1/2 in mouse calvarial cells (NPL49; NPL50; NPL51). PGRN also suppresses neutrophil recruitment into the ischemia-reperfusion brain (NPL52).

[0016] Sortilin regulates multiple ligands associated with atherogenesis mechanisms including inflammation, dyslipidemia, vascular calcification and insulin resistance (NPL53). Progranulin in the hematopoietic compartment has been demonstrated to protect mice from atherosclerosis. The size of atherosclerotic lesions in bone marrow progranulin KO mice, in a Ldlr-/- genetic background, was increased by 47% in aortic roots and by 62% in whole aortas. Progranulin-deficient macrophages also exhibit increased cholesterol uptake and foam cell formation (NPL54). Sortilin KO mice have been observed to decrease plasma cholesterol levels by 20% on the wild-type LDL receptor background and by 30% in Ldlr-/- animals (NPL55). Sortilin hepatocyte deficiency also attenuates diet induced hypercholesterolemia in mice. AF38469 treatment also was shown to reduce hepatic VLDL secretion (NPL56). Sortilin also aids secretion of PCSK9, which leads to LDLR turnover and elevated LDL-C (NPL57). Elevated PCSK9 levels are correlated with increased risk of coronary artery disease, therefore targeting sortilin has the therapeutic potential to affect multiple ligands which impact coronary artery disease. Sortilin inhibition is also possibly a target for treatment of major depression, as it has been proved to have effect on depressive symptoms through TREK-1 channel (NPL65), brain-derived neurotrophic factor (BDNF) and vascular endothelial growth factor (VEGF) (NPL66; NPL67).

[0017] While PGRN is often associated with tumorigenic potential there are examples of particular tumour types where sortilin directed inhibitors have the potential to be anti-oncogenic. Inhibition of progranulin binding to sortilin was shown to block progranulin-induced metastatic breast cancer using a triple-negative in vivo xenograft model (NPL58). Xenograft models also indicate that a sortilin inhibitor, AF38469, which blocks interaction with PGRN blocked lung metastases (NPL59) and pancreatic cancer cell invasion (NPL60).

[0018] Methods of screening for sortilin binding antagonists (PTL1) and for treating and monitoring progranulin-associated disorders (PTL2) have been described.

[0019] Sortlin antagonists have also been described (NPL61; PTL3).

Citation List

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Summary of Invention

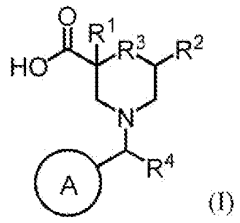
Technical Problem

[0022] There remains a need for the identification of modulators of sortilin. Such modulators may demonstrate enhanced in vivo potency, selectivity, acceptable safety profile, or desirable pharmacokinetic parameters.

Solution to Problem

[0023] Provided is a compound of formula (I):

[Chem.1]



(I)

wherein:

R^1 is

1) H,

2) R^{11} optionally substituted with one or more R^{12}, or

3) -O-R^{11} optionally substituted with one or more R^{12},

R^{11} is C_{1-6} alkyl or C_{2-6} alkenyl,

R^{12} is each independently halogen, C_{1-6} alkyl-O-, C_{3-8} cycloalkyl, or saturated 3- to 8-membered monocyclic heterocyclyl comprising at least one heteroatom independently selected from the group consisting of nitrogen, oxygen, and sulfur, wherein R^{12} is optionally substituted with the same or different one or more halogen;

R^2 is

1) C_{1-6} alkyl optionally substituted with the same or different one or more halogen, hydroxy, or cyano,

2) C_{3-8} cycloalkyl optionally substituted with the same or different one or more C_{1-6} alkyl, halogen, or cyano, or

3) $Si(C_{1-6}alkyl)_3$;

R^3 is CH_2 or O;

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

Ring A is optionally substituted partially unsaturated or unsaturated 7- to 15-membered bicyclic or tricyclic heterocyclyl comprising at least one heteroatom independently selected from the group consisting of nitrogen, oxygen, and sulfur;

or a salt thereof.

[0024] Also provided are sortilin inhibitors comprising a compound of formula (I), or a salt

thereof.

[0025] Also provided are pharmaceutical compositions comprising a compound of formula (I), or a salt thereof, and a pharmaceutically acceptable carrier or excipient.

[0026] Also provided are agents and/or medicaments for use in treating, preventing, and/or diagnosing a disease or disorder associated with sortilin ligands, comprising a compound of formula (I), or a salt thereof.

[0027] Also provided are methods for treating, preventing, and/or diagnosing a disease or disorder associated with sortilin ligands, which comprise administering to a human in need thereof an effective amount of a compound of formula (I), or a salt thereof.

[0028] Also provided is a compound of formula (I), or a salt thereof, for use in the treatment, prevention, and/or diagnosis of a disease or disorder associated with sortilin ligands.

[0029] Also provided is use of a compound of formula (I), or a salt thereof, in the manufacture of a medicament for treating, preventing, and/or diagnosing a disease or disorder associated with sortilin ligands.

[0030] Also provided are processes for preparing a compound of formula (I), or a salt thereof, and novel intermediates of use in the preparation of a compound of formula (I), or a salt thereof.

[0031] The compounds of formula (I) or salts thereof may be used as medicaments, for example, for use in the treatment, prophylaxis, or diagnosis of a disease or disorder associated with sortilin ligands.

Description of Embodiments

[0032] The phrases and terms used in this specification are explained in detail below.

[0033] The term “halogen” used herein is fluorine, chlorine, bromine, or iodine. It is preferably fluorine, chlorine, or bromine, and more preferably fluorine or chlorine.

[0034] The term "C_{1-6} alkyl" used herein is a straight or a branched hydrocarbon group containing 1 to 6 carbon atoms (C_{1-6}), and examples of the term include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, 1,1-dimethylpropyl, hexyl, isohexyl, and 3-methylpentyl. "C_{1-6} alkyl" also includes C_{1-6} alkyl having 1 to 7 deuterium atoms substituted for 1 to 7 hydrogen atoms, and examples include methyl-d_{1-3}, ethyl-d_{1-5}, propyl-d_{1-7}, and isopropyl-d_{1-7}, and further examples include methyl-d_1, methyl-d_2, methyl-d_3, ethyl-d_3, ethyl-d_5, propyl-d_3, propyl-d_7, isopropyl-d_3, and isopropyl-d_7.

[0035] The term "C_{2-6} alkenyl" used herein is a straight or branched hydrocarbon group containing 2 to 6 carbon atoms (C_{2-6}) and at least one carbon-carbon double bond, such as one or two double bonds. Examples of the term include $CH{=}CH_2$, $CH_2CH{=}CH_2$, $CH{=}CHCH_3$, $CH_2CH_2CH{=}CH_2$, $CH{=}CHCH_2CH_3$, $CH_2CH{=}CHCH_3$, $CH(CH_3)CH{=}CH_2$

, $CH=C(CH_3)_2$, $CH_2CH_2CH_2CH=CH_2$, $CH=CHCH_2CH_2CH_3$, $CH_2CH=CHCH_2CH_3$, $CH_2CH_2CH=CHCH_3$, $CH=CHCH=CHCH_3$, and $CH_2CH=CHCH=CH_2$.

[0036] The term "C_{2-6} alkynyl" used herein is a straight or branched hydrocarbon group containing 2 to 6 carbon atoms (C_{2-6}) and at least one carbon-carbon triple bond. Examples of the term include $C\equiv CH$, $CH_2C\equiv CH$, $C\equiv CCH_3$, $CH_2CH_2C\equiv CH$, $C\equiv CCH_2CH_3$, $CH_2C\equiv CCH_3$, $CH(CH_3)C\equiv CH$, $CH_2CH_2CH_2C\equiv CH$, $C\equiv CCH_2CH_2CH_3$, $CH_2C\equiv CCH_2CH_3$, $CH_2CH_2C\equiv CCH_3$, $C\equiv CC\equiv CCH_3$, and $CH_2C\equiv CC\equiv CH$.

[0037] The term "C_{3-8} cycloalkyl" used herein is a saturated mono- or poly-cyclic hydrocarbon ring group containing 3 to 8 carbon atoms. Examples of the term include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptanyl, and cyclooctanyl. A cycloalkyl group may be C_{3-6} cycloalkyl such as cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

[0038] The term "C_{3-8} cycloalkenyl" used herein is a partially unsaturated mono- or polycyclic hydrocarbon ring group containing 3 to 8 carbon atoms and at least one carbon-carbon double bond, such as one or two double bonds, for example one double bond. A cycloalkenyl group is suitably monocyclic. Alternatively, a cycloalkenyl group may be polycyclic, such as bicyclic. Examples of the term include cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cyclohexadienyl, cycloheptenyl, and cyclooctenyl.

[0039] The term "C_{6-10} aryl" used herein is a mono- or poly-cyclic ring group (e.g., comprising one or two, such as one additional ring) containing 6 to 10 ring carbon atoms. Additional rings in a polycyclic ring may be saturated (e.g., forming indane or tetralin), partially unsaturated (e.g., forming indene), or fully unsaturated (e.g., forming naphthalene) hydrocarbon rings. Suitably, aryl refers to a mono or a bicyclic ring group containing at least one phenyl ring. Examples of the term include phenyl, indane, tetralin, indene, and naphthalene.

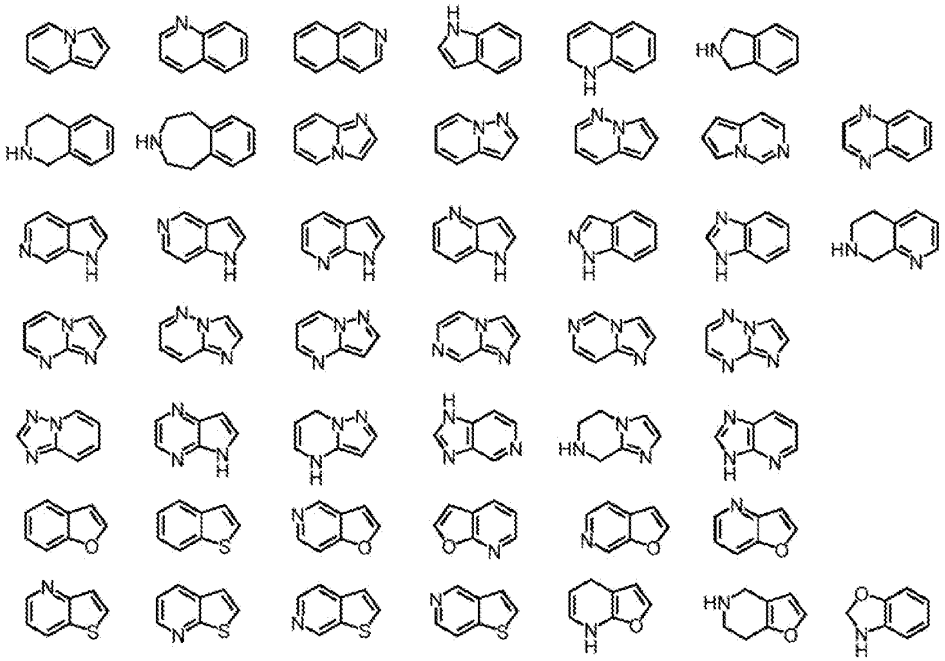
[0040] The term "heterocyclyl" used herein is a saturated, partially unsaturated, or fully unsaturated (i.e., forming an aromatic ring, such as heteroaryl) ring group containing the specified number of carbon and non-carbon ring atoms wherein at least one of the ring atoms is a heteroatom selected from nitrogen, oxygen, and sulfur atoms. As required by valency, the nitrogen atom(s) may be connected to a hydrogen atom to form an NH group. A heterocyclyl group may be monocyclic. Such a monocyclic heterocyclyl group includes 3- to 8-membered monocyclic heterocyclyl comprising at least one heteroatom selected from N, O, and S, wherein the heterocyclyl may be saturated, partially unsaturated, or fully unsaturated. Alternatively, a heterocyclyl group may be polycyclic such as a fused bicyclic, tricyclic, or tetracyclic or a bridged bicyclic, tricyclic, or tetracyclic ring group. In some embodiments, a bicyclic heterocyclyl group is spirocyclic, i.e., a bicyclic cycloalkyl group wherein the two rings are connected

through just one atom. The rings can be different or identical. In some embodiments, a heterocyclyl group may contain one heteroatom selected from N, S, and O. In other embodiments, a heterocyclyl group may contain two heteroatoms selected from N, S, and O, for example N and O, for example N and S, or for example the two are N. In further embodiments, a heterocyclyl group may contain three heteroatoms selected from N, S, and O, for example N and O, for example N and S, or for example the three are N. In still further embodiments, a heterocyclyl group may contain four heteroatoms selected from N, S, and O. When Ring A containing S is substituted with oxo, the heterocyclyl group forms an oxo-substituted heterocyclyl group wherein the S atom(s) is substituted (such as one S atom is substituted) with one or two oxygen atoms to form a sulfone or sulfoxide (i.e., S(O) or $S(O)_2$).

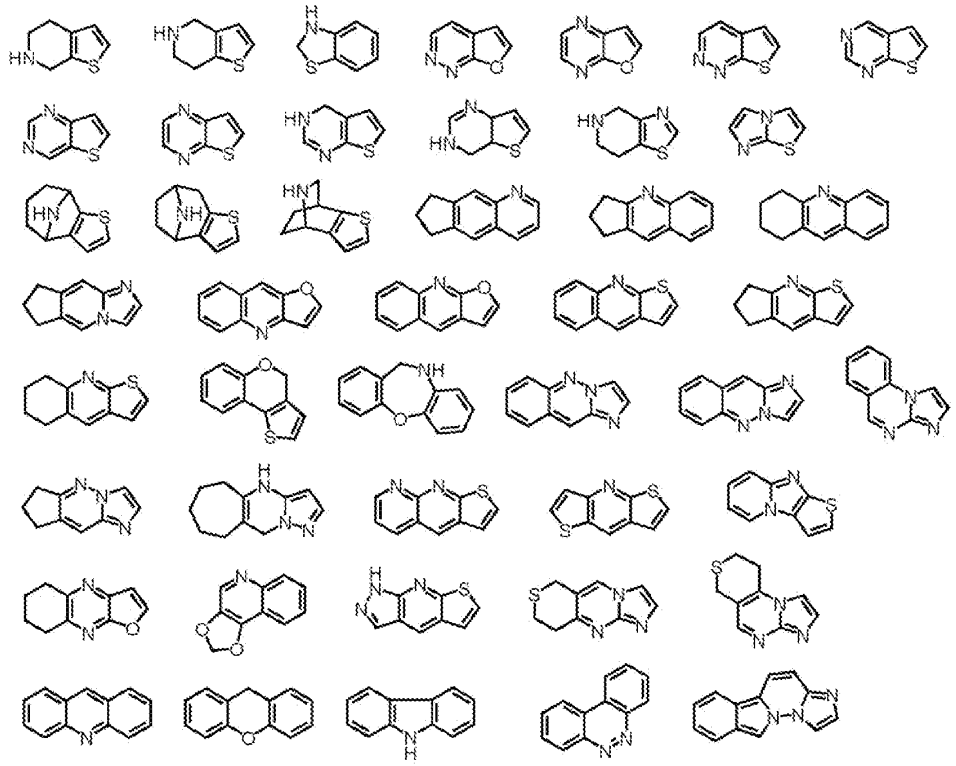
[0041] Examples of the term "heterocyclyl" include 3- to 8-membered monocyclic heterocyclyl, 4- to 10-membered monocyclic or bicyclic heterocyclyl, 5- to 10-membered monocyclic heterocyclyl, 7- to 15-membered bicyclic or tricyclic heterocyclyl, 7- to 16-membered bicyclic, tricyclic, or tetracyclic heterocyclyl, 9- to 14-membered bicyclic or tricyclicc heterocyclyl, and 9- to 16-membered bicyclic, tricyclic, or tetracyclic heterocyclyl. Specific examples of monocyclic heterocyclyl groups include saturated monocyclic heterocyclyl groups such as aziridinyl, oxylanyl, thiylanyl, azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydrothiophenyl, dioxolanyl, piperidinyl, piperazinyl, diazepanyl, tetrahydropyranyl, tetrahydrothiopyranyl, dioxanyl, morpholinyl, azepanyl, oxepanyl, thiepanyl, and azocanyl; and partially unsaturated or fully unsaturated monocyclic heterocyclyl groups such as pyrrolyl, triazolyl, tetrazolyl, pyrazolyl, pyridinyl, dihydropyridinyl, imidazolyl, tetrahydropyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, imidazolidinyl, pyrazolidinyl, triazinyl, azepinyl, oxetanyl, dihydropyranyl, furanyl, pyranyl, oxazolyl, isoxazolyl, oxadiazolyl, thienyl, thiopyranyl, thiazinyl, thiazolyl, thiazolinyl (dihydrothiazolyl), thiadiazolyl, isothiazolyl, and thiazolidinyl. Specific examples of bicyclic, tricyclic, or tetracyclic heterocyclyl groups include pyrrolidinopyrrolidinyl, benzoimidazolyl, dihydrobenzoimidazolyl, indolyl, isoindolyl, indazolyl, indazolinyl (dihydroindazolyl), purinyl, benzotriazolyl, imidazopyridinyl, imidazopyrazinyl, tetrahydroimidazopyrazinyl, pyrazolopyridinyl, tetrahydropyridoindolyl, benzoazepinyl, tetrahydrobenzoazepinyl, pyrrolopyrrolyl, hexahydropyrrolopyrrolyl, benzoxazolyl, dihydrobenzoxazolyl, oxaazabicycloheptanyl, tetrahydrofuropyrrolyl, benzoxadiazolyl, benzoisoxazolyl, benzoxazinyl, dihydrobenzoxazinyl, benzofuranyl, benzimidazolyl, benzothiophenyl, benzoisothiazolyl, benzothiazolyl, thienopyridinyl, quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, cinnolinyl, chromenyl, isochromenyl, dihydroimidazooxazinyl, dihydropyrazolooxazinyl, furopyridinyl, furopyrrolyl, benzoxazepinyl, tetrahydrobenzoxazepinyl, pyrano[4,3-d]thiazolyl, dihy-

dropyrano[4,3-d]thiazolyl, 2-oxabicyclo[2.1.1]hexanyl, azabicycloocctane (for example, azabicyclo[3.2.1]octanyl), octahydropyrrolo[1,2-a]pyrazinyl, diazabicyclo[3.1.1]heptanyl, 2-azaspiro[3.3]heptanyl, 2,6-diazaspiro[3.3]heptanyl, 2-oxa-6-azaspiro[3.3]heptanyl, oxaazaspirooctanyl, 2,6-diazaspiro[3.4]octanyl, and the following groups.

[Chem.2]



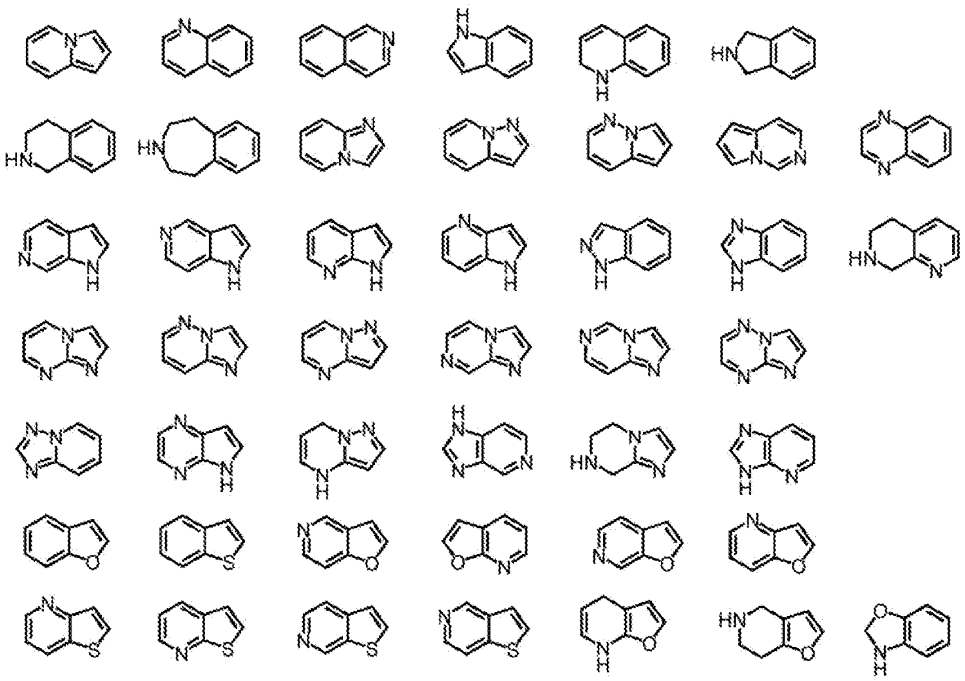
[Chem.3]



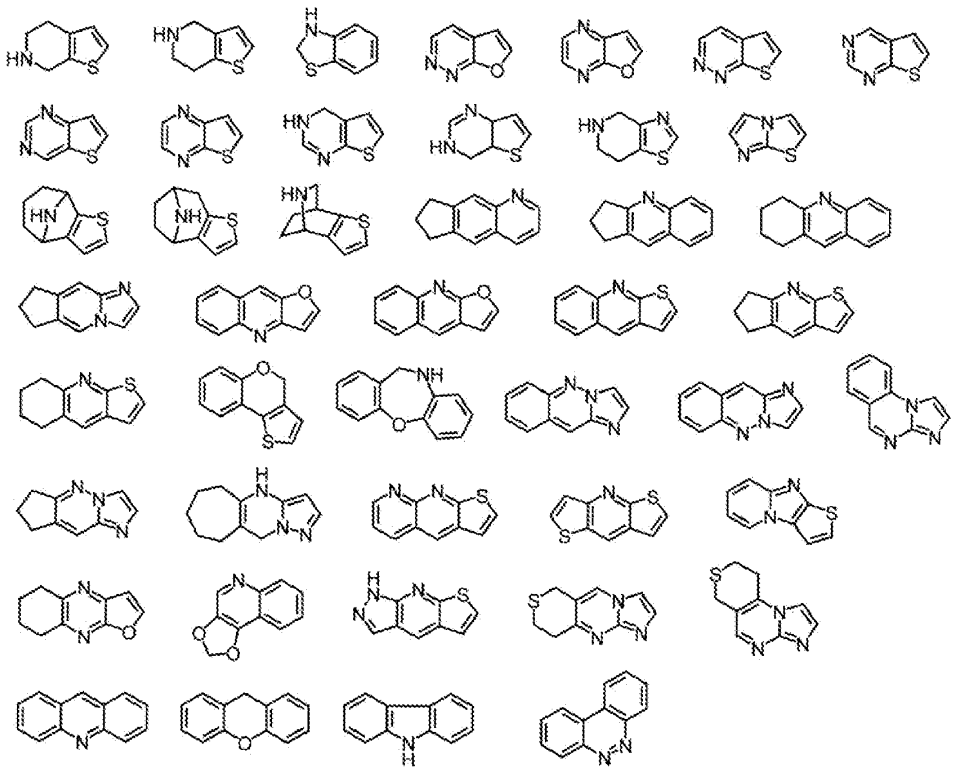
[0042] Various substituents in the compound represented by formula (I) (herein also referred to as "Compound (I)") are explained below. A bond with a wavy line in a chemical formula as used herein refers to a binding site of the moiety, group, or ring system represented by the chemical formula to the remainder of Compound (I).

[0043] In some embodiments of Compound (I), Ring A may bind to the remaining moiety of Compound (I) via any possible binding sites of the ring. In some embodiments, Ring A may bind via a heterocyclyl moiety of Ring A at any suitable position on the heterocyclyl moiety to the alpha position of the nitrogen-containing six-membered cyclic group of Compound (I). In other embodiments, when Ring A comprises an aromatic ring that is fused to the remaining moiety of Ring A, Ring A may bind via the aromatic ring at any suitable position on the aromatic ring to the alpha position of the nitrogen-containing six-membered cyclic group of Compound (I). In some embodiments, Ring A is any one of the heterocyclyl selected from the following groups:

[Chem.4]



[Chem.5]



and is optionally substituted with the same or different one or more R^5.

[0044] In some embodiments, R^1 is R^{11} optionally substituted with the same or different one or more R^{12}, or -O-R^{11} optionally substituted with the same or different one or more R^{12}.

[0045] In some preferable embodiments, R^1 is H, cyclopropylmethyl, methoxyethyl, cyclopropylethyl, propyl, fluoropropyl, difluoropropyl, trifluoropropyl, cyclohexylpropyl, difluorocyclohexylpropyl, difluoropiperidinylpropyl, butyl, isobutyl, trifluorobutyl, methylbutyl, methoxy, ethoxy, methoxyethoxy, propoxy, ethyl, or difluoropropenyl. In further preferable embodiments, R^1 is H, propyl, trifluoropropyl, butyl, methylbutyl, trifluorobutyl, or propoxy.

[0046] In some embodiments, when R^{12} is saturated 3- to 8-membered monocyclic heterocyclyl, the monocyclic heterocyclyl group is preferably piperidinyl, piperazinyl, azocanyl, diazepanyl, azetidinyl, pyrrolidinyl, morpholinyl, tetrahydrofuranyl or tetrahydropyranyl.

[0047] In some embodiments, R^2 is C_{1-6} alkyl, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, neopentyl, and tert-pentyl, optionally substituted with the same or different one or more halogen (e.g., fluoro), hydroxy, or cyano, or C_{3-8} cycloalkyl substituted with C_{1-6} alkyl, such as methylcyclobutyl. In other embodiments, R^2 is C_{2-6} alkyl, optionally substituted with the same or different one or more halogen, hydroxy, or cyano, or C_{3-8} cycloalkyl substituted with the same or different one or more C_{1-6} alkyl. In still other embodiments, R^2 is isopropyl, tert-butyl, tert-pentyl, methylcyclobutyl, hydroxy-tert-butyl, or fluoro-isopropyl.

[0048] In some embodiments, R^4 is H or methyl.

[0049] In some embodiments, R^5 is fluoro, chloro, cyano, oxo, methyl, fluoromethyl, difluoromethyl, trifluoromethyl, dimethylaminomethyl, thiophenylmethyl, ethyl, isopropyl, dimethylaminopropyl, cyclopropyl, cyclohexenyl, dimethylaminomethylpropynyl, phenyl, fluorophenyl, chlorophenyl, difluorophenyl, trifluoromethylphenyl, benzyl, azetidinyl, thiophenyl, thiazolyl, methylthiazolyl, isothiazolyl, pyridyl, methylpyridyl, ethylpyridyl, isopropylpyridyl, cyclopropylpyridyl, methoxypyridyl, ethoxypyridyl, fluoropyridyl, chloropyridyl, fluoromethylpyridyl, difluoromethylpyridyl, dimethylpyridyl, dimethylaminopyridyl, chloromethylpyridyl, N-methyltetrahydropyridyl, pyrrolidinyl, methylpyrrolidinyl, dihydropyranyl, pyrimidyl, fluoropyrimidyl, methylpiperazinyl, ethylpiperazinyl, isopropylpiperazinyl, tert-butylpiperazinyl, cyclopropylpiperazinyl, cyclobutylpiperazinyl, dimethylpiperazinyl, difluoroethylpiperazinyl, trifluoromethylpiperazinyl, trifluoromethylmethylpiperazinyl, pyrazolyl, methylpyrazolyl, fluoropyrazolyl, chloromethylpyrazolyl, fluoromethylpyrazolyl, thienopyridyl, benzoisothiazolyl, hydroxy, methoxy, ethoxy, dimethylaminoethoxy, phenoxy, fluorophenoxy, methylamino, dimethylamino, dimethylaminoethylmethylamino, or hydroxymethyl.

[0050] In some embodiments, when R^{51} is 5- to 10-membered monocyclic heterocyclyl, the monocyclic heterocyclyl group is preferably thiophenyl.

[0051] In some embodiments, Compound (I) is not
5-(1,1-dimethylethyl)-1-(pyrazolo[1,5-a]pyridin-4-ylmethyl)-3-piperidinecarboxylic acid,
5-(1,1-dimethylethyl)-1-(imidazo[2,1-b]thiazol-6-ylmethyl)-3-piperidinecarboxylic acid,
5-(1,1-dimethylethyl)-1-(imidazo[1,2-a]pyridin-5-ylmethyl)-3-piperidinecarboxylic acid,
5-(1,1-dimethylethyl)-1-(imidazo[1,2-a]pyridin-3-ylmethyl)-3-piperidinecarboxylic acid,
5-(1,1-dimethylethyl)-1-(imidazo[2,1-b]thiazol-2-ylmethyl)-3-piperidinecarboxylic acid,
5-(1,1-dimethylethyl)-1-(imidazo[2,1-b]thiazol-6-ylmethyl)-3-piperidinecarboxylic acid,
5-(1,1-dimethylethyl)-1-(pyrazolo[1,5-a]pyridin-4-ylmethyl)-3-piperidinecarboxylic acid, or
1-[(7,8-dihydro-5H-pyrano[4,3-b]pyridin-3-yl)methyl]-5-(1,1-dimethylethyl)-3-piperidinecarboxylic acid.

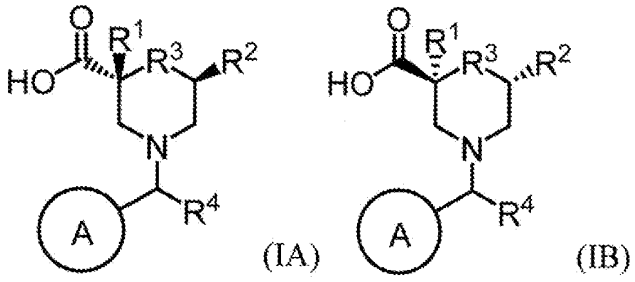
[0052] In some embodiments, R^2 is attached to the nitrogen-containing six-membered cyclic group:

[Chem.6]



in formula (I) in a trans-configuration manner to the carboxy group that is attached to the nitrogen-containing ring to have any of the following structures (IA), (IB), and/or their mixture, for example when R^2 is optionally substituted $C_{1\text{-}6}$ alkyl.

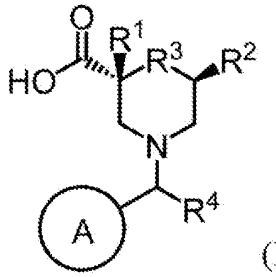
[Chem.7]



(IA) (IB)

[0053] In some embodiments, a compound of formula (I) has the following structure (IA):

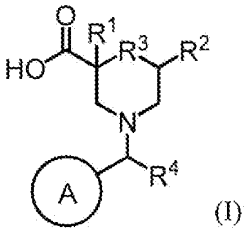
[Chem.8]



(IA)

[0054] In a further aspect of the invention, there is provided a method of preparation of a compound of formula (I):

[Chem.9]

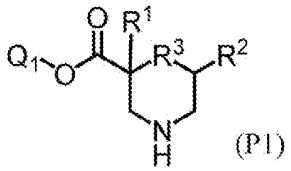


(I)

or a salt thereof,

wherein R^1, R^2, R^3, R^4, and Ring A are as defined above, the method which comprises reacting a compound of formula (P1):

[Chem.10]



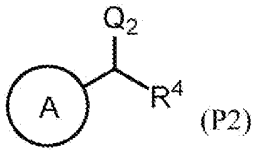
(P1)

or a salt thereof,

wherein R^1, R^2, and R^3 are as defined above and Q_1 is either a suitable protecting group, such as alkyl groups and aralkyl groups (e.g. benzyl), or is hydrogen;

with a compound of formula (P2):

[Chem.11]



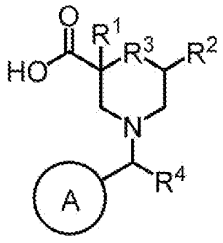
(P2)

or a protected derivative or salt thereof,

wherein Ring A and R^4 are as defined above and Q_2 is a suitable leaving group, such as halogen, methylsulfonyloxy, or trifluoromethylsulfonyloxy.

[0055] In a further aspect of the invention, there is provided a method of preparation of a compound of formula (I):

[Chem.12]

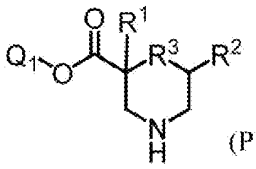


(I)

or a salt thereof,

wherein R^1, R^2, R^3, R^4, and Ring A are as defined above, the method which comprises reacting a compound of formula (P1):

[Chem.13]



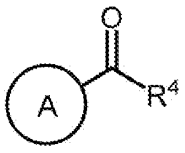
(P1)

or a salt thereof,

wherein R^1, R^2, and R^3 are as defined above and Q_1 is either a suitable protecting group, such as alkyl groups and aralkyl groups (e.g. benzyl), or is hydrogen;

with a compound of formula (P3):

[Chem.14]



(P3)

or a protected derivative or salt thereof,

wherein Ring A and R^4 are as defined above.

[0056] In the present specification, the options and preferred embodiments for the different features of the compound, method and composition of the present invention as presented include all possible combinations of the options and preferred embodiments for these different features as long as they are consistent combinations.

[0057] Methods of manufacture

Methods of manufacturing Compound (I) are explained below. Compound (I) may be manufactured, but is not limited thereto, based on the methods described in the General syntheses and Examples below. Unless otherwise specified, reaction temperatures may be optionally adjusted depending on reactants, solvents, and other conditions used in each reaction herein.

[0058] An alkylation reaction, hydrolysis reaction, amination reaction, esterification reaction, amidation reaction etherification reaction, nucleophilic substitution reaction, addition reaction, oxidation reaction, reduction reaction, and the like in the General syntheses may be performed in accordance with any known methods. Examples of such methods include the methods described in Experimental Chemistry (Fifth Edition, edited by The Chemical Society of Japan, Maruzen Co., Ltd.); Organic Functional Group Preparations Second Edition, Academic Press, Inc., 1989; Comprehensive Organic Transformations, VCH Publishers, Inc., 1989; and P.G.M. Wuts and T.W. Greene, Greene's Protective Groups in Organic Synthesis (Fourth Edition, 2006), and the like.

[0059] As used herein, the term "C_{1-18} alkanesulfonyl" is a linear or branched alkanesulfonyl having 1 to 18 carbon atoms (C_{1-18}), and examples thereof include methanesulfonyl, 1-propanesulfonyl, 2-propanesulfonyl, butanesulfonyl, cyclohexanesulfonyl, dodecanesulfonyl, octadecanesulfonyl, and the like.

[0060] As used herein, the term "lower alkanesulfonyloxy" is a linear or branched alkanesulfonyloxy having 1 to 6 carbon atoms (C_{1-6}), and examples thereof include methanesulfonyloxy, ethanesulfonyloxy, 1-propanesulfonyloxy, 2-propanesulfonyloxy, 1-butanesulfonyloxy, 3-butanesulfonyloxy, 1-pentanesulfonyloxy, 1-hexanesulfonyloxy, and the like.

[0061] As used herein, the term "arylsulfonyloxy" is phenylsulfonyloxy, naphthylsulfonyloxy, and the like, that is optionally substituted with 1 to 3 groups selected from the group consisting of a linear or branched alkyl having 1 to 6 carbon atoms (C_{1-6}), a linear or branched alkoxy having 1 to 6 carbon atoms (C_{1-6}), nitro, and halogen, on the benzene or naphthalene ring. Examples of phenylsulfonyloxy optionally having substituent(s) include phenylsulfonyloxy, 4-methylphenylsulfonyloxy, 2-methylphenylsulfonyloxy, 4-nitrophenylsulfonyloxy, 4-methoxyphenylsulfonyloxy, 2-nitrophenylsulfonyloxy, 3-chlorophenylsulfonyloxy, and the like. Specific examples of naphthylsulfonyloxy include α-naphthylsulfonyloxy, β-naphthylsulfonyloxy, and the like.

[0062] As used herein, the term "aralkylsulfonyloxy" is a linear or branched alkanesulfonyloxy having 1 to 6 carbon atoms (C_{1-6}) that is substituted with phenyl optionally substituted with 1 to 3 groups selected from the group consisting of a linear or

branched alkyl having 1 to 6 carbon atoms (C_{1-6}), a linear or branched alkoxy having 1 to 6 carbon atoms (C_{1-6}), nitro, and halogen on the benzene ring; or a linear or branched alkanesulfonyloxy having 1 to 6 carbon atoms (C_{1-6}) that is substituted with naphthyl, and the like. Examples of alkanesulfonyloxy substituted with phenyl include benzylsulfonyloxy, 2-phenylethylsulfonyloxy, 4-phenylbutylsulfonyloxy, 4-methylbenzylsulfonyloxy, 2-methylbenzylsulfonyloxy, 4-nitrobenzylsulfonyloxy, 4-methoxybenzylsulfonyloxy, 3-chlorobenzylsulfonyloxy, and the like. Specific examples of alkanesulfonyloxy substituted with naphthyl include α-naphthylmethylsulfonyloxy, β-naphthylmethylsulfonyloxy, and the like.

[0063] Examples of the term "perhaloalkanesulfonyloxy" used herein include trifluoromethanesulfonyloxy and the like.

[0064] Examples of the term "sulfonio" used herein include dimethylsulfonio, diethylsulfonio, dipropylsulfonio, di-(2-cyanoethyl)sulfonio, di-(2-nitroethyl)sulfonio, di-(aminoethyl)sulfonio, di-(2-methylaminoethyl)sulfonio, di-(2-dimethylaminoethyl)sulfonio, di-(2-hydroxyethyl)sulfonio, di-(3-hydroxypropyl)sulfonio, di-(2-methoxyethyl)sulfonio, di-(2-carbamoylethyl)sulfonio, di-(2-carbamoylethyl)sulfonio, di-(2-carboxyethyl)sulfonio, di-(2-methoxycarbonylethyl)sulfonio, diphenylsulfonio, and the like.

[0065] As used herein, the term "solvent" may be an inert solvent in a reaction described herein, and examples thereof include water, ethers (e.g., dioxane, tetrahydrofuran, diethyl ether, 1,2-dimethoxyethane, cyclopentyl methyl ether, diethylene glycol dimethyl ether, and ethylene glycol dimethyl ether), hydrocarbons, halogenated hydrocarbons (e.g., methylene chloride, chloroform, 1,2-dichloroethane, and carbon tetrachloride), aromatic hydrocarbons (e.g., benzene, toluene, and xylene), alcohols (e.g., methanol, ethanol, and isopropanol), esters, ketones, amides, nitriles, sulfoxides, and polar solvents (e.g., N,N-dimethylformamide (DMF), N-methylpyrrolidone (NMP), dimethyl sulfoxide (DMSO), hexamethylphosphoric triamide, and acetonitrile). These solvents may be used alone or as a mixture of any two or more of them with optional ratios. Examples of "hydrocarbons" herein include, for example, aliphatic hydrocarbons such as hexane and pentane; alicyclic hydrocarbons such as cyclopentane and cyclohexane; and aromatic hydrocarbons such as benzene and toluene. Examples of "alcohols" herein include, for example, methanol, ethanol, 2-propanol, propanol, and tert-butanol. Examples of "ethers" herein include, for example, chained ethers such as diethyl ether, diisopropyl ether, dibutyl ether, dimethoxyethane, and diphenyl ether; and circular ethers such as 1,4-dioxane and tetrahydrofuran. Examples of "esters" herein include, for example, ethyl acetate and ethyl propionate. Examples of "ketones" herein include, for example, acetone, methyl ethyl ketone, and methyl isobutyl ketone.

Examples of "amides" herein include, for example, N,N-dimethylformamide, N,N-dimethylacetamide, and N-methyl-2-pyrrolidone. Examples of "nitriles" herein include, for example, acetonitrile and propionitrile. Examples of "sulfoxides" herein include, for example, dimethyl sulfoxide.

[0066] As used herein, the term “catalyst” to be used in reduction reactions is not particularly limited to examples used herein, but examples thereof include palladium on carbon (Pd/C), platinum on carbon (Pt/C), platinum oxide (PtO_2), and the like.

[0067] As used herein, the term “halogenating agent” is not particularly limited to examples used herein, but examples thereof include fluorinating agents, chlorinating agents, brominating agents, and iodinating agents, such as potassium fluoride, tetrabutylammonium fluoride, (diethylamino)sulfur trifluoride, phosphorus oxychloride, phosphorus trichloride, phosphorus pentachloride, thionyl chloride, oxalyl chloride, trichlorophosphoric acid, bromine, phosphorus oxybromide, phosphorus tribromide, iodine, sodium iodide, N-chlorosuccinimide, N-bromosuccinimide, N-iodosuccinimide, and the like.

[0068] As used herein, the term “acid” is not particularly limited to examples used herein, but includes an inorganic acid, an organic acid, and the like. Examples of the “inorganic acid” include hydrochloric acid, sulfuric acid, nitric acid, hydrobromic acid, phosphoric acid, and the like. Examples of the “organic acid” include acetic acid, trifluoroacetic acid, oxalic acid, phthalic acid, fumaric acid, tartaric acid, maleic acid, citric acid, succinic acid, methanesulfonic acid, p-toluenesulfonic acid, 10-camphorsulfonic acid, and the like. These acids may be used alone or as a mixture of any two or more of them.

[0069] As used herein, the term “base” is not particularly limited to examples used herein, but includes an inorganic base, an organic base, and the like. Examples of the “inorganic base” include alkali metal hydroxides (e.g., lithium hydroxide, sodium hydroxide, potassium hydroxide, and cesium hydroxide), alkaline earth metal hydroxides (e.g., magnesium hydroxide, calcium hydroxide, and barium hydroxide), alkali metal carbonates (e.g., lithium carbonate, sodium carbonate, potassium carbonate, and cesium carbonate), alkaline earth metal carbonates (e.g., magnesium carbonate, calcium carbonate, and barium carbonate), alkali metal carboxylates (e.g., sodium acetate, potassium acetate, and sodium butyrate), alkali metal hydrogen carbonates (e.g., sodium hydrogen carbonate, potassium hydrogen carbonate, and cesium hydrogen carbonate), alkali metal phosphates (e.g., sodium phosphate, potassium phosphate, and cerium phosphate), alkaline earth metal phosphates (e.g., magnesium phosphate and calcium phosphate), alkali metal alkoxides (e.g., sodium methoxide, sodium ethoxide, sodium tert-butoxide, and potassium tert-butoxide), alkali metal hydride (e.g., sodium hydride, potassium hydride, and cesium hydride), and the

like. Examples of the "organic base" include aromatic amines (e.g., pyridine and lutidine), trialkylamines (e.g., trimethylamine, triethylamine, tripropylamine, tributylamine, N,N-diisopropylethylamine (DIPEA)), cyclohexyldimethylamine, 4-dimethylaminopyridine (DMAP), N,N-dimethylaniline, N-methylpiperidine, N-methylpyrrolidine, N-methylmorphiline, tetramethylethylenediamine, tetramethylpropylenediamine, picoline, 1,5-diazabicyclo[4.3.0]non-5-ene, 1,4-diazabicyclo[2.2.2]octane, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), dialkylamine (e.g., diethylamine and diisopropylamine), metal amides (e.g., lithium diisopropylamide and lithium hexamethyldisilazide), metal alkoxides (e.g., sodium methoxide, sodium ethoxide, sodium tert-butoxide, potassium tert-butoxide, and sodium phenoxide), and the like. These bases may be used alone or as a mixture of any two or more of them. The organic base herein is preferably DMAP or TEA.

[0070] As used herein, the term "palladium catalyst" is not particularly limited to examples used herein, and examples thereof include tetravalent palladium catalysts such as sodium hexachloropalladium (IV) acid tetrahydrate and potassium hexachloropalladium (IV) acid; divalent palladium catalysts such as [1,1'-bis(diphenylphosphino)ferrocene]palladium (II) dichloride dichloromethane adduct ($PdCl_2$(dppf).DCM), (2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium (II) methanesulfonate (XPhos Pd G3), palladium (II) chloride, palladium (II) bromide, palladium (II) acetate, palladium (II) acetylacetonate, dichlorobis(benzonitrile)palladium (II), dichlorobis(acetonitrile)palladium (II), dichlorobis(triphenylphosphine)palladium (II), dichlorotetraammine palladium (II), dichloro(cycloocta-1,5-diene)palladium (II), and palladium (II) trifluoroacetate; and zerovalent palladium catalysts such as tris(dibenzylideneacetone)dipalladium (0) ($Pd_2(dba)_3$), tris(dibenzylideneacetone)dipalladium (0)-chloroform complex, and tetrakis(triphenylphosphine)palladium (0) ($Pd(PPh_3)_4$). These palladium compounds may be used alone or as a mixture of any two or more of them.

[0071] As used herein, the term "leaving group" is not particularly limited to examples used herein, and examples thereof include halogen (e.g., fluorine, chlorine, bromine, and iodine), C_{1-18} alkylsulfonyl, alkylsulfonyloxy (e.g., methylsulfonyloxy, ethylsulfonyloxy, and trifluoromethylsulfonyloxy), phenyloxy (e.g., 4-nitrophenyloxy), arylsulfonyloxy (e.g., benzenesulfonyloxy, p-toluenesulfonyloxy, 2,4,6-trimethylbenzenesulfonyloxy, 2-nitrobenzenesulfonyloxy, and 4-nitrobenzenesulfonyloxy), aralkylsulfonyloxy, perhaloalkanesulfonyloxy, sulfonio, toluenesulfoxy, nitrophenylcarbonate, imidazolecarbonate, and the like.

[0072] Examples of a condensation agent used herein include, but not limited to: T3P; PyBOP; DMT-MM; COMU; HBTU; HATU; DCC; N-cy-

clohexyl-N'-morpholinoethylcarbodiimide; N-cyclohexyl-N'-(4-diethylaminocyclohexyl)carbodiimide; N,N'-diethylcarbodiimide; N,N'-diisopropylcarbodiimide; N,N-diisopropylethylamine; WSC or a hydrochloride salt thereof; N,N'-carbonylbis(2-methylimidazole); pentamethyleneketene-N-cyclohexylimine; diphenylketene-N-cyclohexylimine; ethoxyacetylene, 1-alkoxy-1-chloroethylene; trialkyl phosphite; ethyl polyphosphate; isopropyl polyphosphate; phosphoryl chloride; phosphorus trichloride; diphenylphosphoryl azide; thionyl chloride; oxalyl chloride; alkyl haloformate such as ethyl chloroformate and isopropyl chloroformate; triphenylphosphine; 2-ethyl-7-hydroxybenzisoxazolium salt; 2-ethyl-5-(m-sulfophenyl)isoxazolium hydroxide inner salt; benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate; 1-(p-chlorobenzenesulfonyloxy)-6-chloro-1H-benzotriazole; and so-called Vilsmeier agents prepared by reactions of DMF with thionyl chloride, phosgene, trichloromethyl chloroformate, or phosphorus oxychloride.

[0073] In addition to a condensation agent, a condensation accelerator may be added. Examples of a condensation accelerator used herein include, but not limited to, 1-hydroxybenzotriazole (HOBt), N-hydroxysuccinimide (HOSu), 1-hydroxy-7-azabenzotriazole (HOAt), and hydroxy-3,4-dihydro-4-oxo-1,2,3-benzotriazine (HOOBt).

[0074] Examples of a reducing agent used herein include, but not limited to, sodium borohydride, lithium borohydride, sodium cyanoborohydride, sodium triacetoxyborohydride, sodium triethylborohydride, lithium triethylborohydride, lithium aluminum hydride, sodium dihydridobis(2-methoxyethoxy)aluminate, borane-tetrahydrofuran complex, diisobutylaluminium hydride, and hydrosilane such as triethylsilane and phenylsilane.

[0075] Examples of a reducing agent for the reductive amination reaction herein include, but not limited to:

sodium borohydride ($NaBH_4$), lithium borohydride, sodium cyanoborohydride, sodium triacetoxyborohydride ($NaBH(OAc)_3$), sodium triethylborohydride, lithium triethylborohydride, lithium aluminum hydride, sodium dihydridobis(2-methoxyethoxy)-aluminate, borane-tetrahydrofuran complex, diisobutylaluminium hydride, formic acid, sodium formate, ammonium formate, and phenylsilane.

Examples of a catalyst for the reductive amination reaction herein include, but not limited to:

Iridium catalysts such as chloro(pentamethylcyclopentadienyl)(8-quinolinolato)iridium (III), chlorido(8-quinolinolato-κ2N,O)(η5-pentamethylcyclopentadienyl)iridium (III), [5,5'-bis(trifluoromethyl)-2,2'-bipyridine-κN,κN]bis[3,5-difluoro-2-[5-(trifluoromethyl

)-2-pyridinyl-κN]phenyl] iridium hexafluorophosphate and (4,4'-Di-tert-butyl-2,2'-bipyridine)bis[3,5-difluoro-2-[5-trifluoromethyl-2-pyridinyl-kappaN)phenyl-kappaC] iridium (III) hexafluorophosphate.

[0076] Examples of a "protecting group of hydroxy" used herein include, but not limited to, any protecting groups of hydroxy used in the field of synthetic organic chemistry, and include, for example, alkyl groups (e.g., methyl, ethyl, isopropyl, tert-butyl, trifluoromethyl, hydroxymethyl, 2-hydroxyethyl, acetylmethyl); alkenyl groups (e.g., ethenyl, 1-propenyl, 2-propenyl, 1-methyl-2-propenyl); alkynyl groups (e.g., ethynyl, 1-propynyl, 2-propynyl, 1-methyl-2-propynyl); formyl; alkyl (alkenyl) carbonyl groups (e.g., acetyl, propionyl, butyryl, isobutyryl, pentanoyl, pivaloyl, valeryl, isovaleryl, chloroacetyl, dichloroacetyl, trichloroacetyl, trifluoroacetyl, methoxyacetyl, acryloyl, propioloyl, methacryloyl, crotonoyl, isocrotonoyl, (E)-2-methyl-2-butenoyl); arylcarbonyl groups (e.g., benzoyl, α-naphthoyl, β-naphthoyl, 2-bromobenzoyl, 4-chlorobenzoyl, 2,4,6-trimethylbenzoyl, 4-toluoyl, 4-anisoyl, 4-nitrobenzoyl, 2-nitrobenzoyl, 2-(methoxycarbonyl)benzoyl, 4-phenylbenzoyl); alkoxycarbonyl groups (e.g., methoxycarbonyl, tert-butoxycarbonyl, 2,2,2-trichloroethoxycarbonyl, 2-trimethylsilylethoxycarbonyl, 9-fluorenylmethyloxycarbonyl); tetrahydro (thio) pyranyl (furanyl) groups (e.g., tetrahydropyran-2-yl, 3-bromotetrahydropyran-2-yl, 4-methoxytetrahydropyran-4-yl, tetrahydrothiopyran-2-yl, 4-methoxytetrahydrothiopyran-4-yl, tetrahydrofuran-2-yl, tetrahydrothiofuran-2-yl); silyl groups (e.g., trimethylsilyl, triethylsilyl, isopropyl dimethylsilyl, tert-butyldimethyl silyl, methyldiisopropyl silyl, methyl di-tert-butylsilyl, triisopropylsilyl, diphenylmethyl silyl, diphenylbutyl silyl, diphenylisopropyl silyl, phenyldiisopropyl silyl); alkoxymethyl groups (e.g., methoxymethyl, 1,1-dimethyl-1-methoxymethyl, ethoxymethyl, propoxymethyl, isopropoxymethyl, butoxymethyl, tert-butoxymethyl, 2-methoxyethoxymethyl, 2,2,2-trichloroethoxymethyl, bis(2-chloroethoxy)methyl); alkoxyethyl groups (e.g., 1-ethoxyethyl, 1-(isopropoxy)ethyl); halogenated ethyl groups (e.g., 2,2,2-trichloroethyl); aralkyl groups (e.g., benzyl, α-naphthylmethyl, β-naphthylmethyl, diphenylmethyl, triphenylmethyl, α-naphthyldiphenylmethyl, 9-anthrylmethyl, 4-methylbenzyl, 2,4,6-trimethylbenzyl, 3,4,5-trimethylbenzyl, 4-methoxybenzyl, 4-methoxyphenyldiphenylmethyl, 2-nitrobenzyl, 4-nitrobenzyl, 4-chlorobenzyl, 4-bromobenzyl, 4-cyanobenzyl); alkenyloxycarbonyl groups (e.g., vinyloxycarbonyl, allyloxycarbonyl); and aralkyloxycarbonyl groups (e.g., benzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 3,4-dimethoxybenzyloxycarbonyl, 2-nitrobenzyloxycarbonyl, 4-nitrobenzyloxycarbonyl).

[0077] Examples of a "protecting group of carboxy" used herein include, but not limited to, any protecting groups of carboxy used in the field of synthetic organic chemistry, and include, for example, the "alkyl groups", "alkenyl groups", "alkynyl groups", "aralkyl

groups", and "silyl groups" as above listed in the examples of the "protecting group of hydroxy" and similar groups thereof.

[0078] Examples of a "protecting group of amino" used herein include, but not limited to, any protecting groups of amino used in the field of synthetic organic chemistry, and include, for example, the "alkyl (alkenyl) carbonyl groups", "arylcarbonyl groups", "alkoxycarbonyl groups", "silyl groups", "aralkyl groups", "alkenyloxycarbonyl groups", and "aralkyloxycarbonyl groups" as above listed in the "protecting group of hydroxy" and similar groups thereof.

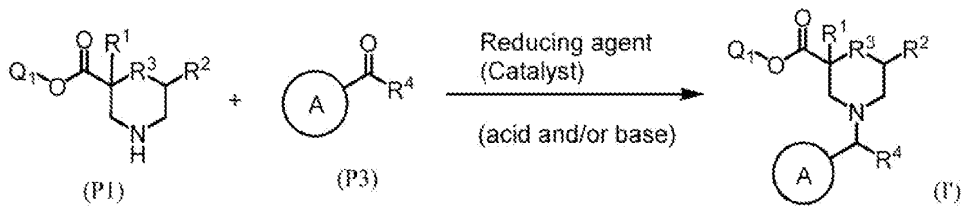
[0079] The reaction temperature in each step in the General syntheses herein typically ranges from -80 to 150°C. The reaction time in each step typically ranges from 0.1 to 200 hours.

[0080] General syntheses

In general, the compounds of the invention and intermediates of use in the synthesis of such compounds may be made according to synthesis techniques known to those skilled in this field, as well as by the representative methods set forth below, those in the Examples and the Reference Examples, and any modifications thereof. In the following schemes, reactive groups can, as appropriate, be protected with protecting groups and deprotected according to established techniques well known to the skilled person. The processes of the invention include any individual step of a multi-step scheme.

[0081] General synthesis 1: Reductive amination

[Chem.15]



In the scheme, R^1, R^2, R^3, R^4, Q_1, and Ring A are as defined above.

When Q_1 is hydrogen, Compound (I') is Compound (I).

[0082] Compound (I') may be prepared by the reaction of compound (P1) with compound (P3) in the presence of a reducing agent or catalyst for reductive amination reaction in an inert solvent. The reaction may be performed in the presence or absence of an acid or base.

Any reducing agents that are described above may be used in this reaction, and the reducing agent preferably used herein includes $NaBH(OAc)_3$, phenylsilane, and formic acid.

Any catalysts for reductive amination that are described above may be used in this reaction, and the catalyst preferably used herein includes chloro(pentamethylcyclopentadienyl)(8-quinolinolato)iridium (III), chlorido(8-quinolinolato-κ2N,O)(η5-pentamethylcyclopentadienyl)iridium (III), [5,5'-bis(trifluoromethyl)-2,2'-bipyridine-κN,κN]bis[3,5-difluoro-2-[5-(trifluoromethyl)-2-pyridinyl-κN]phenyl] iridium hexafluorophosphate and (4,4'-di-tert-butyl-2,2'-bipyridine)bis[3,5-difluoro-2-[5-trifluoromethyl-2-pyridinyl-kappaN)phenyl-kappaC]iridium (III) hexafluorophosphate.

Any acids that are described above may be used in this reaction, and the acid preferably used herein includes acetic acid.

Any bases that are described above may be used in this reaction, and the base preferably used herein includes triethylamine.

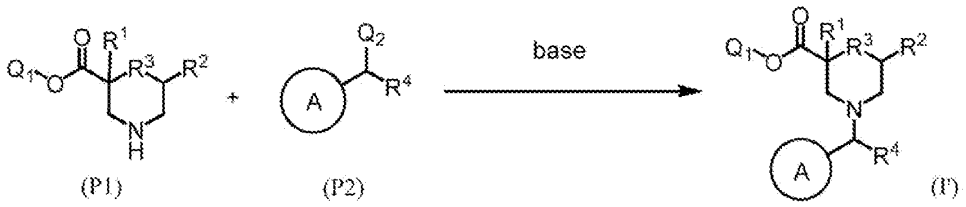
Any solvents that are described above may be used in this reaction, and the solvent preferably used herein includes 2-methyltetrahydrofuran, DMF, DMSO, DCM, DCE or acetonitrile.

The compound (P1) may optionally be used in the form of a salt, such as that formed with an acid (e.g. a hydrochloric acid, DTTA).

When Q_1 is hydrogen, the compound (P1) may optionally be used in the form of a salt, such as that formed with an inorganic base, e.g. an alkali metal salt such as a sodium or potassium salt.

[0083] General synthesis 2: N-alkylation

[Chem.16]



(P1) (P2) (I')

In the scheme, R^1, R^2, R^3, R^4, Q_1, and Ring A are as defined above, and Q_2 is any one of the leaving groups described above, preferably halogen, methylsulfonyloxy or trifluoromethylsulfonyloxy.

When Q_1 is hydrogen, Compound (I') is Compound (I).

[0084] Compound (I') may be prepared by the reaction of compound (P1) with compound (P2) in the presence of a base in an inert solvent.

Any bases that are described above may be used in this reaction, and the base preferably used herein includes DIPEA or K_2CO_3.

Any solvents that are described above may be used in this reaction, and the solvent preferably used herein includes DMF, THF, 2-methyltetrahydrofuran, DCM or ace-

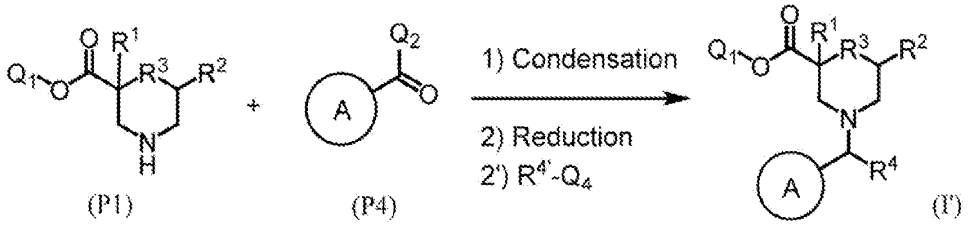
tonitrile.

The compound (P1) may optionally be used in the form of a salt, such as that formed with an acid (e.g. a hydrochloric acid, DTTA).

When Q_1 is hydrogen, the compound (P1) may optionally be used in the form of a salt, such as that formed with an inorganic base, e.g. an alkali metal salt such as a sodium or potassium salt.

[0085] General synthesis 3: Amidation

[Chem.17]



In the scheme, R^1, R^2, R^3, R^4, Q_1, Q_2, and Ring A are as defined above; $R^{4'}$ is $C_{1\text{-}6}$ alkyl; and Q_4 is any metal (e.g. alkali metal) or any metal halide (e.g. earth metal halide), preferably lithium, magnesium bromide or zinc.

When Q_1 is hydrogen, Compound (I') is Compound (I).

[0086] The reaction herein includes the following steps: (Step 1) the condensation reaction of compound (P1) with compound (P4) in the presence of a base and a condensation agent in an inert solvent, and (Step 2) the reduction reaction. When R^4 is not H, i.e., $C_{1\text{-}6}$ alkyl, then the reaction further includes Step 2': the reaction of the resultant of Step 1 with $R^{4'}$-Q_4.

Step 1: Any bases that are described above may be used in this step, and the base preferably used herein includes TEA, DIPEA or K_2CO_3. Any condensation agents that are described above may be used in this step, and the condensation agent preferably used herein includes T3P, PyBOP, DMT-MM, COMU, HBTU or HATU.

Step 2: Any reducing reagents that are described above may be used in this step, and the reducing reagent preferably used herein includes TMDS, methyldiethoxysilane, diethylsilane, triethylsilane, diphenylsilane and phenylsilane.

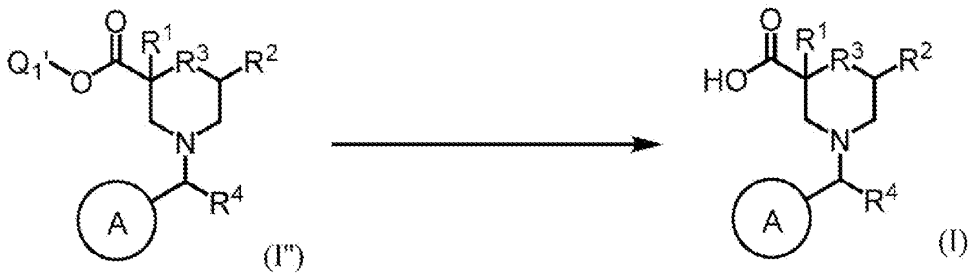
Any solvents that are described above may be used in these reactions, and the solvent preferably used herein includes THF, 2-methyltetrahydrofuran, DCM or acetonitrile.

The compound (P1) may optionally be used in the form of a salt, such as that formed with an acid (e.g. a hydrochloric acid, DTTA). When Q_1 is hydrogen, the compound (P1) may optionally be used in the form of a salt, such as that formed with an inorganic base, e.g. an alkali metal salt such as a sodium or potassium salt.

[0087] General synthesis 4: Deprotection

In a still further aspect of the invention, there is provided a process for preparation of compound of formula (I) comprising the step of deprotection of a protected derivative of a compound of formula (I). Deprotection comprises any suitable deprotection reaction, the conditions of which will depend upon the nature of the protecting group. A number of deprotection reactions are illustrated in the Examples. For example, a silyl ether may be deprotected to the corresponding alcohol (hydroxyl compound) in an inert solvent by deprotection of silyl with a suitable fluoride source or a suitable acid. Examples of a suitable fluoride source include tetrabutylammonium fluoride, hydrofluoric acid and cesium fluoride. Examples of a suitable acid include inorganic acids (e.g. hydrochloric acid) or organic acids (e.g. acetic acid, trifluoroacetic acid). For example, an alkyl ester may be deprotected to the corresponding carboxylic acid as below.

[0088] [Chem.18]



In the scheme, R^1, R^2, R^3, R^4, and Ring A are as defined above, and $Q_{1'}$ is a suitable protecting group, such as an alkyl group or an aralkyl group, and not hydrogen.

The deprotection herein comprises any suitable deprotection reactions, the conditions of which depend upon the nature of a protecting group used.

For example, when $Q_{1'}$ is an alkyl group, the alkyl ester may be deprotected to the corresponding carboxylic acid by hydrolysis with a suitable aqueous inorganic acid or a suitable base. Any acids that are described above may be used in this reaction, and the acid preferably used herein includes inorganic acids (e.g. hydrochloric acid). Any bases that are described above may be used in this reaction, and the base preferably used herein includes inorganic bases (e.g. lithium hydroxide or sodium hydroxide). Any solvents may be used in this reaction, and the solvent preferably used herein includes water, esters (e.g. AcOEt), ethers (e.g. dioxane, THF), alcohols (e.g. methanol), and a mixed solvent of water and any of the organic co-solvents herein (e.g. dioxane, THF, and methanol).

For example, when $Q_{1'}$ is an aralkyl group (e.g., benzyl), the aralkyl group may be deprotected to the corresponding carboxylic acid by hydrogenative deprotection with a suitable catalyst. Any catalysts that are described above may be used in this reaction,

and the catalyst preferably used herein includes palladium on carbon (Pd/C), platinum on carbon (Pt/C), platinum oxide (PtO_2). Any solvents may be used in this reaction, and the solvent preferably used herein includes esters (e.g. AcOEt), ethers (e.g. dioxane) and alcohols (e.g. ethanol, methanol).

[0089] A substituent R^5 may be introduced to synthesize Compound (I), Compound (I') or Compound (I") according to synthesis techniques known to those skilled in this field including, but not limited to, an amination reaction, etherification reaction, nucleophilic substitution reaction, addition reaction, as well as by the representative methods set forth below, those in the Examples and the Reference Examples, and any modifications thereof.

[0090] In each of the reactions in the above synthetic schemes, the reaction product may be used in the next reaction either as is in the form dissolved in the reaction solution or as a crude product, but it may also be isolated from the reaction mixture by ordinary methods and easily purified by ordinary separation techniques. Examples of ordinary separation techniques include recrystallization, distillation, and chromatography.

[0091] Any starting compounds, intermediate compounds, and product compounds in each of the above steps and Compound (I) include geometric isomers, stereoisomers, optical isomers, and tautomers thereof. Respective isomers may be separated by ordinary optical resolution methods. They may also be manufactured from raw material compounds having suitable optical activity.

[0092] Compound (I) may be manufactured according to any of the above synthetic schemes, or analogous methods thereof.

[0093] Unless otherwise specified, any starting compounds used in the manufacture of Compound (I) are commercially available, or may be produced by known methods or analogous methods thereof.

[0094] Any starting compounds and product compounds in each step above may be used in the form of appropriate salts thereof. Examples of such salts include salts similar to those listed for salts of Compound (I) below.

[0095] When any compounds obtained in each step or commercially available compounds used herein are in the free form, they may be converted to corresponding salts by known methods. When any compounds obtained in each step or commercially available compounds used herein are in the salt form, they may be converted to corresponding free forms or into other salts by known methods.

[0096] Compound (I) may also exist as any pharmaceutically acceptable salts thereof, and in some embodiments, Compound (I) may form an acid addition salt or a salt with a base depending on substituent(s) that are present in Compound (I). Examples of the "acid" herein include inorganic acids such as hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, and phosphoric acid; and organic acids such as methanesulfonic acid, p-

toluenesulfonic acid, acetic acid, trifluoroacetic acid, citric acid, tartaric acid, maleic acid, fumaric acid, malic acid, lactic acid, formic acid and the like. Examples of the "base" herein include inorganic bases such as sodium hydroxide, potassium hydroxide, calcium hydroxide, sodium carbonate, potassium carbonate, sodium bicarbonate, and potassium bicarbonate; organic bases such as methylamine, diethylamine, trimethylamine, triethylamine, ethanolamine, diethanolamine, triethanolamine, ethylenediamine, tris(hydroxymethyl)methylamine, dicyclohexylamine, N,N'-dibenzylethylenediamine, guanidine, pyridine, picoline, and choline; and ammonium salts, and the like. These inorganic bases may generate a salt, such as sodium salt, potassium salt, and calcium salt, of Compound (I). Compound (I) may also form a salt with an amino acid such as lysine, arginine, aspartic acid, glutamic acid, and the like.

[0097] The present invention also encompasses various hydrates, solvates, and crystal polymorphs of Compound (I) and any salts thereof.

[0098] Compound (I) also includes compounds in which one or more isotope atoms have been substituted for any one or more atoms in any proportions. Examples of isotope atoms include deuterium (^{2}H or D), tritium (^{3}H), ^{11}C, ^{13}C, ^{14}C, ^{13}N, ^{15}N, ^{15}O, ^{17}O, ^{18}O, ^{32}P, ^{35}S, ^{36}Cl, ^{37}Cl, ^{18}F, ^{123}I, ^{125}I, and the like.

[0099] In one embodiment, Compound [I], or a salt thereof, may be useful as a Positron Emission Topography (PET) tracer, preferably a PET imaging agent, that may be useful for in vitro, exo vivo, in vivo, or clinical trial tests and diagnostic imaging in humans and/or non-humans. Substitution with positron emitting isotopes, such as ^{11}C, ^{18}F, ^{15}O, and ^{13}N, can be useful in PET studies for examining target occupancy. For example, compounds labeled with ^{11}C or ^{18}F may be used for a PET tracer.

[0100] One embodiment of the present invention includes pharmaceutically acceptable prodrugs of Compound (I). Compound (I) may be modified on any group(s) including any reactive functional groups of Compound (I) such as -OH, -COOH, amino, and the like, so as to provide prodrugs of Compound (I). These functional groups may be modified with any group(s) selected appropriately from the protecting groups of hydroxy, carboxy, and amino.

[0101] Compound (I), or a salt thereof, may be in the form of a pharmaceutically acceptable co-crystal. The co-crystal herein means a crystalline substance composed of two or more independent substances each having different physical properties at room temperature, such as structures, melting points, heat of fusion, and the like. Co-crystals and co-crystal salts may be manufactured appropriately by well-known co-crystallization methods.

[0102] Medical uses

Compound (I), or a salt thereof, may show sortilin-binding inhibitory activity in a

subject including mammals. Compound (I), or a salt thereof, may be useful for treating, preventing, and/or diagnosing a disease or disorder that is associated with sortilin ligands, such as PGRN, neurotensin, proNGF, and proBDNF. In some embodiments, the disease or disorder may be mediated by PGRN-sortilin binding, neurotensin-sortilin binding, proNGF-sortilin binding, or proBDNF-sortilin binding. ProNGF and proBDNF are known apoptotic ligands that bind to the receptor complex of p75NTR and sortilin. The term "prophylaxis", "prevention", or "preventing" is used herein to mean the provision in advance, and as such may involve preventing symptoms of a disease or disorder in a subject or preventing recurrence of symptoms of a disease or disorder in an afflicted subject and is not limited to complete prevention of an affliction. The term "treatment" or "treating" as used herein includes the control, mitigation, reduction, or modulation of the disease state or its symptoms. The term "diagnosis" or "diagnosing" as used herein includes detection or monitoring of a disease or disorder in a subject. A subject will typically be a subject in need of treatment or prophylaxis according to the invention. A subject is typically a mammal. Suitably, the subject is a human.

[0103] Non-limiting examples of a disease or disorder associated with sortilin ligands herein include inflammatory diseases including rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), systemic sclerosis (SSc), inflammatory bowel disease (IBD), psoriasis, type 1 diabetes mellitus (T1DM), and multiple sclerosis (MS); cancers including progranulin-induced metastatic breast cancer, lung metastases, and pancreatic cancer cell invasion; wounds (i.e., wound healing) and traumatic brain injury; CNS diseases such as stroke, schizophrenia-like psychosis, schizophrenia, or bipolar disorder (BPD); atypical parkinsonism, such as corticobasal syndrome (CBS), and progressive supranuclear palsy (PSP); spinocerebellar ataxia 3 (SCA3), limbic-predominant age-related TDP-43 encephalopathy (LATE), and Huntington's diseases (HD); age-related macular degeneration (AMD), retinal degeneration, and other neurodegenerative disease of the eye; atherosclerosis; neurodegenerative disease such as frontotemporal dementia (FTD), frontotemporal lobar degeneration (FTLD), neuronal ceroid lipofuscinosis (NCL, a lysosomal storage disease), Niemann-Pick disease type A (NPA), Niemann-Pick disease type B (NPB), Niemann-Pick disease type C (NPC), amyotrophic lateral sclerosis (ALS), C9ORF72-associated ALS/FTD, sporadic ALS, Alzheimer's disease (AD), Gaucher disease types 2 and 3, Parkinson's disease (PD), and major depression; pain; and hearing loss.

[0104] In some embodiments, Compound (I), or a salt thereof, may increase PGRN levels. In some embodiments, PGRN levels may be increased in the central nervous system. In other embodiments, PGRN levels may be increased in the serum. PGRN is a secreted pleiotropic growth factor associated with multiple biological processes, and

Compound (I), or a salt thereof, may be useful for treating, preventing, and/or diagnosing a disease or disorder involving regulation of cell growth, migration, transformation, cell cycle, inflammation, neuroinflammation, lysosomal dysfunction and characterised by PGRN insufficiency.

[0105] Compound (I), or a salt thereof, may be beneficial to treat, prevent, or diagnose inflammatory diseases. In one embodiment, the inflammatory diseases include rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), systemic sclerosis (SSc), inflammatory bowel disease (IBD), psoriasis, type 1 diabetes mellitus (T1DM), and multiple sclerosis (MS).

[0106] PGRN may be a promising target for inflammation-related osteoporosis. PGRN inhibited TNF-α-induced osteoclastogenesis from spleen cells of PGRN-KO mice. Moreover, PGRN significantly promoted ALP activity, osteoblast-related mRNA (ALP, osteocalcin) expression in a dose-dependent manner and up-regulated osteoblastic differentiation by down-regulating phosphorylation of ERK1/2 in mouse calvarial cells. PGRN is a ligand of TNFR, an antagonist of TNFα signaling and plays a critical role in the pathogenesis of inflammatory arthritis in mice. Progranulin (PGRN), an anti-inflammatory molecule with therapeutic effect in inflammatory arthritis, was identified as an endogenous antagonist of TNFα by competitively binding to NFR. rhPGRN and Atsttrin also inhibited the TNFα-induced phosphorylation of p38, JNK and ERK1/2, mitogen activated protein kinase (MAPK) family members known to play an important role in TNFα-mediated inflammation. PGRN prevented inflammation in multiple arthritis mouse models and inhibited TNFα-activated intracellular signaling. In one embodiment, Compound (I), or a salt thereof, may be beneficial for use in the treatment or prophylaxis of cancer including progranulin-induced metastatic breast cancer, lung metastases, and pancreatic cancer cell invasion.

[0107] Compound (I), or a salt thereof, may also be beneficial to treat or prevent wounds (i.e., wound healing) and traumatic brain injury.

[0108] Progranulin could protect against acute focal cerebral ischaemia by a variety of mechanisms including attenuation of blood-brain barrier disruption, neuroinflammation suppression, and neuroprotection. Progranulin could regulate vascular permeability via vascular endothelial growth factor, suppress neuroinflammation after ischaemia via anti-inflammatory interleukin 10 in the microglia, and render neuroprotection in part by inhibition of cytoplasmic redistribution of TAR DNA-binding protein-43. Administered recombinant progranulin reduced cerebral infarct and oedema, suppressed haemorrhagic transformation, and improved motor outcomes. PGRN treatment suppressed neutrophil recruitment into the ischemia-reperfusion brain, and this led to a reduction of NF-κB and MMP-9 activation. In the in vitro in-

flammation models, PGRN suppressed both the neutrophil chemotaxis and ICAM-1 expression caused by TNF-α in endothelial cells. In one embodiment, Compound (I), or a salt thereof, may be beneficial for use in the treatment or prophylaxis of CNS diseases such as stroke, schizophrenia-like psychosis, schizophrenia, or bipolar disorder (BPD).

[0109] Intra-articular delivery of PGRN protects against osteoarthritis (OA) progression. Atsttrin, an engineered protein composed of three tumor necrosis factor receptor (TNFR)-binding fragments of progranulin, exhibited a preventative effect in OA by protecting articular cartilage and reducing OA-associated pain in both nonsurgically induced rat and surgically induced murine OA models. Mechanistic studies revealed that Atsttrin stimulated TNFR2-Akt-Erk1/2-dependent chondrocyte anabolism, while inhibiting TNFα/TNFR1-mediated inflammatory catabolism.

[0110] Frontotemporal dementia (FTD) is a progressive neurodegenerative disorder. FTD includes a spectrum of clinically, pathologically, and genetically heterogeneous diseases presenting selective involvement of the frontal and temporal lobes. Clinical manifestations of FTD include alterations in behavior and personality, frontal executive deficits, and language dysfunction. Based on the diversity of clinical phenotypes, different presentations have been identified, such as behavioral variants of FTD (bvFTD) and primary progressive aphasia (PPA), which can either be the nonfluent/agrammatic variant PPA (avPPA) or the semantic variant PPA (svPPA). These clinical presentations can also overlap with atypical parkinsonism, such as corticobasal syndrome (CBS), progressive supranuclear palsy (PSP), and amyotrophic lateral sclerosis (ALS). FTD is associated with various neuropathological hallmarks, including tau pathology in neurons and astrocytes or cytoplasmic ubiquitin inclusions in neurons. The Trans-activating DNA-binding Protein with a molecular weight of 43 kDa (TDP-43) is the most prominent, ubiquitinated protein pathology accumulating in the majority of cases of FTD as well as in ALS. FTD is a significant cause of early-onset dementia with up to 80% of cases presenting between ages 45 and 64. The disease also presents a significant familial component, with about 30-50% of cases reporting family history of the disease.

[0111] While several genes have been linked to FTD, one of the most frequently mutated genes in FTD is GRN, which maps to human chromosome 17q21 and encodes the cysteine-rich protein PGRN (also known as proepithelin and acrogranin). Recent estimates suggest that GRN mutations account for 5-20% of FTD patients with positive family history and 1-5% of sporadic cases). The precise molecular and cellular mechanisms underlying neurodegeneration and disease processes in GRN-associated FTD are unknown, although phenotypic characterization of Grn knockout mice combined with histological analyses of patients' brain suggests that both inflammation

and lysosomal defects are central to the disease. Indeed, massive gliosis is present in cortical regions of patients and lipofuscin, a lysosomal pigment denoting lysosomal disorder, has been reported in the eye and cortex of mutated GRN carriers including both presymptomatic individuals and patients. More than seventy GRN disease mutations have been reported and mapped throughout the gene, where they result in confirmed or predicted loss of function (LOF) alleles. Most heterozygous mutations linked to FTD cause about 50% reduction in mRNA levels primarily as a result of non-sense mRNA decay and a comparable reduction in PGRN protein levels. Lower levels of PGRN are also found in the blood (serum) and cerebrospinal fluid (CSF) of carriers, including presymptomatic individuals. Therefore, haploinsufficiency is believed to be the main disease mechanism in GRN-associated FTD, suggesting that therapeutic ap-proaches that elevate PGRN levels in carriers may delay the age of onset as well as the progression of FTD. This notion is supported by human genetic studies indicating that a variant of the gene TMEM106B both enhances the levels of PGRN by 25% and delays the age of onset of GRN-associated FTD by 13 years. Homozygous GRN mutations have also been reported, although carriers present a vastly different clinical phenotype known as neuronal ceroid lipofuscinosis (NCL) (Batten disease; incidence 1-2.5 in 100,000 live births), which is a lysosomal storage disorder. GRN is in fact one of the 14 ceroid-lipofuscinosis neuronal (CLN) genes reported to be linked to NCL and GRN is also known as CLN11.

[0112] PGRN levels have also been associated with increased GBA activity and therefore modulation of PGRN has therapeutic potential in diseases driven by GBA as well as other lysosomal hydrolases (NPL62). Patients with Gaucher's disease who carry ho-mozygous mutations in the GBA gene have lower levels of PGRN in their serum. Parkinson's disease patients with heterozygous mutations in GBA may also have lower levels of PGRN. The invention may also provide a method comprising the steps of (i) determining if a subject has homozygous mutations in the GBA gene, and (ii) treating the subject by administering Compound (I), or a salt thereof. Variants in GRN have been linked to AD and the TDP-43 pathology is common in the brain of AD patients. PGRN gene delivery has also been shown to decrease amyloid burden in mouse models of AD.

[0113] Niemann-Pick disease types A and B (NPA and NPB) result from mutations in the gene encoding acid sphingomyelinase (SMPD1). Niemann-Pick disease type C (NPC) results from mutations in the genes involved in cholesterol transport, i.e., NPC1 and NPC2.

[0114] The vast majority of ALS cases present the TDP-43 pathology, which is also shared with patients harboring GRN mutations. Among all ALS cases, GGGGCC repeat ex-pansions within the C9ORF72 gene are the most common cause of ALS and a sig-

nificant cause of FTD. The average mutation frequencies reported in North American and European populations are 37% for familial ALS, 6% for sporadic ALS, 21% for familial FTD, and 6% for sporadic FTD patients. Additionally, the TMEM106B variant that is protective in GRN-associated FTD is also protective in FTD patients harboring repeat expansions in the C9ORF72 gene. The invention may also provide a method comprising the steps of (i) determining if a subject has TDP-43 pathology, and (ii) treating the subject by administering Compound (I), or a salt thereof. Based on the cytoplasmic accumulations of TDP-43, Compound (I), or a salt thereof, may also be expected to be potent for spinocerebellar ataxia 3 (SCA3), limbic-predominant age-related TDP-43 encephalopathy (LATE), and Huntington's diseases (HD).

[0115] Age-related macular degeneration (AMD) is a degenerative disease and a major cause of blindness in the developed world. It causes damage to the macula, a small spot near the center of the retina and the part of the eye needed for sharp, central vision. The degenerative changes in the eye and loss of vision may be caused by impaired function of lysosomes and harmful protein accumulations behind the retina. As the disease progresses, retinal sensory cells in the central vision area are damaged, leading to loss of central vision. In some embodiments, Compound (I), or a salt thereof, may also be expected to be effective for AMD, retinal degeneration, and other neurodegenerative disease of the eye.

[0116] In some embodiments, a disease or disorder where inhibition of PGRN-sortilin binding may be beneficial is a disorder related to PGRN expression, processing, glycosylation, cellular uptake, trafficking, and/or function. In other embodiments, a disease or disorder where inhibition of PGRN-sortilin binding may be beneficial is atherosclerosis, Gaucher disease, or AMD. In some embodiments, a subject has a decreased level of PGRN and/or a disorder associated with a decreased level of PGRN. In some embodiments, the subject has a mutation in a granulin (GRN) gene. In some embodiments, the mutation in the GRN gene decreases PGRN expression and/or activity.

[0117] Hematopoietic progranulin deficiency promotes diet-induced atherosclerosis in Ldlr-/- mice (mice prone to atherosclerosis because of low-density lipoprotein receptor-deficient), possibly due to increased exophagy-mediated cholesterol uptake. Bone marrow transplanted from wild-type (WT) or Grn-/- (progranulin KO) mice to Ldlr-/- mice to generate mice in which the immune cells, such as lesion macrophages, either expressed or lacked endogenous progranulin. After feeding these mice a high-fat diet for 10 weeks, despite abundant circulating levels of progranulin, the size of atherosclerotic lesions in bone marrow progranulin KO mice was increased by 47% in aortic roots and by 62% in whole aortas. Aortic root lesions in Tx-KO mice had increased macrophage content and larger necrotic cores, consistent with more

advanced lesions. Cultured progranulin-deficient macrophages exhibited increased lysosome-mediated exophagy of aggregated low-density lipoproteins resulting in increased cholesterol uptake and foam cell formation.

[0118] In some embodiments, the disease or disorder where inhibition of PGRN-sortilin binding may be beneficial is Gaucher disease type 1. In further embodiments, the disease or disorder where inhibition of PGRN-sortilin binding may be beneficial is a disorder associated with TDP-43. In some embodiments the TDP-43 associated disorder is AD or ALS. In still further embodiments, the disease or disorder where inhibition of PGRN-sortilin binding may be beneficial is a neurodegenerative disease. In still further embodiments, the neurodegenerative disease is selected from the group consisting of frontotemporal dementia (FTD), frontotemporal lobar degeneration (FTLD), neuronal ceroid lipofuscinosis (NCL, a lysosomal storage disease), Niemann-Pick disease type A (NPA), Niemann-Pick disease type B (NPB), Niemann-Pick disease type C (NPC), amyotrophic lateral sclerosis (ALS), C9ORF72-associated amyotrophic lateral sclerosis (ALS)/FTD, sporadic ALS, Alzheimer's disease (AD), Gaucher disease types 2 and 3, Parkinson's disease (PD), and major depression.

[0119] In some embodiments, the disease or disorder where increasing in PGRN levels and inhibition of neurotensin signaling may be beneficial is neuropathic pain.

[0120] Compound (I), or a salt thereof, may be effective in the treatment, prevention, and/or diagnosis of any two or more diseases described above. Moreover, Compound (I), or a salt thereof, may be useful as active ingredients in pharmaceuticals, and for example may show enhanced in vivo potency, selectivity, acceptable safety profile, side effects, tolerability, stability (including storage stability, metabolic stability, etc.), pharmacokinetic parameters, for example high brain availability and/or low clearance rate that may reduce the dose required for effect in vivo, and the like.

[0121] Pharmaceutical compositions

In one embodiment, a medical preparation (herein also referred to as a "pharmaceutical composition") comprising Compound (I) or a salt thereof as an active ingredient is provided.

[0122] A medical preparation herein may be selected from various forms depending on therapeutic objectives. Any administration routes of a medical preparation may be chosen depending on dosage forms, the age and sex of a patient to be administered, disease status, and other conditions. A medical preparation may be administered orally, intravenously, intramuscularly, intradermally, subcutaneously, intraperitoneally, or rectally as necessary. Examples of the medical preparation include tablets, pills, powders, liquids, suspensions, emulsions, granules, capsules, suppositories, and injections (liquids, suspensions, etc.). Tablets include coated tablets such as sugar-coated tablets, gelatin-coated tablets, enteric-coated tablets, film-coated tablets, double tablets,

and multilayered tablets.

[0123] Compound (I), or a salt thereof, may be combined with a pharmaceutically acceptable carrier to be formulated into any forms of a medical preparation. Examples of the carrier include commonly used substances for a component of a medical preparation, including excipients such as lactose; binders such as polyvinylpyrrolidone; disintegrants such as starch; absorption aids such as sodium lauryl sulfate; humectants such as glycerin and starch; adsorbents such as colloidal silicic acid; and lubricants such as magnesium stearate and polyethylene glycol; diluents; fillers; bulking agents; and surfactants.

[0124] Pharmaceutically acceptable carriers to be used in formulating into a tablet specifically include excipients such as lactose; binders such as polyvinylpyrrolidone; disintegrants such as starch; absorption aids such as sodium lauryl sulfate; humectants such as glycerin and starch; adsorbants such as colloidal silicic acid; and lubricants such as magnesium stearate and polyethylene glycol.

[0125] Pharmaceutically acceptable carriers to be used in formulating into a pill specifically include excipients such as glucose; binders such as gum arabic powder; and disintegrants such as laminaran.

[0126] Pharmaceutically acceptable diluents to be used in formulating into a liquid, emulsion, or suspension specifically include water. Any ordinary solubilizing agents and/or buffers as well as colorants, preservatives, aromatics, flavorings, and sweeteners may also be comprised in the preparation, and other drugs may also be comprised as necessary.

[0127] Pharmaceutically acceptable carriers to be used in formulating into a suppository specifically include cocoa butter.

[0128] In some embodiments, Compound (I), or a salt thereof, may be formulated into the form of a liquid, emulsion, or suspension to prepare an injection. In one embodiment, the injection is preferably sterilized, and is also preferably isotonic with blood. The isotonic injection may comprise a sufficient amount of sodium chloride and soothing agents, and may also optionally comprise other drugs.

[0129] The amount (herein also referred to as "effective amount") of Compound (I), or a salt thereof, comprised in a medical preparation may be, but is not limited thereto, any amounts conventionally used in the art, and preferably includes any amounts of 1% to 70% of the medical preparation. The dose of Compound (I), or a salt thereof, to be administered may be any doses selected depending on administration routes, the age and sex of a patient to be administered, the severity of diseases, and other conditions, and includes 0.01 to 100 mg, preferably 0.1 to 50 mg, per 1 kg of body weight per day. The dose may be administered once or separately in several times.

[0130] Compound (I), or a salt thereof, may be used or administered in combination with at

least one therapeutic or preventive drug or standard-of-care agent, which may be referred to as a combined drug herein, useful for one of the above-mentioned diseases. When Compound (I), or a salt thereof, is used in combination with a combined drug, Compound (I), or a salt thereof, and the drug may be administered simultaneously or at the same time, separately or sequentially at about the same time, or separately or sequentially at different times with a suitable interval in between. Compound (I), or a salt thereof, and the combined drug may be formulated into separate preparations or mixed and formulated into a single preparation.

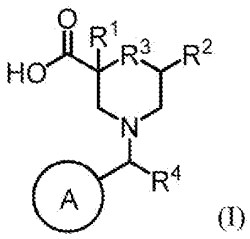
[0131] Disclosures of all literature cited herein are incorporated by reference in the present specification in their entireties.

[0132] Embodiments

The present invention is further illustrated by reference to the following clauses:

Clause 1-1. A compound of formula (I):

[Chem.19]



(I)

wherein:

R^1 is

1) H,

2) R^{11} optionally substituted with one or more R^{12}, or

3) -O-R^{11} optionally substituted with one or more R^{12},

R^{11} is C_{1-6} alkyl or C_{2-6} alkenyl,

R^{12} is each independently halogen, C_{1-6} alkyl-O-, C_{3-8} cycloalkyl, or saturated 3- to 8-membered monocyclic heterocyclyl comprising at least one heteroatom independently selected from the group consisting of nitrogen, oxygen, and sulfur, wherein R^{12} is optionally substituted with the same or different one or more halogen;

R^2 is

1) C_{1-6} alkyl optionally substituted with the same or different one or more halogen, hydroxy, or cyano, preferably C_{2-6} alkyl optionally substituted with the same or different one or more halogen, hydroxy, or cyano,

2) C_{3-8} cycloalkyl optionally substituted with the same or different one or more C_{1-6} alkyl, halogen, or cyano, or

3) $Si(C_{1-6}alkyl)_3$;

R^3 is CH_2 or O;

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

Ring A is optionally substituted partially unsaturated or unsaturated 7- to 15-membered bicyclic or tricyclic heterocyclyl comprising at least one heteroatom independently selected from the group consisting of nitrogen, oxygen, and sulfur;

or a salt thereof.

[0133] Clause 1-2. The compound according to clause 1-1, or a salt thereof, wherein R^2 is

1) C_{1-6} alkyl optionally substituted with the same or different one or more halogen, hydroxy, or cyano, preferably C_{2-6} alkyl optionally substituted with the same or different one or more halogen, or cyano, or

2) C_{3-8} cycloalkyl optionally substituted with the same or different one or more C_{1-6} alkyl.

[0134] Clause 1-3. The compound according to clause 1-1 or 1-2, or a salt thereof, wherein Ring A is optionally substituted with one or more R^5;

R^5 is each independently selected from the group consisting of:

1) halogen,

2) cyano,

3) oxo,

4) C_{1-6} alkyl,

5) C_{2-6} alkynyl,

6) C_{3-8} cycloalkyl,

7) C_{3-8} cycloalkenyl,

8) C_{6-10} aryl,

9) 4- to 10-membered monocyclic or bicyclic heterocyclyl,

10) -O-R^{5a}, and

11) -N(R^{5b})(R^{5c}),

wherein R^{5a}, R^{5b}, and R^{5c} are each independently selected from H, C_{1-6} alkyl, or C_{6-10} aryl;

R^5 is optionally substituted with one or more R^{51},

R^{51} is each independently selected from the group consisting of:

1) halogen,

2) C_{1-6} alkyl optionally substituted with one or more halogen,

3) C_{3-8} cycloalkyl,

4) C_{6-10} aryl,

5) 5- to 10-membered monocyclic heterocyclyl,

6) oxo,

7) -O-R^{51a}, and

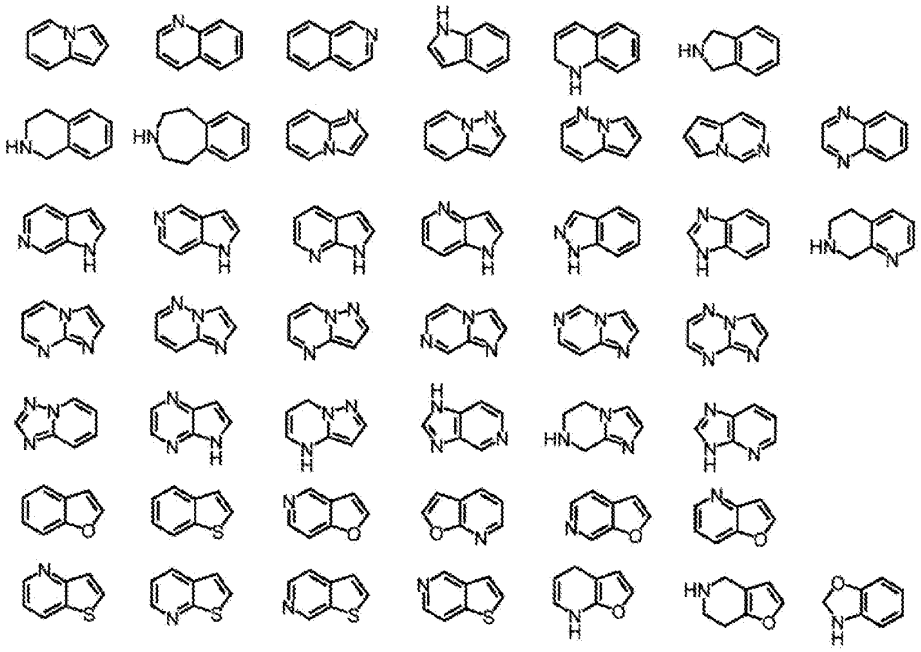
8) -N(R^{51b})(R^{51c}),

wherein R^{51a}, R^{51b}, and R^{51c} are each independently selected from H or C_{1-6} alkyl.

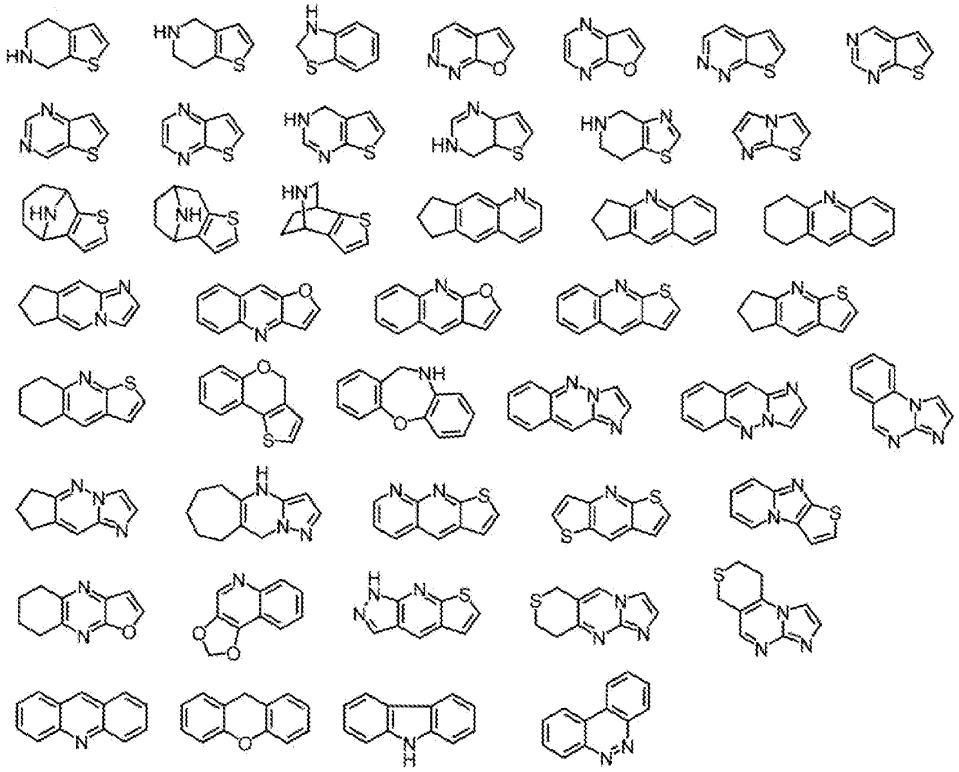
[0135] Clause 1-4. The compound according to any one of clauses 1-1 to 1-3, or a salt thereof, wherein Ring A is partially unsaturated or unsaturated 9- to 14-membered bicyclic or tricyclic heterocyclyl comprising 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, oxygen, and sulfur and is optionally substituted with the same or different 1 to 4 R^5.

[0136] Clause 1-5. The compound according to any one of clauses 1-1 to 1-4, or a salt thereof, wherein Ring A is any one of the heterocyclyl selected from the following groups:

[Chem.20]



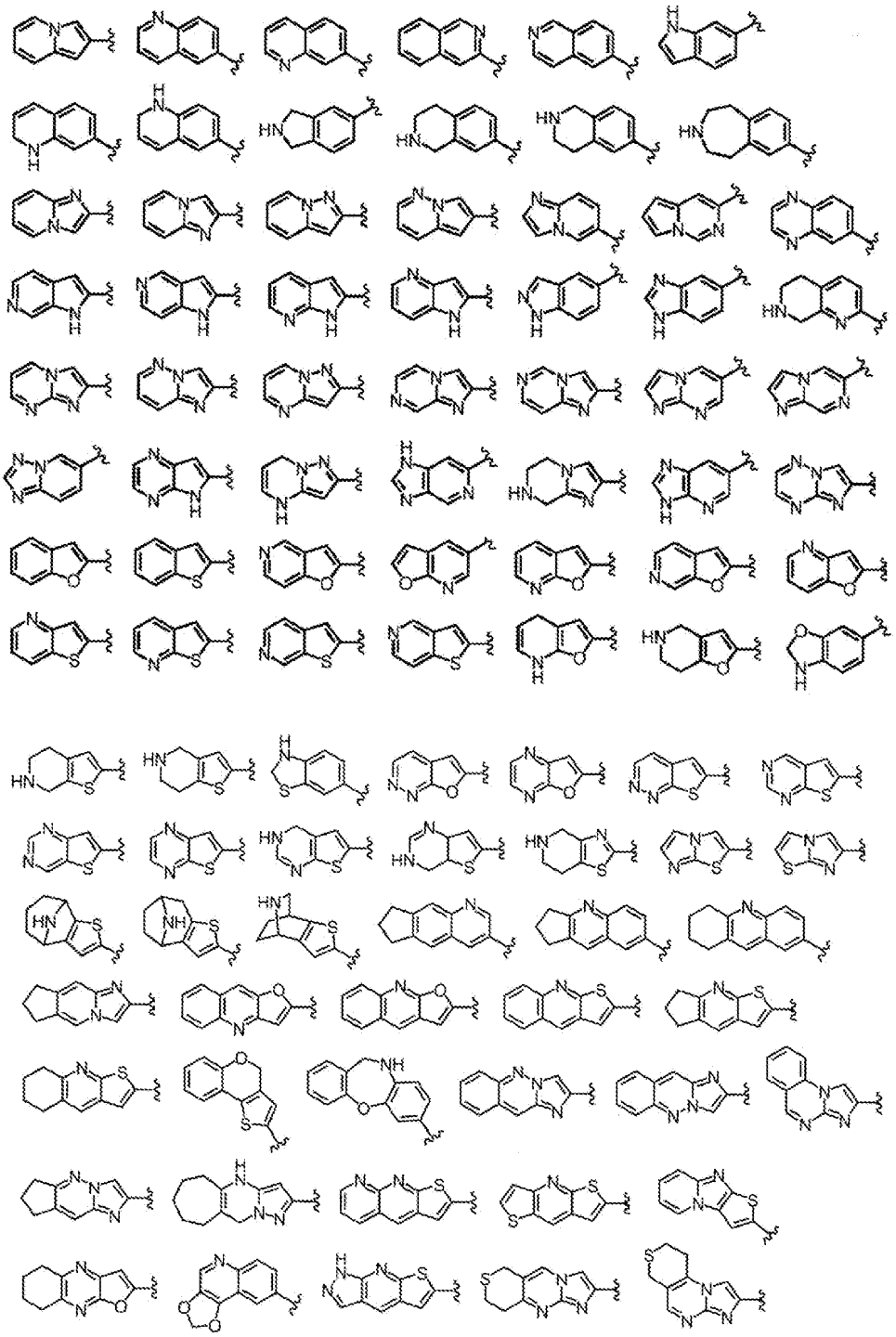
[Chem.21]



and is optionally substituted with the same or different 1 to 4 R^5; and preferably, Ring A may bind via any aromatic ring at any suitable position on the aromatic ring to the alpha position of the nitrogen-containing six-membered cyclic group of Compound (I).

[0137] Clause 1-6. The compound according to any one of clauses 1-1 to 1-5, or a salt thereof, wherein Ring A is any one of the heterocyclyl selected from the following groups:

[Chem.22]

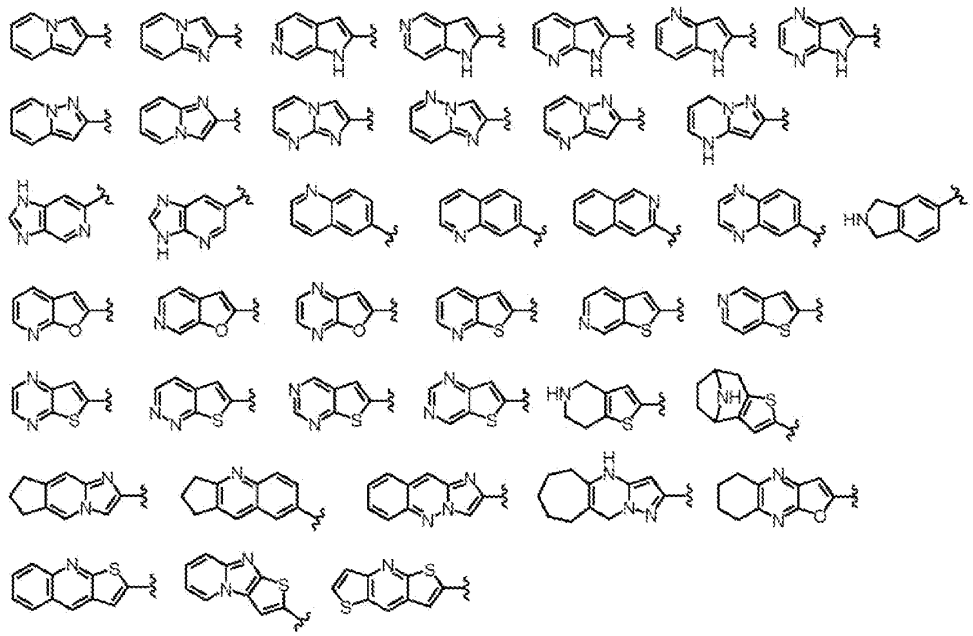


and is optionally substituted with the same or different 1 to 4 R^5.

[0138] Clause 1-7. The compound according to any one of clauses 1-1 to 1-6, or a salt

thereof, wherein Ring A is any one of the heterocyclyl selected from the following groups:

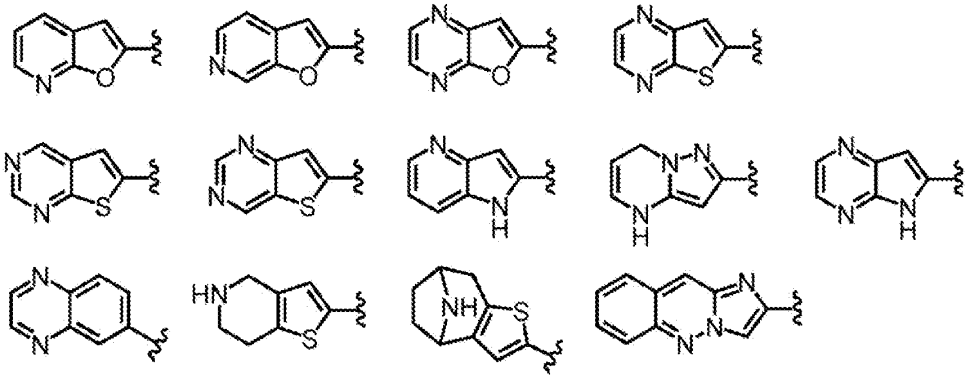
[Chem.23]



and is optionally substituted with the same or different 1 to 4 R^5.

[0139] Clause 1-8. The compound according to any one of clauses 1-1 to 1-7, or a salt thereof, wherein Ring A is any one of the heterocyclyl selected from the following groups:

[Chem.24]



and is optionally substituted with the same or different 1 to 3 R^5.

[0140] Clause 1-9. The compound according to any one of clauses 1-1 to 1-8, or a salt thereof, wherein R^4 is H or methyl.

[0141] Clause 1-10. The compound according to any one of clauses 1-1 to 1-9, or a salt

thereof, wherein R^4 is H.

[0142] Clause 1-11. The compound according to any one of clauses 1-1 to 1-10, or a salt thereof, wherein R^2 is C_{2-6} alkyl, halogen- or hydroxy-substituted C_{2-6} alkyl, or C_{1-6} alkyl-substituted C_{3-6} cycloalkyl.

[0143] Clause 1-12. The compound according to any one of clauses 1-1 to 1-11, or a salt thereof, wherein R^2 is C_{2-6} alkyl.

[0144] Clause 1-13. The compound according to any one of clauses 1-1 to 1-12, or a salt thereof, wherein R^2 is tert-butyl.

[0145] Clause 1-14. The compound according to any one of clauses 1-1 to 1-13, or a salt thereof, wherein R^{12} is each independently halogen, C_{1-6} alkyl-O-, C_{3-6} cycloalkyl, or saturated 3- to 8-membered monocyclic heterocyclyl.

[0146] Clause 1-15. The compound according to any one of clauses 1-1 to 1-14, or a salt thereof, wherein R^{11} is C_{1-6} alkyl optionally substituted with one or more R^{12}, and R^{12} is each independently halogen.

[0147] Clause 1-16. The compound according to any one of clauses 1-1 to 1-13, or a salt thereof, wherein R^1 is H, cyclopropylmethyl, methoxyethyl, cyclopropylethyl, propyl, fluoropropyl, difluoropropyl, trifluoropropyl, cyclohexylpropyl, difluorocyclohexylpropyl, difluoropiperidinylpropyl, butyl, isobutyl, trifluorobutyl, methylbutyl, methoxy, ethoxy, methoxyethoxy, propoxy, ethyl, or difluoropropenyl.

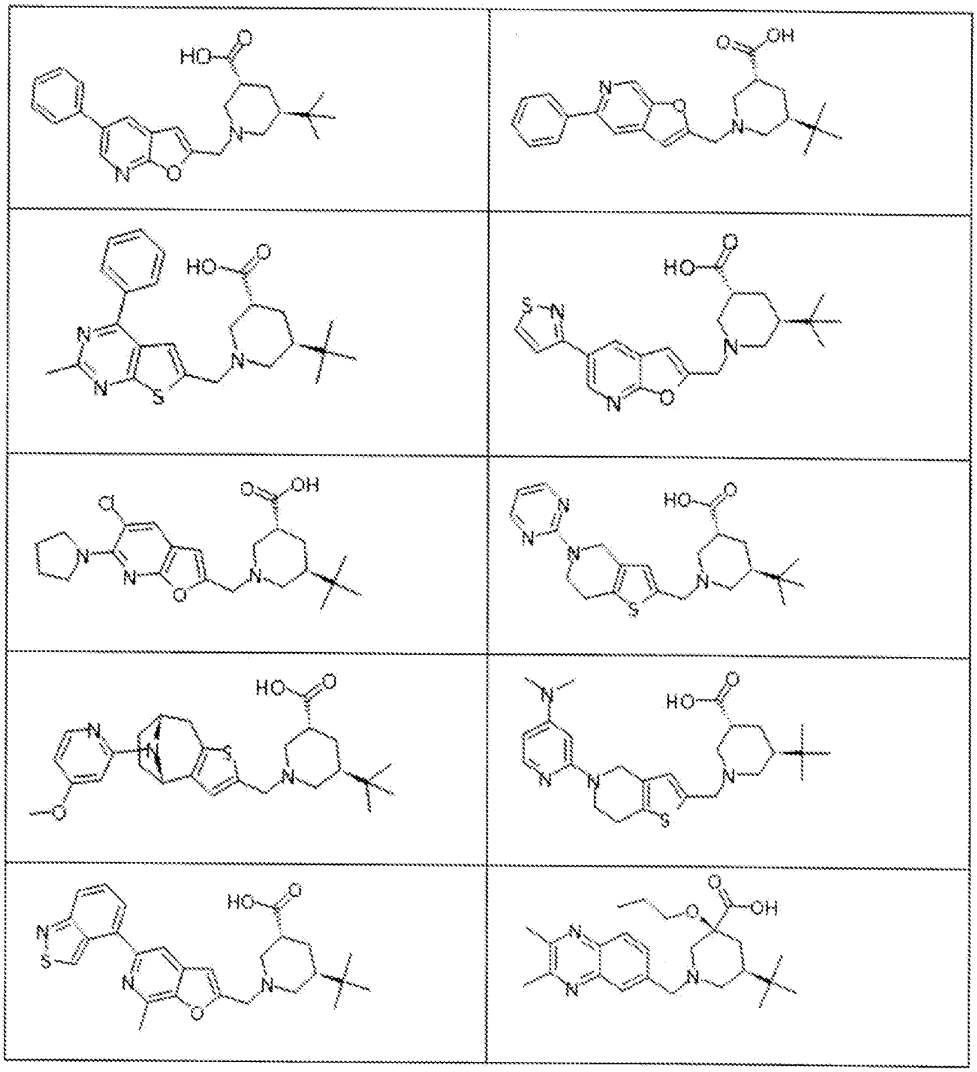
[0148] Clause 1-17. The compound according to any one of clauses 1-1 to 1-16, or a salt thereof, wherein R^5 is fluoro, chloro, cyano, oxo, methyl, fluoromethyl, difluoromethyl, trifluoromethyl, dimethylaminomethyl, thiophenylmethyl, ethyl, isopropyl, dimethylaminopropyl, cyclopropyl, cyclohexenyl, dimethylaminomethylpropynyl, phenyl, fluorophenyl, chlorophenyl, difluorophenyl, trifluoromethylphenyl, benzyl, azetidinyl, thiophenyl, thiazolyl, methylthiazolyl, isothiazolyl, pyridyl, methylpyridyl, ethylpyridyl, isopropylpyridyl, cyclopropylpyridyl, methoxypyridyl, ethoxypyridyl, fluoropyridyl, chloropyridyl, fluoromethylpyridyl, difluoromethylpyridyl, dimethylpyridyl, dimethylaminopyridyl, N-methyltetrahydropyridyl, pyrrolidinyl, methylpyrrolidinyl, dihydropyranyl, pyrimidyl, fluoropyrimidyl, methylpiperazinyl, ethylpiperazinyl, isopropylpiperazinyl, tert-butylpiperazinyl, cyclopropylpiperazinyl, cyclobutylpiperazinyl, dimethylpiperazinyl, difluoroethylpiperazinyl, trifluoromethylpiperazinyl, trifluoromethylmethylpiperazinyl, pyrazolyl, methylpyrazolyl, fluoropyrazolyl, chloromethylpyrazolyl, fluoromethylpyrazolyl, thienopyridyl, benzoisothiazolyl, hydroxy, methoxy, ethoxy, dimethylaminoethoxy, phenoxy, fluorophenoxy, methylamino, dimethylamino, dimethylaminoethylmethylamino, or hydroxymethyl.

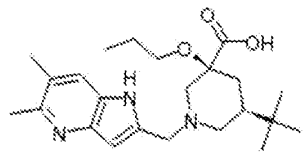
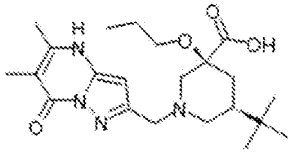
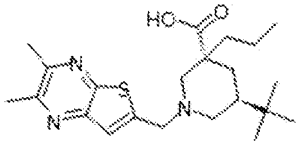
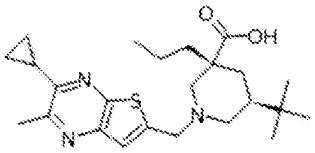
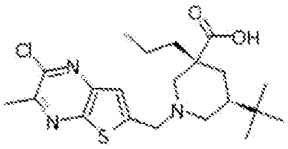
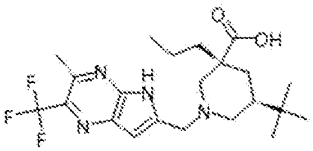
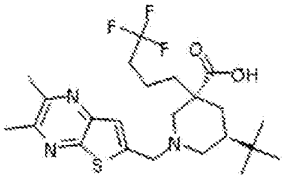
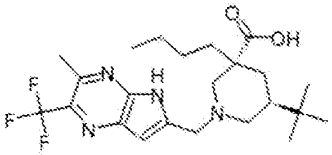
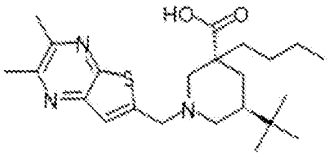
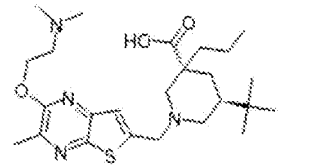
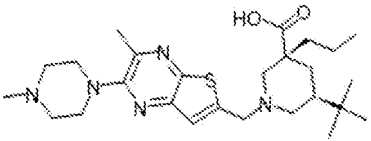
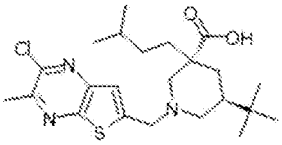
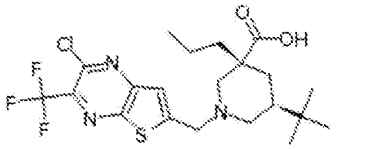
[0149] Clause 1-18. The compound according to any one of clauses 1-1 to 1-17, or a salt thereof, which is not

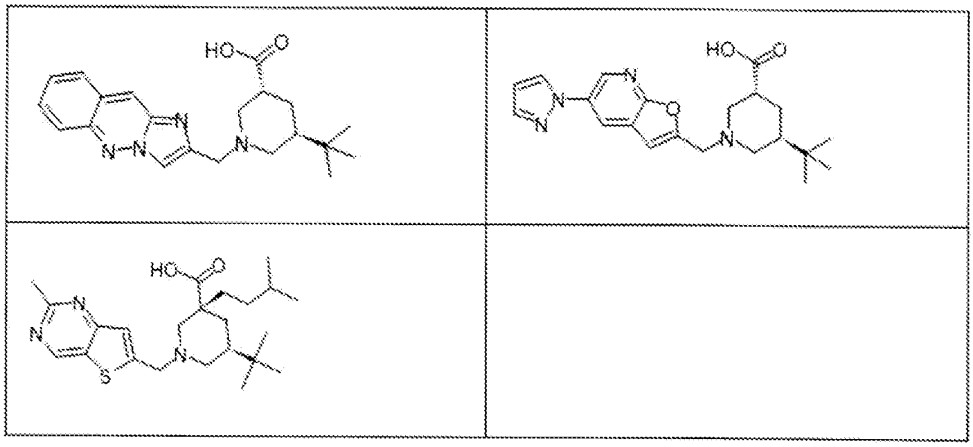
5-(1,1-dimethylethyl)-1-(pyrazolo[1,5-a]pyridin-4-ylmethyl)-3-piperidinecarboxylic acid,
5-(1,1-dimethylethyl)-1-(imidazo[2,1-b]thiazol-6-ylmethyl)-3-piperidinecarboxylic acid,
5-(1,1-dimethylethyl)-1-(imidazo[1,2-a]pyridin-5-ylmethyl)-3-piperidinecarboxylic acid,
5-(1,1-dimethylethyl)-1-(imidazo[1,2-a]pyridin-3-ylmethyl)-3-piperidinecarboxylic acid,
5-(1,1-dimethylethyl)-1-(imidazo[2,1-b]thiazol-2-ylmethyl)-3-piperidinecarboxylic acid,
5-(1,1-dimethylethyl)-1-(imidazo[2,1-b]thiazol-6-ylmethyl)-3-piperidinecarboxylic acid,
5-(1,1-dimethylethyl)-1-(pyrazolo[1,5-a]pyridin-4-ylmethyl)-3-piperidinecarboxylic acid, or
1-[(7,8-dihydro-5H-pyrano[4,3-b]pyridin-3-yl)methyl]-5-(1,1-dimethylethyl)-3-piperidinecarboxylic acid.

[0150] Clause 1-19. The compound according to clause 1-1, or a salt thereof, selected from the following formulae:

[Chem.25]

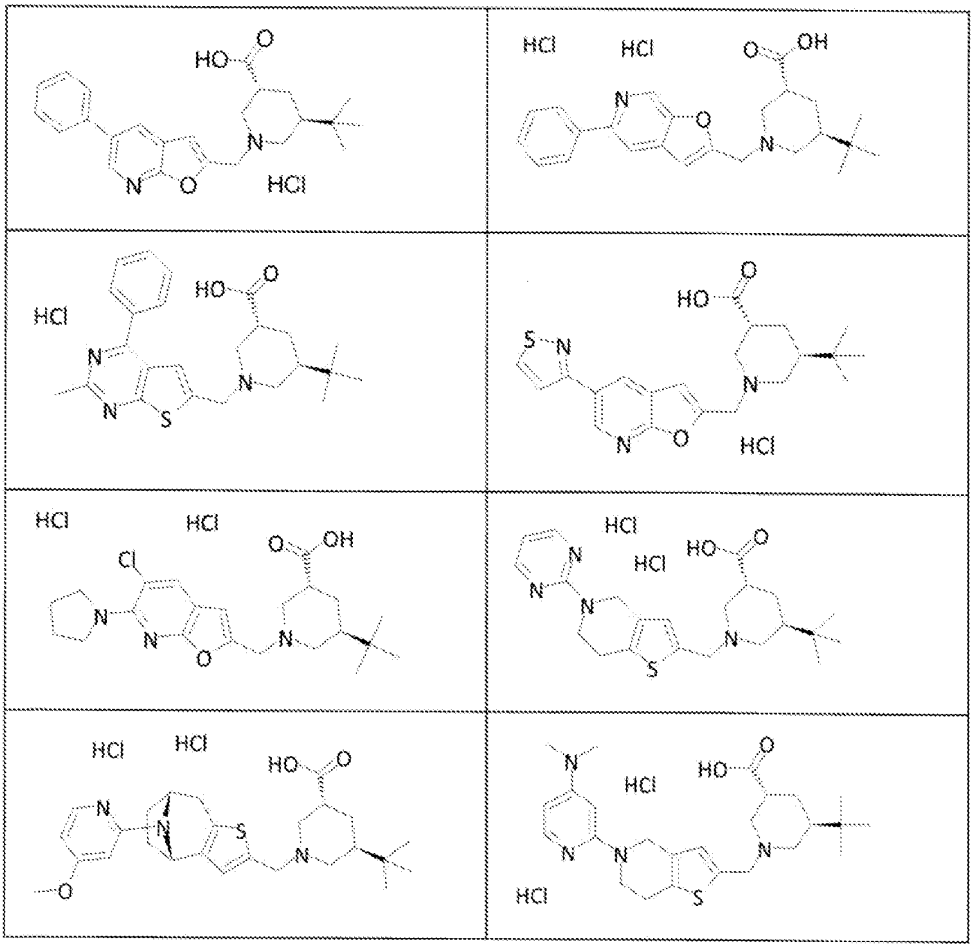


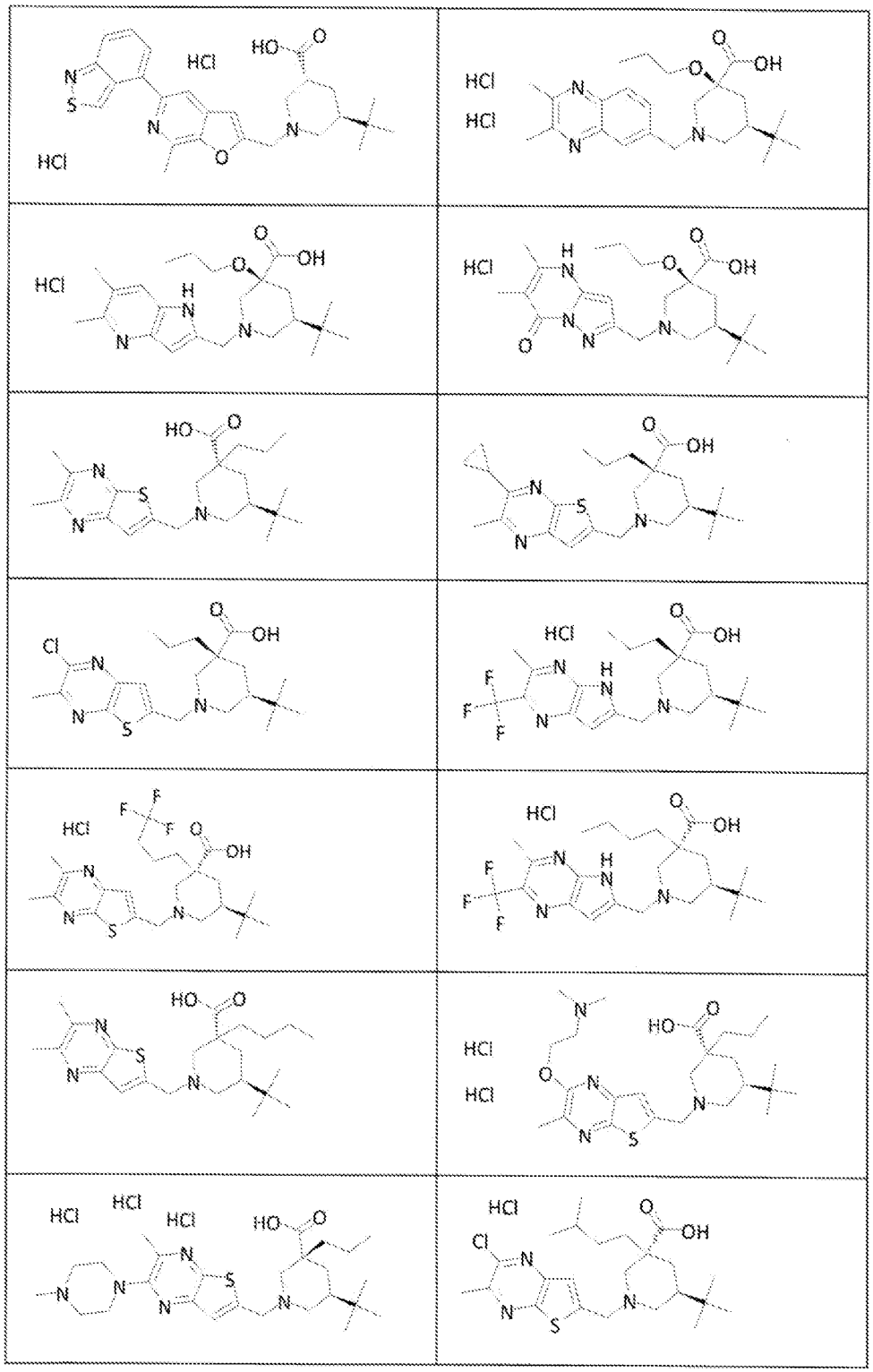
	
	
	
	
	
	
	

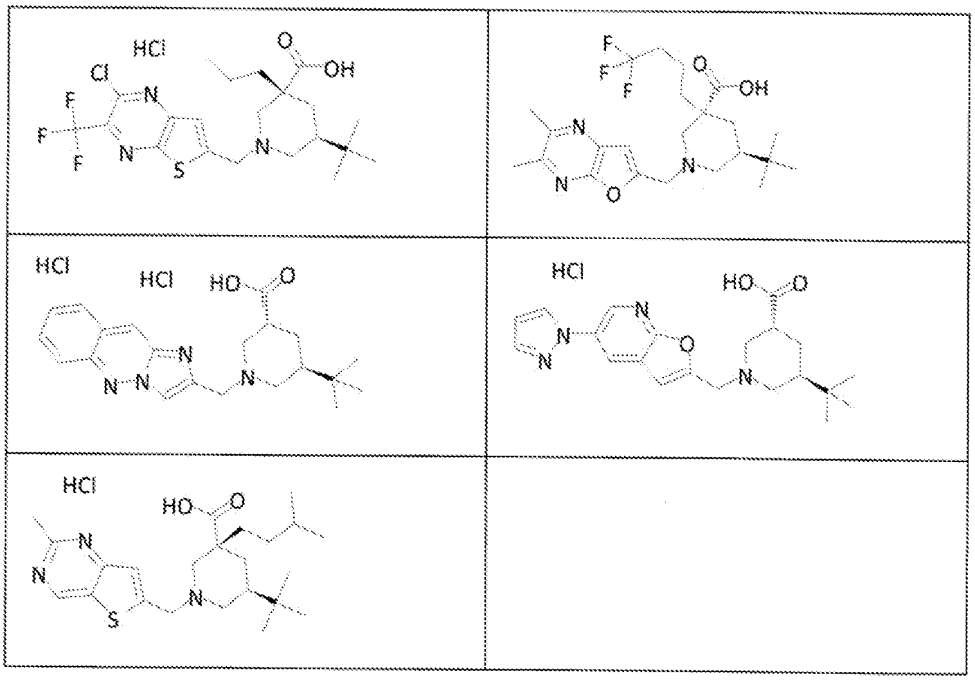


[0151] Clause 1-20. The compound according to clause 1-1 selected from the following formulae:

[Chem.26]



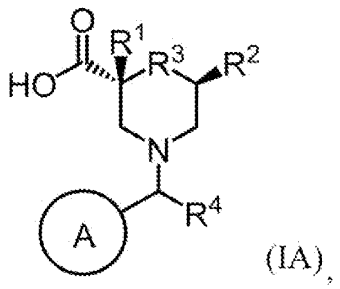




[0152] Clause 1-21. The compound according to clause 1-1, or a salt thereof, wherein the compound is selected from the compounds of Examples as shown in Table 3.

[0153] Clause 1-22. The compound according to any one of clauses 1-1 to 1-21, or a salt thereof, having the following structure (IA):

[Chem.27]



(IA),

wherein R^1, R^2, R^3, R^4, and Ring A are those as defined in clause 1-1.

[0154] Clause 2-1. A sortilin inhibitor comprising a compound according to any one of clauses 1-1 to 1-22 or a salt thereof.

[0155] Clause 2-2. The sortilin inhibitor according to clause 2-1, wherein the inhibitor is a PGRN-sortilin binding inhibitor.

[0156] Clause 2-3. The sortilin inhibitor according to clause 2-1, wherein the inhibitor is a neurotensin-sortilin binding inhibitor.

[0157] Clause 2-4. The sortilin inhibitor according to clause 2-1, wherein the inhibitor is a BDNF-signaling inhibitor.

[0158] Clause 2-5. The sortilin inhibitor according to clause 2-1, wherein the inhibitor is a proNGF-signaling inhibitor.

[0159] Clause 2-6. The sortilin inhibitor according to clause 2-1, wherein the inhibitor is a proBDNF-signaling inhibitor.

[0160] Clause 3. A pharmaceutical composition comprising a compound according to any one of clauses 1-1 to 1-22, or a salt thereof, and a pharmaceutically acceptable carrier or excipient.

[0161] Clause 4. The compound according to any one of clauses 1-1 to 1-22, or a salt thereof, for use as a medicament.

[0162] Clause 5. Use of a compound according to any one of clauses 1-1 to 1-22, or a salt thereof, in the manufacture of a medicament.

[0163] Clause 6-1. The compound according to any one of clauses 1-1 to 1-22, or a salt thereof, for use as a sortilin inhibitor.

[0164] Clause 6-2. The compound according to clause 6-1, or a salt thereof, for use in the inhibition of PGRN-sortilin binding.

[0165] Clause 6-3. The compound according to clause 6-1, or a salt thereof, for use in the inhibition of neurotensin-sortilin binding.

[0166] Clause 6-4. The compound according to clause 6-1, or a salt thereof, for use in the inhibition of BDNF signaling.

[0167] Clause 6-5. The compound according to clause 6-1, or a salt thereof, for use in the inhibition of proNGF signaling.

[0168] Clause 6-6. The compound according to clause 6-1, or a salt thereof, for use in the inhibition of proBDNF signaling.

[0169] Clause 7-1. The compound according to any one of clauses 1-1 to 1-22, or a salt thereof, for use in increasing PGRN levels, inhibiting neurotensin signaling, inhibiting BDNF signaling, inhibiting proNGF signaling, or inhibiting proBDNF signaling.

[0170] Clause 7-2. The compound according to clause 7-1, or a salt thereof, for use in increasing PGRN levels.

[0171] Clause 7-3. The compound according to clause 7-1, or a salt thereof, for use in inhibiting neurotensin signaling.

[0172] Clause 7-4. The compound according to clause 7-1, or a salt thereof, for use in inhibiting BDNF signaling.

[0173] Clause 7-5. The compound according to clause 7-1, or a salt thereof, for use in inhibiting proNGF signaling.

[0174] Clause 7-6. The compound according to clause 7-1, or a salt thereof, for use in inhibiting proBDNF signaling.

[0175] Clause 8-1. The compound according to any one of clauses 1-1 to 1-22, or a salt thereof, for use in the treatment, prophylaxis, or diagnosis of a disease or disorder as-

sociated with sortilin ligands.

[0176] Clause 8-2. The compound according to clause 8-1, or a salt thereof, for use in the treatment, prophylaxis, or diagnosis of a disease or disorder mediated by PGRN-sortilin binding.

[0177] Clause 8-3. The compound according to clause 8-1, or a salt thereof, for use in the treatment, prophylaxis, or diagnosis of a disease or disorder mediated by neurotension-sortilin binding.

[0178] Clause 8-4. The compound according to clause 8-1, or a salt thereof, for use in the treatment, prophylaxis, or diagnosis of a disease or disorder mediated by BDNF signaling.

[0179] Clause 8-5. The compound according to clause 8-1, or a salt thereof, for use in the treatment, prophylaxis, or diagnosis of a disease or disorder mediated by proNGF signaling.

[0180] Clause 8-6. The compound according to clause 8-1, or a salt thereof, for use in the treatment, prophylaxis, or diagnosis of a disease or disorder mediated by proBDNF signaling.

[0181] Clause 9-1. A method of treatment, prophylaxis, or diagnosis of a disease or disorder associated with sortilin ligands, the method which comprises administering to a subject in need thereof a compound according to any one of clauses 1-1 to 1-22, or a salt thereof.

[0182] Clause 9-2. The method according to clause 9-1, wherein the disease or disorder is mediated by PGRN-sortilin binding.

[0183] Clause 9-3. The method according to clause 9-1, wherein the disease or disorder is mediated by neurotension -sortilin binding.

[0184] Clause 9-4. The method according to clause 9-1, wherein the disease or disorder is mediated by BDNF signaling.

[0185] Clause 9-5. The method according to clause 9-1, wherein the disease or disorder is mediated by proNGF signaling.

[0186] Clause 9-6. The method according to clause 9-1, wherein the disease or disorder is mediated by proBDNF signaling.

[0187] Clause 9-7. A method of treatment, prophylaxis, or diagnosis of a disease or disorder, comprising administering to a subject in need thereof a compound according to any one of clauses 1-1 to 1-22, or a salt thereof, wherein the disease or disorder is selected from the group consisting of inflammatory diseases including rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), systemic sclerosis (SSc), inflammatory bowel disease (IBD), psoriasis, type 1 diabetes mellitus (T1DM), and multiple sclerosis (MS); cancers including progranulin-induced metastatic breast cancer, lung metastases, and pancreatic cancer cell invasion; wounds (i.e., wound healing) and

traumatic brain injury; CNS diseases such as stroke, schizophrenia-like psychosis, schizophrenia, or bipolar disorder (BPD); atypical parkinsonism, such as corticobasal syndrome (CBS), and progressive supranuclear palsy (PSP); spinocerebellar ataxia 3 (SCA3), limbic-predominant age-related TDP-43 encephalopathy (LATE), and Huntington's diseases (HD); age-related macular degeneration (AMD), retinal degeneration, and other neurodegenerative diseases of the eye; atherosclerosis; neurodegenerative diseases such as frontotemporal dementia (FTD), frontotemporal lobar degeneration (FTLD), neuronal ceroid lipofuscinosis (NCL, a lysosomal storage disease), Niemann-Pick disease type A (NPA), Niemann-Pick disease type B (NPB), Niemann-Pick disease type C (NPC), amyotrophic lateral sclerosis (ALS), C9ORF72-associated ALS/FTD, sporadic ALS, Alzheimer's disease (AD), Gaucher disease types 2 and 3, Parkinson's disease (PD), and major depression; pain; and hearing loss.

[0188] Clause 10-1. Use of a compound according to any one of clauses 1-1 to 1-22, or a salt thereof, in the manufacture of a medicament for the treatment, prophylaxis, or diagnosis of a disease or disorder associated with sortilin ligands.

[0189] Clause 10-2. Use of a compound according to any one of clauses 1-1 to 1-22, or a salt thereof, in the manufacture of a medicament for the treatment, prophylaxis, or diagnosis of a disease or disorder, wherein the disease or disorder is selected from the group consisting of inflammatory diseases including rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), systemic sclerosis (SSc), inflammatory bowel disease (IBD), psoriasis, type 1 diabetes mellitus (T1DM), and multiple sclerosis (MS); cancers including progranulin-induced metastatic breast cancer, lung metastases, and pancreatic cancer cell invasion; wounds (i.e., wound healing) and traumatic brain injury; CNS diseases such as stroke, schizophrenia-like psychosis, schizophrenia, or bipolar disorder (BPD); atypical parkinsonism, such as corticobasal syndrome (CBS), and progressive supranuclear palsy (PSP); spinocerebellar ataxia 3 (SCA3), limbic-predominant age-related TDP-43 encephalopathy (LATE), and Huntington's diseases (HD); age-related macular degeneration (AMD), retinal degeneration, and other neurodegenerative diseases of the eye; atherosclerosis; neurodegenerative diseases such as frontotemporal dementia (FTD), frontotemporal lobar degeneration (FTLD), neuronal ceroid lipofuscinosis (NCL, a lysosomal storage disease), Niemann-Pick disease type A (NPA), Niemann-Pick disease type B (NPB), Niemann-Pick disease type C (NPC), amyotrophic lateral sclerosis (ALS), C9ORF72-associated ALS/FTD, sporadic ALS, Alzheimer's disease (AD), Gaucher disease types 2 and 3, Parkinson's disease (PD), and major depression; pain; and hearing loss.

[0190] Clause 11-1. A medicament comprising a compound according to any one of clauses 1-1 to 1-22, or a salt thereof, for use in the treatment, prophylaxis, or diagnosis of a disease or disorder associated with sortilin ligands.

[0191] Clause 11-2. A medicament comprising a compound according to any one of clauses 1-1 to 1-22, or a salt thereof, for use in the treatment, prophylaxis, or diagnosis of a disease or disorder wherein the disease or disorder is selected from the group consisting of inflammatory diseases including rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), systemic sclerosis (SSc), inflammatory bowel disease (IBD), psoriasis, type 1 diabetes mellitus (T1DM), and multiple sclerosis (MS); cancers including progranulin-induced metastatic breast cancer, lung metastases, and pancreatic cancer cell invasion; wounds (i.e., wound healing) and traumatic brain injury; CNS diseases such as stroke, schizophrenia-like psychosis, schizophrenia, or bipolar disorder (BPD); atypical parkinsonism, such as corticobasal syndrome (CBS), and progressive supranuclear palsy (PSP); spinocerebellar ataxia 3 (SCA3), limbic-predominant age-related TDP-43 encephalopathy (LATE), and Huntington's diseases (HD); age-related macular degeneration (AMD), retinal degeneration, and other neurodegenerative diseases of the eye; atherosclerosis; neurodegenerative diseases such as frontotemporal dementia (FTD), frontotemporal lobar degeneration (FTLD), neuronal ceroid lipofuscinosis (NCL, a lysosomal storage disease), Niemann-Pick disease type A (NPA), Niemann-Pick disease type B (NPB), Niemann-Pick disease type C (NPC), amyotrophic lateral sclerosis (ALS), C9ORF72-associated ALS/FTD, sporadic ALS, Alzheimer's disease (AD), Gaucher disease types 2 and 3, Parkinson's disease (PD), and major depression; pain; and hearing loss.

[0192] Clause 11-3. A medicament comprising a compound according to any one of clauses 1-1 to 1-22, or a salt thereof, for use in increasing PGRN levels, inhibiting neurotensin signaling, inhibiting BDNF signaling, inhibiting proNGF signaling, or inhibiting proBDNF signaling.

[0193] Clause 12-1. The compound according to any one of clauses 1-1 to 1-22, or a salt thereof, inhibitor, composition, method, use, or medicament according to any one of clauses 2-1 to 2-6, 3 to 5, 6-1 to 6-6, 7-1 to 7-6, 8-1 to 8-6, 9-1 to 9-7, 10-1 to 10-2, 11-1 and 11-2, for use in the treatment, prophylaxis, or diagnosis of a disease or disorder, wherein the disease or disorder is selected from the group consisting of inflammatory diseases including rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), systemic sclerosis (SSc), inflammatory bowel disease (IBD), psoriasis, type 1 diabetes mellitus (T1DM), and multiple sclerosis (MS); cancers including progranulin-induced metastatic breast cancer, lung metastases, and pancreatic cancer cell invasion; wounds (i.e., wound healing) and traumatic brain injury; CNS diseases such as stroke, schizophrenia-like psychosis, schizophrenia, or bipolar disorder (BPD); atypical parkinsonism, such as corticobasal syndrome (CBS), and progressive supranuclear palsy (PSP); spinocerebellar ataxia 3 (SCA3), limbic-predominant age-related TDP-43 encephalopathy (LATE), and Huntington's diseases

(HD); age-related macular degeneration (AMD), retinal degeneration, and other neurodegenerative diseases of the eye; atherosclerosis; neurodegenerative diseases such as frontotemporal dementia (FTD), frontotemporal lobar degeneration (FTLD), neuronal ceroid lipofuscinosis (NCL, a lysosomal storage disease), Niemann-Pick disease type A (NPA), Niemann-Pick disease type B (NPB), Niemann-Pick disease type C (NPC), amyotrophic lateral sclerosis (ALS), C9ORF72-associated ALS/FTD, sporadic ALS, Alzheimer's disease (AD), Gaucher disease types 2 and 3, Parkinson's disease (PD), and major depression; pain; and hearing loss.

[0194] Clause 12-2. The compound, or a salt thereof, inhibitor, composition, method, use, or medicament according to clause 12-1, wherein the disease or disorder is selected from frontotemporal dementia, Alzheimer's disease, Parkinson's disease, or amyotrophic lateral sclerosis.

[0195] Clause 12-3. The compound, or a salt thereof, inhibitor, composition, method, use, or medicament according to clause 12-1, wherein the disease or disorder is frontotemporal dementia.

[0196] Clause 12-4. The compound, or a salt thereof, method, use or medicament according to clause 12-1, wherein the disease or disorder is Alzheimer's disease.

[0197] Clause 12-5. The compound, or a salt thereof, method, use or medicament according to clause 12-1, wherein the disease or disorder is Parkinson's disease.

[0198] Clause 12-6. The compound, or a salt thereof, method, use or medicament according to clause 12-1, wherein the disease or disorder is amyotrophic lateral sclerosis.

[0199] Clause 13. The compound according to any one of clauses 1-1 to 1-22, or a salt thereof, inhibitor, method, use, or medicament according to any one of clauses 2-1 to 2-6, 4 to 5, 6-1 to 6-6, 7-1 to 7-6, 8-1 to 8-6, 9-1 to 9-7, 10-1 and 10-2, 11-1 to 11-3, wherein the compound, or a salt thereof, is provided in the form of a pharmaceutical composition according to clause 3.

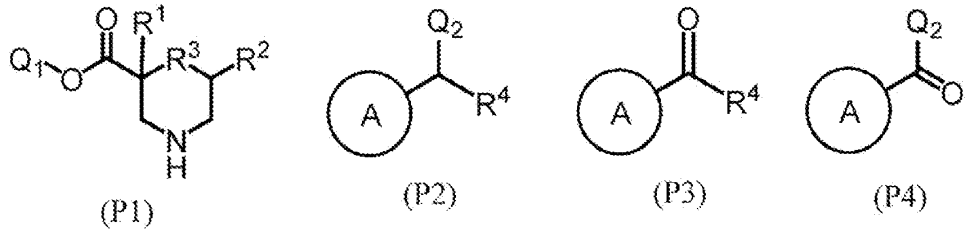
[0200] Clause 14-1. The compound according to any one of clauses 1-1 to 1-22, or a salt thereof, inhibitor, composition, method, use, or medicament according to any one of clauses 2-1 to 2-6, 3 to 5, 6-1 to 6-6, 7-1 to 7-6, 8-1 to 8-6, 9-1 to 9-7, 10-1 and 10-2, 11-1 to 11-3, wherein the compound or a salt thereof, is administered orally.

[0201] Clause 15. A process for the preparation of a compound of formula (I) according to any one of clauses 1-1 to 1-22, or a salt thereof, as described herein.

[0202] Clause 16-1. An intermediate compound in the process for preparing a compound of formula (I), or a salt thereof, as described herein.

[0203] Clause 16-2. The compound according to clause 16-1, or a salt thereof, represented by any one of the compounds of formulae (P1), (P2), (P3), and (P4):

[Chem.28]



(P1) (P2) (P3) (P4)

wherein R^1, R^2, R^3, R^4, Q_1, Q_2, and Ring A are as defined above.

[0204] Clause 16-3. The compound according to clause 16-1, or a salt thereof, wherein the compound is selected from the compounds of Reference Examples as shown in Table 2.

Examples

[0205] The present invention is explained in more detail with reference to Test Examples, Reference Examples, and Examples as below, which are not to be construed as limitative, and the examples may be modified without departing from the scope of the invention.

Herein, the following abbreviations may be used.

[0206]

[Table 1]

Abbreviations	Words
REX	Reference Example number
EX	Example number
STR	Structural formula
RProp	Manufacturing method (numbers indicate that the compound was manufactured using the corresponding raw materials in the same way as the reference example compound having that number as a reference example number)
Prop	Manufacturing method (numbers indicate that the compound was manufactured using the corresponding raw materials in the same way as the example compound having that number as an example number)
Data	Physical property data (NMR1: δ (ppm) in ^{1}H-NMR in DMSO-d_6; NMR2: δ (ppm) in ^{1}H-NMR in $CDCl_3$; NMR3: δ (ppm) in ^{1}H-NMR in CD_3OD); MS: Mass spectrum)
AcOEt/EtOAc	Ethyl acetate
AcOH	Acetic acid
AcONa	Sodium acetate
aq.	aqueous solution
AUC	Area under curve
BBr_3	Boron tribromide
BF_3OEt_2	Boron trifluoride-diethyl ether complex
BINAP	2,2'-Bis(diphenylphosphuno)-1,1'-binaphthyl
BippyPhos	5-(Di-tert-butylphosphino)-1',3',5'-triphenyl-1'H-[1,4']bipyrazole
Bn	Benzyl
Boc	tert-Butoxycarbonyl
Bpin	Boronic acid pinacol ester
BPO	Benzoyl peroxide
Bz	Benzoyl
$CaCl_2$	Calcium Chloride
CDI	1,1'-Carbonyldiimidazole
CH_3CN/MeCN	Acetonitrile
$CHCl_3$	Chloroform
Cmax	The maximum plasma concentration that a drug achieved
COMU	Ethyl 2-cyano-2-((dimethylimimio)(morpholino)methyloxyimino)acetate hexafluorophosphate
conc.	concentrated
Cs_2CO_3	Cesium carbonate
CuI	Cupper (I) iodide
d	day/days
DAST	(Diethylamino)sulfur trifluoride
DBU	1,8-Diazabicyclo[5.4.0]-7-undecene
DCC	Dicyclohexylcarbodiimide
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DEA	Diethylamine
DEAD	Diethylazodicarboxylate
DMP/Dess-	1,1,1-Triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one

Martin periodinane	
DHP	3,4-Dihydro-2H-pyran
DIBAL	Diisobutylaluminum hydride
DIBOC	Di-t-butyl dicarbonate
DIPEA	Diisopropylethylamine
DMA	N,N-Dimethylacetamide
DMAP	4-(Dimethylamino)pyridine
DME	Dimethoxyethane
DMF	N,N-Dimethylformamide
DMSO	Dimethyl sulfoxide
DMT-MM	4-(4,6-Dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride
DPPA	Diphenylphosphoryl azide
Et_2O	Diethyl ether
EtOH	Ethanol
Fmoc	Fluorenylmethyloxycarbonyl
GPC	Gel permeation chromatography
h	hour/hours
HATU	1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate
HBTU	1-[Bis(dimethylamino)methylene]-1H-benzotriazolium 3-oxide hexafluorophosphate
HCl	Hydrochloric acid
Hexane	n-Hexane
HOAt	3H-[1,2,3]Triazolo[4,5-b]pyridin-3-ol
HOBt	1-Hydroxybenzotriazole
IPA	2-Propanol
IPE	Diisopropyl ether
K_2CO_3	Potassium carbonate
KF	Potassium fluoride
K_3PO_4	Tripotassium phosphate
$KHCO_3$	Potassium hydrogen carbonate
KHMDS	Potassium bis(trimethylsilyl)amide
KOAc	Potassium acetate
KOH	Potassium hydroxide
KOtBu	Potassium tert-butoxide
LAH	Lithium aluminum hydride
LDA	Lithium diisopropylamide
L-DTTA	(2R,3R)-2,3-bis(4-methylbenzoyloxy)butanedioic acid or Di-p-toluoyl-L-tartaric acid
LHMDS	Lithium hexamethyldisilazide
LiOH	Lithium hydroxide
MCPBA	m-Chloroperoxybenzoic acid
MEK	2-Butanone
MeOH	Methanol
MsCl	Methanesulfonyl Chloride
$MgSO_4$	Magnesium sulfate
MnO_2	Manganese dioxide
N_2	Nitrogen molecule

$NaBH_4$	Sodium borohydride
$NaBH(OAc)_3$	Sodium triacetoxyborohydride
Na_2CO_3	Sodium carbonate
NaH	Sodium hydride
$NaHCO_3$	Sodium hydrogen carbonate
NaHMDS	Sodium hexamethyldisilazide
NaOH	Sodium hydroxide
NaOtBu	Sodium t-butoxide
Na_2SO_4	Sodium sulfate
Na_2SO_4-$10H_2O$	Sodium sulfate decahydrate
$Na_2S_2O_3$	Sodium thiosulfate
NBS	N-Bromosuccinimide
n-BuLi	n-Butyllithium
NCS	N-Chlorosuccinimide
NH_3	Ammonia
NH_4Cl	Ammonium chloride
NMP	N-Methylpyrrolidone
ODS	Octadecylsilyl
OsO_4	Osmium (VIII) oxide
PCy_3HBF_4	Tricyclohexylphosphine tetrafluoroborate
Pd/C	Palladium on carbon
$Pd_2(dba)_3$	Tris(dibenzylideneacetone)dipalladium (0)
$Pd(dppf)Cl_2$	1,1'-Bis(diphenylphosphino)ferrocene]palladium
$Pd(dtbpf)Cl_2$	1,1'-Bis(di-t-butylphosphino)ferrocene palladium dichloride
$Pd(OAc)_2$	Palladium (II) acetate
$Pd(OH)_2$-C	Palladium hydroxide on carbon
Pd-PEPPSI IPent	[1,3-Bis(2,6-Di-3-pentylphenyl)imidazol-2-ylidene](3-chloropyridyl)palladium(II) dichloride
$Pd(PPh_3)_4$	Tetrakis(triphenylphosphine)palladium (0)
$Pd(PPh_3)_2Cl_2$	Bis(triphenylphosphine)palladium(II) dichloride
PEG	Polyethylene glycol
PPTS	Pyridinium p-toluenesulfonate
PtO_2	Platinum oxide
PyBOP	Benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate
RuPhos Pd G3	(2-Dicyclohexylphosphino-2',6'-diisopropoxy-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium (II) methanesulfonate
sat.	saturated
SEMCl	2-(Chloromethoxy)ethyltrimethylsilane
T3P	Propylphosphonic anhydride
TBAF	Tetra-n-butylammonium fluoride
TBME	tert-Butyl methyl ester
t-BuOH	tert-butyl alcohol
TEA	Triethylamine
TEB	Triton extraction buffer
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
t_{max}	The time at which the Cmax was observed
TMB	Tetramethylbenzidine

TMDS	1,1,3,3-Tetramethyldisiloxane
TMEDA	N,N,N',N'-Tetramethlethylenediamine
TMS-Cl	Chlorotrimethylsilane
$TMSCF_3$	(Trifluoromethyl)trimethylsilane
XPhos	2-Dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl
XPhos Pd G3	(2-Dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium (II) methanesulfonate
WSC	3-Ethyl-1-(3-dimethylaminopropyl)carbodiimide
ZCl	Benzyl chloroformate
Zn	Zinc
$ZnMe_2$	Dimethylzinc

[0207] In the following Examples, "room temperature (RT, r.t., or rt)" generally means about 10°C to about 35°C. The ratios indicated for mixed solvents are volume mixing ratios, unless otherwise specified. % means wt%, unless otherwise specified.

[0208] ^{1}H-NMR (proton nuclear magnetic resonance spectrum) was measured by Fourier-transform type NMR (either of Bruker AVANCE III 400 (400 MHz), Bruker AVANCE III HD (400 MHz) or Bruker AVANCE III HD (500 MHz)).

[0209] Mass spectrum (MS) was measured by LC/MS (either of ACQUITY UPLC H-Class, Agilent 1290 Infinity II/6130 or Shimadzu Nexera/LCMS-2020). As an ionization method, ESI method was used. The data indicate actual measured values (found). Generally, molecular ion peaks ($[M+H]^+$, $[M-H]^-$, etc.) were observed. In the case of a salt, a molecular ion peak or fragment ion peak of free form was generally observed.

[0210] Supercritical fluid chromatography (SFC) was used for chiral separation.

[0211] In silica gel column chromatography, when denoted as basic, aminopropylsilane-bound silica gel was used.

[0212] The absolute configuration of a compound was determined by known X-ray crystal structure analysis (e.g., "Basic Course for Chemists 12, X-ray Crystal Structure Analysis" written by Shigeru Ohba and Shigenobu Yano, 1st edition, 1999) or estimated from the empirical rule of Shi asymmetric epoxidation (Waldemar Adam, Rainer T. Fell, Chantu R. Saha-Moller and Cong-Gui Zhao: Tetrahedron: Asymmetry 1998, 9, 397-401; Yuanming Zhu, Yong Tu, Hongwu Yu, Yian Shi: Tetrahedron Lett. 1988, 29, 2437-2440).

[0213] Reference Examples

Reference Example 2: Synthesis of methyl (3R,5S)-5-tert-butyl-1-[(5-phenylfuro[2,3-b]pyridin-2-yl)methyl]piperidine-3-carboxylate

A suspension of methyl (3R,5S)-1-((5-bromofuro[2,3-b]pyridin-2-yl)methyl)-5-(tert-butyl)piperidine-3-carboxylate (60 mg), phenylboronic acid (20 mg), $Pd(PPh_3)_4$ (8 mg), and K_3PO_4 (40 mg) in 1,4-dioxane-water (1:1, 1 mL) was stirred at 50°C under N_2 for 2 h and at 60°C for 2 h.

The mixture was cooled to r.t., then diluted with sat.$NaHCO_3$ aq., extracted with EtOAc, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, hexane/AcOEt) to give the desired product (59 mg).

[0214] Reference Example 3: Synthesis of methyl (3R,5S)-1-[(5-bromofuro[2,3-b]pyridin-2-yl)methyl]-5-tert-butylpiperidine-3-carboxylate

A suspension of 5-bromofuro[2,3-b]pyridine-2-carbaldehyde (360 mg), methyl (3R,5S)-5-(tert-butyl)piperidine-3-carboxylate hydrochloride (413 mg) and $NaBH(OAc)_3$ (506 mg) in DCE (10 mL) was stirred at 0°C under N_2 for 4 h. The mixture was diluted with sat. $NaHCO_3$ aq., extracted with EtOAc, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/AcOEt) to give the desired product (275 mg).

[0215] Reference Example 6: Synthesis of methyl (3R,5S)-1-[(5-bromofuro[2,3-b]pyridin-2-yl)methyl]-5-tert-butylpiperidine-3-carboxylate

Cs_2CO_3 (2.47 g) was added portionwise to a stirred solution of (3R,5S)-1-((benzyloxy)carbonyl)-5-(tert-butyl)piperidine-3-carboxylic acid (22.0 g) in anhydrous DMF (65.0 mL). Benzyl bromide (11.0 mL) was added as a gentle stream with ice cooling. On complete addition the mixture stirred at r.t. for 2 h. The mixture was diluted with EtOAc and washed with water, brine, dried over $MgSO_4$ and the solvent evaporated. The residue was purified by silica gel column chromatography (EtOAc/cyclohexane) to afford the desired product (22.3 g).

[0216] Reference Example 14: Synthesis of methyl (3R,5S)-5-tert-butyl-1-(4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-ylmethyl)piperidine-3-carboxylate

To a solution of tert-butyl 2-(((3S,5R)-3-(tert-butyl)-5-(methoxycarbonyl)piperidin-1-yl)methyl)-6,7-dihydrothieno[3,2-c]pyridine-5(4H)-carboxylate (372 mg) in DCM (6 mL) was added TFA (1.5 mL) at 0°C and stirred at r.t. for 5 h. The mixture was diluted with sat. $NaHCO_3$ aq., extracted with EtOAc, dried over Na_2SO_4, filtered and concentrated to give the desired product (282 mg).

[0217] Reference Example 15: Synthesis of tert-butyl 2-[[(3S,5R)-3-tert-butyl-5-methoxycarbonylpiperidin-1-yl]methyl]-6,7-dihydro-4H-thieno[3,2-c]pyridine-5-carboxylate

A suspension of tert-butyl 2-formyl-6,7-dihydrothieno[3,2-c]pyridine-5(4H)-carboxylate (270 mg), methyl (3R,5S)-5-(tert-butyl)piperidine-3-carboxylate

(2R,3R)-2,3-bis((4-methylbenzoyl)oxy)succinate (591 mg) and $NaBH(OAc)_3$ (321 mg) in DMF (5 mL) was stirred at 0°C to r.t. overnight. The mixture was diluted with sat. $NaHCO_3$ aq., extracted with EtOAc, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/AcOEt) to give the desired product (275 mg).

[0218] Reference Example 17: Synthesis of methyl (3R,5S)-5-tert-butyl-1-[(5-phenylfuro[2,3-c]pyridin-2-yl)methyl]piperidine-3-carboxylate

A suspension of methyl (3R,5S)-5-(tert-butyl)-1-((5-chlorofuro[2,3-c]pyridin-2-yl)methyl)piperidine-3-carboxylate (100 mg), Phenylboronic acid (37 mg), $Pd(PPh_3)_4$ (16 mg) and K_3PO_4 (76 mg) in 1,4-dioxane:water (2:1, 2 mL) was stirred at 90°C under N_2 for 7 h. The mixture was cooled to r.t., then diluted with sat. $NaHCO_3$ aq., extracted with EtOAc, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/AcOEt) to give the desired product (80 mg).

[0219] Reference Example 18: Synthesis of methyl (3R,5S)-5-tert-butyl-1-[(5-chlorofuro[2,3-c]pyridin-2-yl)methyl]piperidine-3-carboxylate

A suspension of 5-chlorofuro[2,3-c]pyridine-2-carbaldehyde (276 mg), methyl (3R,5S)-5-(tert-butyl)piperidine-3-carboxylate (2R,3R)-2,3-bis((4-methylbenzoyl)oxy)succinate (979 mg) and $NaBH(OAc)_3$ (419 mg) in DMF (10 mL) was stirred at 0°C to r.t. overnight. The mixture was diluted with sat. $NaHCO_3$ aq., extracted with EtOAc, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/AcOEt) to give the desired product (435 mg).

[0220] Reference Example 21: Synthesis of methyl (3R,5S)-5-tert-butyl-1-[(2-methyl-4-phenylthieno[2,3-d]pyrimidin-6-yl)methyl]piperidine-3-carboxylate

To a solution of 2-methyl-4-phenylthieno[2,3-d]pyrimidine-6-carbaldehyde (91 mg) and (2R,3R)-2,3-bis[(4-methylbenzoyl)oxy]butanedioic acid;methyl (3R,5S)-5-tert-butylpiperidine-3-carboxylate (210 mg) in DMF (3 mL) was added $NaBH(OAc)_3$ (99 mg) and stirred overnight. The reaction mixture was quenched with sat. $NaHCO_3$ aq. and extracted with AcOEt. The organic phase was dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography (AcOEt/Hexane) to give the desired product (275 mg).

[0221] Reference Example 26: Synthesis of methyl (3R,5S)-5-tert-butyl-1-[[5-(1,2-thiazol-3-yl)furo[2,3-b]pyridin-2-yl]methyl]piperidine-

3-carboxylate

A suspension of methyl (3R,5S)-1-[(5-bromofuro[2,3-b]pyridin-2-yl)methyl]-5-tert-butylpiperidine-3-carboxylate (200 mg), Bis(pinacolato)diboron (149 mg), $Pd(dppf)Cl_2$ (20 mg) and KOAc (96 mg) in 1,4-dioxane (2.5 mL) was stirred at 90°C under N2 for 3 h. 3-Bromoisothiazole (160 mg), K_3PO_4 (207 mg) and additional $PdCl_2(dppf)$ (20 mg) were added to the mixture and stirred at 90°C under N_2 for 4 h. The reaction mixture was cooled to r.t., diluted with sat. $NaHCO_3$ aq., extracted with EtOAc, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by amino silica gel column chromatography (hexane/AcOEt) to give the desired product (40 mg).

[0222] Reference Example 33: Synthesis of methyl (3R,5S)-5-tert-butyl-1-[(5,6-dichlorofuro[2,3-b]pyridin-2-yl)methyl]piperidine-3-carboxylate

To a mixture of methyl (3R,5S)-5-tert-butylpiperidine-3-carboxylate (6.44 g) and 5,6-dichlorofuro[2,3-b]pyridine-2-carbaldehyde (2.16 g) in DMF (15 mL) was added $NaBH(OAc)_3$ (2.97 g) at 0°C and the reaction was stirred at r.t. overnight. $NaHCO_3$ aq. was added and extracted with AcOEt, washed with water and brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by amino silica gel column chromatography (EtOAc/Hexane) to afford the desired product (3.20 g).

[0223] Reference Example 36: Synthesis of methyl (3R,5S)-5-tert-butyl-1-[(5-chloro-6-pyrrolidin-1-ylfuro[2,3-b]pyridin-2-yl)methyl]piperidine-3-carboxylate

A mixture of methyl (3R,5S)-5-tert-butyl-1-[(5,6-dichlorofuro[2,3-b]pyridin-2-yl)methyl]piperidine-3-carboxylate (153 mg), RuPhos Pd G3 (9.6 mg), pyrrolidine (0.16 mL) and Cs_2CO_3 (375 mg) in toluene (4 mL) was degassed, purged with N_2 and heated at 100°C overnight. The cooled mixture was purified by silica gel column chromatography (EtOAc/Hexane) to give the desired product (103 mg).

[0224] Reference Example 41: Synthesis of methyl (3R,5S)-5-tert-butyl-1-[(5-pyrimidin-2-yl-6,7-dihydro-4H-thieno[3,2-c]pyridin-2-yl)methyl]piperidine-3-carboxylate

To a solution of methyl (3R,5S)-5-(tert-butyl)-1-((4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)methyl)piperidine-3-carboxylate (250 mg) in toluene (5 mL) were added 2-bromopyrimidine (125 mg), $Pd(OAc)_2$ (8.25 mg), BINAP (35.1 mg), NaOtBu (77 mg). After stirring at 100°C for 1 h, to the reaction mixture was added 2-bromopyrimidine (125 mg), $Pd(OAc)_2$ (8.25 mg), BINAP (35.1 mg) and NaOtBu (77 mg). After stirring at 100°C for 1 h, the reaction mixture was cooled to r.t. and water was added, then extracted with AcOEt.

The organic phase was washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography (Hexane/AcOEt) to afford the desired product (209 mg).

[0225] Reference Example 49: Synthesis of methyl (3R,5S)-1-[(5-bromo-7-methylfuro[2,3-c]pyridin-2-yl)methyl]-5-tert-butylpiperidine-3-carboxylate

To a mixture of 5-bromo-7-methylfuro[2,3-c]pyridine-2-carbaldehyde (0.277 g) and (2R,3R)-2,3-bis[(4-methylbenzoyl)oxy]butanedioic acid;methyl (3R,5S)-5-tert-butylpiperidine-3-carboxylate (0.675 g) in DMF (12 mL) was added $NaBH(OAc)_3$ (0.318 g) at 0°C. The mixture was stirred at r.t. for 14 h. The reaction was quenched with $NaHCO_3$ aq. and extracted with AcOEt. The organic phase was washed with water and brine, and dried over Na_2SO_4. The organic phase was concentrated and the residue was purified by silica gel column chromatography (AcOEt/Hexane) to give the desired product (191 mg).

[0226] Reference Example 71: Synthesis of methyl (3R,5S)-5-tert-butyl-1-[[(1S,8R)-5-thia-11-azatricyclo[6.2.1.02,6]undeca-2(6),3-dien-4-yl]methyl]piperidine-3-carboxylate;2,2,2-trifluoroacetic acid

To a solution of tert-butyl (1S,8R)-4-[[(3S,5R)-3-tert-butyl-5-methoxycarbonylpiperidin-1-yl]methyl]-5-thia-12-azatricyclo[6.3.1.02,6]dodeca-2(6),3-diene-12-carboxylate (3.87 g) in DCM (30 mL) was added TFA (3.13 mL) at 0°C. The mixture was stirred at 0°C for 2 h. The mixture was diluted with sat. $NaHCO_3$ aq., extracted with EtOAc, dried over Na_2SO_4, filtered and concentrated to give the desired product (4.09 g).

[0227] Reference Example 72: Synthesis of tert-butyl (1S,8R)-4-[[(3S,5R)-3-tert-butyl-5-methoxycarbonylpiperidin-1-yl]methyl]-5-thia-11-azatricyclo[6.2.1.02,6]undeca-2(6),3-diene-11-carboxylate

A suspension of tert-butyl (1S,8R)-4-formyl-5-thia-11-azatricyclo[6.2.1.02,6]undeca-2(6),3-diene-11-carboxylate (8.92 g), methyl (3R,5S)-5-(tert-butyl)piperidine-3-carboxylate (2R,3R)-2,3-bis((4-methylbenzoyl)oxy)succinate (17.8 g) and $NaBH(OAc)_3$ (8.38 g) in DMF (100 mL) was stirred at 0°C for 2 h and at r.t. for 4 h. The mixture was diluted with sat. $NaHCO_3$ aq., extracted with EtOAc, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/AcOEt) to give the desired product (3.87 g).

[0228] Reference Example 76: Synthesis of methyl (3R,5S)-5-tert-butyl-1-[[(1S,8R)-11-(4-methoxy-2-pyridinyl)-5-thia-11-azatricyclo[6.2.1.0^{2,6}]undeca-2(6),3-dien-4-yl]methyl]piperidine-3-carboxylate

A mixture of methyl (3R,5S)-5-tert-butyl-1-[[(1S,8R)-5-thia-11-azatricyclo[6.2.1.0^{2,6}

]undeca-2(6),3-dien-4-yl]methyl]piperidine-3-carboxylate; 2,2,2-trifluoroacetic acid (200 mg), Pd-PEPPSI IPent (32 mg), 2-chloro-4-methoxypyridine (0.093 mL) and Cs_2CO_3 (664 mg) in DME (2.5 mL) was degassed, purged with N_2 and heated at 100°C overnight. The cooled mixture was purified by silica gel column chromatography (EtOAc/Hexane) to give the desired product (125 mg).

[0229] Reference Example 89: Synthesis of methyl (3R,5S)-5-tert-butyl-1-[[5-[4-(dimethylamino)-2-pyridinyl]-6,7-dihydro-4H-thieno[3,2-c]pyridin-2-yl]methyl]piperidine-3-carboxylate

A round-bottom flask placed with methyl (3R,5S)-5-(tert-butyl)-1-((4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)methyl)piperidine-3-carboxylate (310 mg), Pd-PEPPSI IPent (65.1 mg), Cs_2CO_3 (1.34 g), and 2-chloro-N,N-dimethylpyridin-4-amine (258 mg), was evacuated and backfilled with N_2. DME (6 mL) was added and the reaction mixture was stirred under reflux for 21 h. After cooling, sat. NH_4Cl aq. was added and extracted with AcOEt. The organic phase was washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel column chromatography (AcOEt/Hexane) followed by GPC ($CHCl_3$) to give the desired product (220 mg).

[0230] Reference Example 94: Synthesis of 1-(5-bromofuro[2,3-b]pyridin-2-yl)ethan-1-ol

A suspension of 5-bromo-3-iodopyridin-2-ol (6.7 g), DIPEA (20.0 mL), but-3-yn-2-ol (2.5 mL), $PdCl_2(PPh_3)_2$ (1.1 g) and CuI (0.250 g) in DMF (50.0 mL) was stirred at 45°C under N_2 overnight.

The reaction was quenched with $NaHCO_3$ and extracted with EtOAc. The organic phase was washed with $NaHCO_3$ and brine and then concentrated in vacuo. The crude material was purified by silica gel column chromatography (EtAOc/heptane) to give the desired product (3.3 g).

[0231] Reference Example 100: Synthesis of methyl (3R,5S)-1-[[5-(2,1-benzothiazol-4-yl)-7-methylfuro[2,3-c]pyridin-2-yl]methyl]-5-tert-butylpiperidine-3-carboxylate

A mixture of methyl (3R,5S)-1-[(5-bromo-7-methylfuro[2,3-c]pyridin-2-yl)methyl]-5-tert-butylpiperidine-3-carboxylate (125 mg), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,1-benzothiazole (77 mg), $Pd(dppf)Cl_2$_DCM (12.0 mg), K_3PO_4 (125 mg) in 1,4-Dioxane:water (4:1) (5 mL) was degassed, purged with Ar and heated at 70°C for 1.5 h. The reaction mixture was cooled and diluted with DCM. The organic phase was separated by phase separator and concentrated. The residue was purified by silica gel column chromatography (AcOEt/Hexane) to afford the desired product (106 mg).

[0232] Reference Example 129: Synthesis of methyl

(3S,5S)-5-tert-butyl-1-[(5,6-dimethyl-1H-pyrrolo[3,2-b]pyridin-2-yl)methyl]-3-propoxypiperidine-3-carboxylate

To a solution of 5,6-dimethyl-1H-pyrrolo[3,2-b]pyridine-2-carbaldehyde (81 mg) and methyl (3S,5S)-5-tert-butyl-3-propoxypiperidine-3-carboxylate (180 mg) in DCM (4 mL) cooled to 0°C were added AcOH (26.6 μL) and $NaBH(OAc)_3$ (246 mg), and the reaction mixture was stirred at rt for 3 h. sat. $NaHCO_3$ aq. was added, and the aqueous phase was extracted with AcOEt twice. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica (AcOEt/Hexane) to afford the desired product (178 mg).

[0233] Reference Example 130: Synthesis of methyl (3S,5S)-5-tert-butyl-1-[(7-chloro-5,6-dimethylpyrazolo[1,5-a]pyrimidin-2-yl)methyl]-3-propoxypiperidine-3-carboxylate

To a solution of 7-chloro-5,6-dimethylpyrazolo[1,5-a]pyrimidine-2-carbaldehyde (150 mg) and methyl (3S,5S)-5-tert-butyl-3-propoxypiperidine-3-carboxylate (221 mg) in DCM (4 mL) cooled to 0°C were added AcOH (41.0 μL) and $NaBH(OAc)_3$ (379 mg), and the reaction mixture was stirred at r.t. for 3 h. sat. $NaHCO_3$ aq. was added and extracted with AcOEt. The organic phase was washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel column chromatography (AcOEt/Hexane) to afford the desired product (243 mg).

[0234] Reference Example 140: Synthesis of (3R,5S)-5-tert-butyl-1-[[3-methyl-2-[[(2-methylpropan-2-yl)oxycarbonylamino]methyl]thieno[2,3-b]pyrazin-6-yl]methyl]-3-propylpiperidine-3-carboxylic acid

A mixture of (3R,5S)-5-tert-butyl-1-[(2-chloro-3-methylthieno[2,3-b]pyrazin-6-yl)methyl]-3-propyl piperidine-3-carboxylic acid (107 mg), potassium N-Boc-aminomethyltrifluoroborate (96 mg), XPhos Pd G3 (10 mg) and Cs_2CO_3 (247 mg) in 1,4-dioxane/water (9:1, 2 mL) was stirred at 100°C for 12 h. Water was added and extracted with AcOEt. The organic phase was washed with brine, dried over Na_2SO_4 filtered and concentrated. The residue was purified by silica gel column chromatography (hexane/AcOEt) to afford the desired product (45.9 mg).

[0235] Reference Example 141: Synthesis of 1-Benzyl 3-methyl (3R,5S)-3-allyl-5-(tert-butyl)piperidine-1,3-dicarboxylate

The reaction vessel was charged with 1-benzyl 3-methyl (3R,5S)-5-(tert-butyl)piperidine-1,3-dicarboxylate (173.0 g, 519 mmol) and 2-methyltetrahydrofuran (2.0 L). This solution was stirred whilst being cooled in a cardice-acetone bath at -73°C. 1 M potassium bis(trimethylsilyl)amide (700 mL, 700 mmol) in THF was added slowly. After completion of addition (-1 hour) the reaction

mixture was stirred at -70°C for 1 hour. To this cooled mixture was slowly added a solution of allyl bromide (67 mL, 778 mmol). After completion of addition stirring was continued at -70°C for 2.5 h and the reaction mixture was allowed to warm to room temperature slowly. Stirring was continued at room temperature overnight. sat. NH_4Cl aq. (600 mL) was then added slowly. On complete addition (10 min) the mixture was stirred for 20 min, diluted with water (300 mL) and the layers separated. The aqueous layer was extracted with EtOAc (2 x 300 mL) and the pooled organics dried ($MgSO_4$), filtered and evaporated. The residue was purified by chromatography on silica gel (EtOAc/cyclohexane) to afford the desired product (159.4 g).

[0236] Reference Example 142: Synthesis of 2,3-dimethylthieno[2,3-b]pyrazine-6-carbaldehyde

A mixture of (2,3-dimethylthieno[2,3-b]pyrazin-6-yl)methanol (713 mg), MnO_2 (1595 mg) in $CHCl_3$ (10 mL) was stirred at 50°C for 3 h. The mixture was filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/AcOEt) to give the desired product (605 mg).

[0237] Reference Example 146: Synthesis of 1-Benzyl 3-methyl (3S,5S)-5-(tert-butyl)-3-hydroxypiperidine-1,3-dicarboxylate

1 M KHMDS in THF (35 mL) was diluted with THF (220 mL) and cooled to -78°C under an inert atmosphere. To this solution was added a solution of 1-benzyl 3-methyl (3R,5S)-5-(tert-butyl)piperidine-1,3-dicarboxylate (8.17 g) in THF (180 mL) over 35 min and the reaction mixture was stirred at -78°C for 75 min. A solution of 2-(benzenesulfonyl)-3-phenyl-oxaziridine (9.156 g) in THF (150 mL) was added dropwise at -78°C and the reaction mixture was stirred at -78°C for 70 min. The reaction mixture was quenched with a sat. NH_4Cl solution and allowed to warm to r.t.. The reaction was diluted with EtOAc and water and the two phases were separated. The aqueous phase was extracted with EtOAc. The combined organic phases were filtered through a hydrophobic frit and the solvent was concentrated in vacuo. The residue was purified by silica gel column chromatography (EtOAc/cyclohexane) to afford the desired product (7.45 g).

[0238] Reference Example 149: Synthesis of 2-methyl-4-phenylthieno[2,3-d]pyrimidine-6-carbaldehyde

To a solution of 2-methyl-6-[(E)-oct-1-enyl]-4-phenylthieno[2,3-d]pyrimidine (806 mg) in 1,4-Dioxane-water (3:1) (20 mL) were added 2,6-lutidine (570 μL) and OsO_4 (immobilized catalyst 1) (435 mg) and stirred at 0°C. Sodium periodate (2051 mg) was added to the reaction mixture and stirred at r.t. for 2h. The reaction mixture was quenched with DCM/water and sat. $NaHCO_3$ aq. and then extracted with DCM. The organic phase was dried over Na_2SO_4 and concentrated. The crude product was purified by silica gel column chromatography (AcOEt/Hexane) to give the desired

product (445 mg).

[0239] Reference Example 151: Synthesis of 7-chloro-5,6-dimethylpyrazolo[1,5-a]pyrimidine-2-carbaldehyde

To a solution of ethyl 7-chloro-5,6-dimethylpyrazolo[1,5-a]pyrimidine-2-carboxylate (500 mg) in THF (15 mL) cooled to 0°C was added a solution of lithium diisobutyl-tert-butoxyaluminum. The reaction mixture was stirred at 0°C for 2 h. The reaction was quenched with 1M HCl, and basified with sat. $NaHCO_3$ aq. and extracted with DCM. The organic phase was washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was dissolved in DCM (15 mL) and cooled to 0°C. DMP (1.00 g) was added and the reaction mixture was gradually warmed to r.t. and stirred overnight. 0.5M $Na_2S_2O_3$ aq. and sat. $NaHCO_3$ aq. were added and extracted with DCM. The organic phase was dried over Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel column chromatography (AcOEt/Hexane) to afford the desired product (283 mg).

[0240] Reference Example 157: Synthesis of 3-cyclopropyl-2-methylthieno[2,3-b]pyrazine-6-carbaldehyde

To a solution of 3-cyclopropyl-2-methylthieno[2,3-b]pyrazin-6-yl)methanol (357 mg) in DCM (20 mL) was added DMP (722 mg) at 0°C. The reaction mixture was allowed to warm to r.t. and stirred for 30 min. The reaction mixture was poured on to mixed solution of sat. $NaHCO_3$ aq. and DCM and stirred for a while. The mixture was extracted with DCM, dried over Na_2SO_4 and concentrated to the desired product (361 mg).

[0241] Reference Example 159: Synthesis of 5,6-dichlorofuro[2,3-b]pyridine-2-carbaldehyde

A solution of (5,6-dichlorofuro[2,3-b]pyridin-2-yl)methanol (83 mg) in anhydrous DCM (5 mL) was treated portion wise over 5 min with Dess-Martin periodinane (178 mg) and the mixture stirred at r.t. for 1 h. The reaction mixture was concentrated in vacuo and the residue purified by column chromatography (SiO_2, EtOAc/Hexane) to afford 5,6-dichlorofuro[2,3-b]pyridine-2-carbaldehyde (60.5 mg).

[0242] Reference Example 163: Synthesis of 5-bromo-7-methylfuro[2,3-c]pyridine-2-carbaldehyde

A solution of (5-bromo-7-methylfuro[2,3-c]pyridin-2-yl)methanol (279 mg) in anhydrous DCM (12 mL) was treated portion wise over 5 min with Dess-Martin periodinane (538 mg) at 0°C and the mixture was stirred at r.t. for 3 h. The reaction mixture was diluted with AcOEt (40 mL). A mixture of sat. $NaHCO_3$ aq. solution (10 mL) and sat. $Na_2S_2O_3$ aq. (10 mL) was added and stirred for 30 min. The organic phase was extracted with AcOEt and washed with water and brine. The organic phase was dried over Na_2SO_4 and concentrated to give the desired product (297 mg).

[0243] Reference Example 164: Synthesis of tert-butyl (1S,8R)-4-formyl-5-thia-11-azatricyclo[6.2.1.$0^{2,6}$]undeca-2(6),3-diene-11-carboxylate

To a solution of tert-butyl (1S,8R)-4-(hydroxymethyl)-5-thia-11-azatricyclo[6.2.1.$0^{2,6}$]undeca-2(6),3-diene-11-carboxylate (102 mg) in DCM (2 mL) and water (6.2 mg) was added DMP (161 mg) at 0°C. After the mixture was stirred at 0°C for 1 h, the mixture was quenched with sat. $NaHCO_3$ aq, $Na_2S_2O_3$, extracted with AcOEt, dried over Na_2SO_4, concetrated to give the desired product (105 mg), which was used in the next reaction without further purification.

[0244] Reference Example 183: Synthesis of 5,6-dimethyl-1H-pyrrolo[3,2-b]pyridine-2-carbaldehyde

To a solution of (5,6-dimethyl-1H-pyrrolo[3,2-b]pyridin-2-yl)methanol (297 mg) in DCM (30 mL) cooled to 0°C was added DMP (1.13 g), and the reaction mixture was stirred at rt for 3 h. 0.5M $Na_2S_2O_3$ aq. and sat. $NaHCO_3$ aq. were added and extracted with AcOEt. The organic phase was washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel column chromatography (AcOEt/Hexane) to afford the desired product (165 mg).

[0245] Reference Example 186: Synthesis of 2-chloro-3-methylthieno[2,3-b]pyrazine-6-carbaldehyde

To a 1M THF solution of DIBAL (0.247 mL) was added a solution of N,2-dimethoxy-N,3-dimethylthieno[2,3-b]pyrazine-6-carboxamide (60 mg) in THF (2 mL) at -78°C, and the mixture was stirred at -20°C for 2 h. The reaction was quenched with Na_2SO_4-$10H_2O$ and the insoluble materials were removed by filtration. The organic phase was concentrated and the residue was purified by silica gel column chromatography (EtOAc/Hexane) to give the desired product (39 mg).

[0246] Reference Example 189: Synthesis of dibenzyl (3R,5S)-5-tert-butyl-3-prop-2-enylpiperidine-1,3-dicarboxylate

To a -78°C solution of dibenzyl (5S)-5-tert-butylpiperidine-1,3-dicarboxylate (54.6 g) in anhydrous THF (700 mL) under N_2 atmosphere was added 1M KHMDS (200 mL) dropwise. The reaction was stirred for 1 h then 3-Bromopropene (32.3 g) was added dropwise and continued to stir for another 1.5 h. The reaction mixture was allowed to warm to -40°C and quenched with sat. NH_4Cl aq.. The reaction was warmed to r.t. and EtOAc was added. The partitioned organic layer was set aside and the aqueous phase was extracted with EtOAc. The combined organics were then dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/hexane) to afford the desired product (58.8 g).

[0247] Reference Example 191: Synthesis of 3-methyl-2-(trifluoromethyl)-5H-pyrrolo[2,3-b]pyrazine-6-carbaldehyde

To a solution of [3-methyl-2-(trifluoromethyl)-5H-pyrrolo[2,3-b]pyrazin-6-yl]methanol (786 mg) in DCM (40 mL) cooled to 0°C was added DMP (2.27 g), and the reaction mixture was stirred at r.t. for 3 h. 0.5M $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$ were added and extracted with AcOEt. The organic phase was washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel column chromatography (AcOEt/Hexane) to afford the desired product (667 mg).

[0248] Reference Example 194: Synthesis of 2-[2-(dimethylamino)ethoxy]-3-methylthieno[2,3-b]pyrazine-6-carbaldehyde

A solution of [2-[2-(dimethylamino)ethoxy]-3-methylthieno[2,3-b]pyrazin-6-yl]methanol (110 mg) in anhydrous DCM (5 mL) was treated portion wise over 5 min with Dess-Martin periodinane (192 mg) at 0°C and the mixture was stirred at r.t. for 3 h. The reaction mixture was diluted with AcOEt (150 mL). A mixture of sat. $NaHCO_3$ aq. (50 mL) and sat. $Na_2S_2O_3$ aq. (50 mL) was added and stirred for 30 min. The organic phase was extracted with AcOEt and washed with water and brine. The organic phase was dried over Na_2SO_4 and concentrated to give the desired product (107 mg).

[0249] Reference Example 201: Synthesis of 2,3-dimethylfuro[2,3-b]pyrazine-6-carbaldehyde

To a solution of 2,3-dimethylfuro[2,3-b]pyrazin-6-yl)methanol (500 mg) in DCM (20 mL) was added Dess-Martin periodinane (1250 mg) at 0°C. The reaction mixture was allowed to warm to r.t. and stirred for 30 min. The reaction mixture was poured on to mixed solution of sat. $NaHCO_3$ aq. and DCM and stirred for a while. The mixture was extracted with DCM, dried over Na_2SO_4, filtered and concentrated to afford the desired product (440 mg).

[0250] Reference Example 208: Synthesis of 2-chloro-3-(trifluoromethyl)thieno[2,3-b]pyrazine-6-carbaldehyde

To a stirred solution of [2-chloro-3-(trifluoromethyl)thieno[2,3-b]pyrazin-6-yl]methanol (18.3 mg) and water (1.2 μL) in DCM (450 μL) was added Dess-Martin periodinane (31.8 mg) at 0°C, and the mixture was stirred at rt for 1 h. Additional Dess-Martin periodinane (43.3 mg) was added to the mixture, and the mixture was stirred at r.t. for 1 h. The reaction mixture was diluted with EtOAc, sat. $NaHCO_3$ aq. and sat. $Na_2S_2O_3$ aq. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to give the desired product (14.4 mg).

[0251] Reference Example 210: Synthesis of methyl (3R,5S)-5-tert-butylpiperidine-3-carboxylate

(2R,3R)-2,3-bis(4-methylbenzoyloxy)butanedioic acid methyl

(3R,5S)-5-tert-butylpiperidine-3-carboxylate (7.50 g, 12.8 mmol) was loaded onto an SCX-2 cartridge (70 g), which was washed with MeOH. The compound was released using 1M triethylamine in MeOH (200 mL) to give methyl (3R,5S)-5-(tert-butyl)piperidine-3-carboxylate as a free base. The procedure was repeated with another 7.5 g of 2,3-bis[(4-methylbenzoyl)oxy]butanedioic acid methyl (3R,5S)-5-tert-butylpiperidine-3-carboxylate. The two batches of methyl (3R,5S)-5-(tert-butyl)piperidine-3-carboxylate were combined to give the desired product (5.0 g).

[0252] Reference Example 211: Synthesis of (2R,3R)-2,3-bis[(4-methylbenzoyl)oxy]butanedioic acid;methyl (3R,5S)-5-tert-butylpiperidine-3-carboxylate

A suspension of methyl 5-tert-butylpiperidine-3-carboxylate (20 g, 0.1 mol) and di-p-toluoyl-L-tartaric acid (19.4 g, 0.05 mmol) in EtOH (100 mL) was stirred at 85°C for 1 hour and then at 55°C for 1 hour. EtOAc (100 mL) was added to the reaction mixture which was then allowed to cool to room temperature. The precipitate was collected by filtration, washed with EtOH and EtOAc and dried in vacuo to afford the desired product. (7.0 g).

[0253] Reference Example 212: Synthesis of 1-benzyl 3-methyl (3R,5S)-3-butyl-5-tert-butylpiperidine-1,3-dicarboxylate

1M KHMDS in THF (27.0 mL) in THF (120 mL) was cooled to -78°C under N2. To the solution was added a solution of 1-benzyl 3-methyl (3R,5S)-5-tert-butylpiperidine-1,3-dicarboxylate (6.00 g) in THF (30 mL) over 20 min and the reaction mixture was stirred at -78°C for 1 h. 1-Iodobutane (3.07 mL) in THF (30 mL) was added dropwise at -78°C over 10 min and the reaction mixture was stirred at -78°C for 30 min and at r.t. for 30 min. The reaction mixture was quenched with sat. NH_4Cl aq. (50 mL) and water (50 mL), and the aqueous phase was extracted with AcOEt. The organic phase was washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel column chromatography (Hexane/AcOEt) to afford the desired product (5.77 g).

[0254] Reference Example 216: Synthesis of (3R,5S)-5-(tert-Butyl)piperidine-3-carboxylic acid hydrochloride

Na_2CO_3 (17.6 g) was added portion wise over 2 min to a stirred mixture of (2R,3R)-2,3-bis(4-methylbenzoyloxy)butanedioic acid methyl (3R,5S)-5-tert-butylpiperidine-3-carboxylate (40.00 g) in EtOAc (550 mL) and water (550 mL). Over the course of 10 min full solution occurred. The layers were separated and the aqueous phase extracted with EtOAc. The pooled organic phases were dried over $MgSO_4$ and the solvent evaporated under reduced pressure to afford free base methyl (3R,5S)-5-(tert-butyl)piperidine-3-carboxylate (13.7 g). conc. HCl (80 mL) was

added to the free base and the mixture heated at 100°C with stirring for 3 h then allowed to cool and stir at r.t. overnight. The mixture was evaporated under reduced pressure to afford the desired product (15.4 g).

[0255] Reference Example 217: Synthesis of methyl (3S,5S)-5-tert-butyl-3-hydroxypiperidine-3-carboxylate

To a solution of 1-benzyl 3-methyl (3S,5S)-5-(tert-butyl)-3-hydroxypiperidine-1,3-dicarboxylate (6.62 g) in MeOH (150 mL) was added Pd/C (10%, 2.016 g) and ammonium formate (4.779 g). The reaction mixture was stirred at 60°C for 2 h. The reaction mixture was allowed to cool to r.t.. The reaction mixture was filtered through a pad of Celite, which was then washed with MeOH. The solvent was removed in vacuo to give a white solid. The residue was loaded onto an SCX-2 cartridge (70 g), which was washed with MeOH (200 mL). The compound was released using 1 M TEA in MeOH (200 mL) to give the desired product (3.29 g).

[0256] Reference Example 218: Synthesis of methyl (3S,5S)-5-tert-butyl-3-propoxypiperidine-3-carboxylate

TFA (7.7 mL) was added dropwise over 2 min to a stirred, r.t. solution of methyl (3S,5S)-5-(tert-butyl)-3-propoxy-1-tritylpiperidine-3-carboxylate (1.34 g) and water (0.40 mL) in DCM (60 mL) and the resultant bright yellow solution was stirred at r.t. for 30 min. The reaction was evaporated and the residue applied onto a SCX-2 cartridge as a solution in 1:1 MeOH:DCM (50 mL). The cartridge was washed with 1:1 MeOH:DCM (200 mL) and the product eluted with 10% TEA in MeOH (250 mL). The basic eluent was evaporated to yield the desired product (660 mg).

[0257] Reference Example 219: Synthesis of methyl (3R,5S)-5-tert-butyl-3-propylpiperidine-3-carboxylate

A stirred solution of 1-benzyl 3-methyl (3R,5S)-3-allyl-5-(tert-butyl)piperidine-1,3-dicarboxylate (80.7 g) in IMS (Industrial Methylated Spirits) (800 mL) was hydrogenated at room temperature and atmospheric pressure in the presence of Pd/C (10%, 5.00 g) for 108 h. The reaction mixture was filtered, and the filtrate evaporated to afford methyl (3R,5S)-5-(tert-butyl)-3-propylpiperidine-3-carboxylate (51.14 g).

[0258] Reference Example 220: Synthesis of (3R,5S)-5-tert-butyl-3-propylpiperidine-3-carboxylic acid;hydrochloride

A mixture of methyl (3R,5S)-5-(tert-butyl)-3-propylpiperidine-3-carboxylate (51.1 g, 212 mmol) and conc. HCl (800 mL, 9.20 mol) was heated at 100°C for 48 h. In a separate vessel a mixture of methyl (3R,5S)-5-(tert-butyl)-3-propylpiperidine-3-carboxylate (45.4 g, 188 mmol) and conc. HCl (800 mL, 9.20 mol) was heated at 100°C for 48 h. Both reaction mixtures were

combined and evaporated to afford the desired product (103.7 g).

[0259] Reference Example 221: Synthesis of (3R,5S)-5-Isopropyl-3-propylpiperidine-3-carboxylic acid hydrochloride

A stirred solution of methyl (3R,5S)-5-isopropyl-3-propylpiperidine-3-carboxylate (1.81 g) in 6 M HCl (10 mL) was heated at 100°C for 7 days. After cooling to r.t., the reaction mixture was evaporated under reduced pressure. Dioxane was added and evaporated and the resultant residue was triturated in 2% EtOH/EtOAc. The suspension was filtered and the obtained solid was dried in vacuo to afford the desired product (1.88 g).

[0260] Reference Example 222: Synthesis of Methyl (3R,5S)-5-isopropyl-3-propylpiperidine-3-carboxylate

A mixture of 1-benzyl 3-methyl (3R,5S)-3-allyl-5-isopropylpiperidine-1,3-dicarboxylate (3.42 g) and 10% Pd/C (600 mg) in EtOH (30 mL) under H_2 was stirred at r.t. for 8 h. After celite filtration, the residue was evaporated and dried in vacuo to afford the desired product (2.00 g).

[0261] Reference Example 224: Synthesis of (2R,3R)-2,3-Bis(4-methylbenzoyloxy)butanedioic acid methyl (3R,5S)-5-(propan-2-yl)piperidine-3-carboxylate

To a solution of methyl 5-(propan-2-yl)piperidine-3-carboxylate (52.0 g) in ethanol (425 mL) was added (-)-Di-1,4-O-toluoyl-L-tartaric acid (108 g) and the mixture was stirred 1.5 h at 90°C. The resultant clear solution was cooled to r.t. gradually. After 4 h, the precipitate was filtered and washed with a small amount of cold EtOH and dried in vacuo to give the desired product (36.3g).

[0262] Reference Example 228: Synthesis of (3R,5S)-5-tert-butyl-3-(4,4,4-trifluorobutyl)piperidine-3-carboxylic acid

A suspension of dibenzyl (3R,5S)-5-tert-butyl-3-(4,4,4-trifluorobutyl)piperidine-1,3-dicarboxylate (2.22 g) and Pd/C (0.500 g) in EtOH (40 mL) was stirred under H_2 at r.t. for 2 h. The reaction mixture was filtered through Celite, and the filtrate was concentrated and dried in vacuo to afford the desired product (1.17 g).

[0263] Reference Example 229: Synthesis of (3R,5S)-3-butyl-5-tert-butylpiperidine-3-carboxylic acid;hydrochloride

conc. HCl (100 mL) was added to methyl (3R,5S)-3-butyl-5-tert-butylpiperidine-3-carboxylate and stirred at 100°C for 20 h. The reaction was concentrated under reduced pressure with azeotropic removal of water using toluene and AcOEt. The residue was dried in vacuo at 60°C to afford the desired product.

[0264] Reference Example 230: Synthesis of methyl

(3R,5S)-3-butyl-5-tert-butylpiperidine-3-carboxylate

A suspension of 1-benzyl 3-methyl (3R,5S)-3-butyl-5-tert-butylpiperidine-1,3-dicarboxylate (5.77 g) and Pd/C (1.576 g) in EtOH (58 mL) was stirred under H_2 at r.t. for 7 h. The reaction mixture was filtered through Celite, and the filtrate was concentrated and dried in vacuo to afford the desired product.

[0265] Reference Example 231: Synthesis of (3R,5S)-5-tert-butyl-3-(3-methylbutyl)piperidine-3-carboxylic acid;hydrochloride

A mixture of methyl (3R,5S)-5-(tert-butyl)-3-isopentylpiperidine-3-carboxylate (500 mg) in conc. HCl (8.0 mL) was stirred at 100°C for 4 days. The reaction was concentrated in vacuo to afford the desired product (549 mg).

[0266] Reference Example 232: Synthesis of methyl (3R,5S)-5-tert-butyl-3-(3-methylbutyl)piperidine-3-carboxylate

Pd/C (10%, 673 mg) was added to a solution of 1-benzyl 3-methyl (3R,5S)-5-(tert-butyl)-3-(3-methylbut-2-en-1-yl)piperidine-1,3-dicarboxylate (2.54 g) in EtOH (100 mL). The reaction mixture was stirred at r.t. under H_2 for 18 h. The reaction mixture was filtered through Celite and the filtrate was concentrated to dryness to afford the desired product (1.58 g).

[0267] Reference Example 233: Synthesis of (3R,5S)-5-tert-butyl-3-propylpiperidine-3-carboxylic acid

To a solution of dibenzyl (3R,5S)-5-tert-butyl-3-prop-2-enylpiperidine-1,3-dicarboxylate (20 g) in EtOH (150 ml) was added Pd/C (5 g) and H_2 gas was charged. The mixture was stirried at r.t. for 6 h. The reaction was filtered through Celite and the filtrate was concentrated in vacuo. The product was triturated with Et_2O to give the desired product (8.9 g).

[0268] Reference Example 237: Synthesis of 2-methyl-6-[(E)-oct-1-enyl]-4-phenylthieno[2,3-d]pyrimidine

A mixture of 4-chloro-2-methyl-6-[(E)-oct-1-enyl]thieno[2,3-d]pyrimidine (740 mg), phenylboronic acid (612 mg), Pd(dppf)Cl_2_DCM (307 mg), K_3PO_4 (1065 mg) in 1,4-dioxane (20 mL) was degassed, purged with N_2 and heated at reflux for 2 h. The reaction mixture was cooled and diluted with AcOEt. Celite and SiO_2 were added to the mixture and the mixture was stirred and filtered through Celite. The filtrate was concentrated and the residue was purified by silica gel column chromatography (AcOEt/Hexane) to afford the desired product (806 mg).

[0269] Reference Example 238: Synthesis of 4-chloro-2-methyl-6-[(E)-oct-1-enyl]thieno[2,3-d]pyrimidine

A mixture of 6-bromo-4-chloro-2-methylthieno[2,3-d]pyrimidine (7 g), (E)-1-Octenylboronic acid pinacol ester (6.82 mL), Pd(PPh_3)$_4$ (2.61 g), K_2CO_3 (9.18 g)

in 1,4-dioxane:water (5:1) (240 mL) was degassed, purged with N_2 and heated at reflux for 5 h. The reaction mixture was cooled and 1M HCl (3.01 mL) was added to the mixture to adjust pH 7-8. The mixture was extracted with DCM and washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography (DCM/Hexane) to give the desired product (2.34 g).

[0270] Reference Example 239: Synthesis of (5,6-dichlorofuro[2,3-b]pyridin-2-yl)methanol

To a solution of tert-butyl-[(5,6-dichlorofuro[2,3-b]pyridin-2-yl)methoxy]-dimethylsilane (365 mg) in THF (5 mL) was added 1M TBAF in THF (2 mL) and the reaction was stirred at r.t. for 4 h. The reaction was quenched with Na_2CO_3 aq. and extracted with DCM. The organic phase was concentrated and the residue was purified by silica gel column chromatography (EtOAc/Hexane) to give the desired product (83 mg).

[0271] Reference Example 240: Synthesis of tert-butyl-[(5,6-dichlorofuro[2,3-b]pyridin-2-yl)methoxy]-dimethylsilane

A mixture of methyl 5,6-dichloro-3-iodo-1H-pyridin-2-one (431 mg), Pd(dppf)Cl_2 (109 mg), tert-butyldimethyl(2-propynyloxy)silane (329 mg), CuI (28.3 mg) and TEA (0.414 mL) in THF (2 mL) was degassed, purged with N_2 and heated at 70°C for 4 h. Insoluble materials were removed by filtration through celite washing with AcOEt. The organic phase was concentrated and the residue was purified by silica gel column chromatography (EtOAc/Hexane) to give the desired product (382 mg).

[0272] Reference Example 241: Synthesis of tert-butyl (1S,8R)-4-(hydroxymethyl)-5-thia-11-azatricyclo[6.2.1.$0^{2,6}$]undeca-2(6),3-diene-11-carboxylate

To a solution of 11-O-tert-butyl 4-O-methyl (1S,8R)-5-thia-11-azatricyclo[6.2.1.$0^{2,6}$]undeca-2(6),3-diene-4,11-dicarboxylate (7.19 g) in THF (100 mL) was added LAH (1.69 g) at 0°C. The mixture was stirred at 0°C for 1 h. The mixture was carefully quenched with Na_2SO_4-10H_2O and brine, diluted with EtOAc. A formed solid was removed off and washed with AcOEt. The filtrate was concentrated to give the desired product (6.92 g).

[0273] Reference Example 242: Synthesis of 11-O-tert-butyl 4-O-methyl (1S,8R)-5-thia-11-azatricyclo[6.2.1.$0^{2,6}$]undeca-2(6),3-diene-4,11-dicarboxylate

To a solution of methyl (1S,8R)-5-thia-11-azatricyclo[6.2.1.$0^{2,6}$]undeca-2(6),3-diene-4-carboxylate (5.0 g) and TEA (3.75 mL) in THF (100 mL) was added Boc_2O (4.89 g) at 0°C. The mixture was stirred at 0°C for 1 h. The mixture was diluted with sat. $NaHCO_3$ aq., extracted with EtOAc, dried over Na_2SO_4, filtered and concentrated to give the desired product (7.19 g).

[0274] Reference Example 243: Synthesis of methyl (1S,8R)-5-thia-11-azatricyclo[6.2.1.$0^{2,6}$]undeca-2(6),3-diene-4-carboxylate

Methyl rac-(1R,8S)-5-thia-11-azatricyclo[6.2.1.$0^{2,6}$]undeca-2(6),3-diene-4-carboxylate (44 g) was separated by chiral HPLC (column: CHIRALCEL OD-H (RG048) 4.6 mmID x 250 mmL, MP: Hexane/Ethanol = 750/250 (v/v), Temp.: 30°C, Det: UV220 nM). Earlier peak was the desired product (21.5 g).

[0275] Reference Example 244: Synthesis of methyl rac-(1R,8S)-5-thia-11-azatricyclo[6.2.1.$0^{2,6}$]undeca-2(6),3-diene-4-carboxylate

To a solution of 11-O-benzyl 4-O-methyl rac-(1R,8S)-5-thia-11-azatricyclo[6.2.1.$0^{2,6}$]undeca-2(6),3-diene-4,11-dicarboxylate (110 g) in MeCN (750 mL) was added iodotrimethylsilane (49.4 mL) at 0°C over 30 min. The mixture was stirred at 0°C for 1h. The mixture was diluted with hexane (400 mL) quenched with 1M HCl (400 mL) and water (300 mL), washed with hexane. The aqueous layer was basified by K_2CO_3 (55 g), extracted with AcOEt, dreid over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (amino silica, hexane/AcOEt) to give the desired product (43.8 g).

[0276] Reference Example 245: Synthesis of 11-O-benzyl 4-O-methyl rac-(1R,8S)-5-thia-11-azatricyclo[6.2.1.$0^{2,6}$]undeca-2(6),3-diene-4,11-dicarboxylate

$POCl_3$ (83 mL) was added to DMF (72 mL) dropwise carefully at 0°C over 30min. After stirring at 0°C for 1 h, a solution of N-Cbz-nortropinone (100 g) in DCM (100 mL) was added to the mixture at 0°C. The mixture was stirred at 50°C for 45 min. The reaction mixture was quenched with ice and water, extracted with Et_2O (500 mL x 2), washed with brine, dried over Na_2SO_4, filtrated and concentrated to give aldehyde intermediate (113 g, <80% purity). To a solution of the aldehyde in THF (550 mL) were added methyl thioglycollate (51.7 mL) and K_2CO_3 (160 g) and the mixture was refluxed for 2 h. The reaction mixture was quenched with sat. $NaHCO_3$ aq. and water, extracted with AcOEt (500 mL x 2), dried over Na_2SO_4, filtrated and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/AcOEt) to give the desired product (117 g).

[0277] Reference Example 246: Synthesis of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,1-benzothiazole

A mixture of 4-bromo-2,1-benzisothiazole (0.206 mg), Bpin (0.293 g), KOAc (0.188 g), Pd(dppf)Cl_2 (0.039 g) in 1,4-dioxane (10 mL) was stirred at 100°C for 1 h. Pd(dppf)Cl_2 was added and the mixture was stirred for 1.5 h. The reaction mixture was concentrated and the residue was purified by silica gel column chromatography (AcOEt/Hexane) to afford the desired product (155 mg).

[0278] Reference Example 247: Synthesis of (5-bromo-7-methylfuro[2,3-c]pyridin-2-yl)methanol

To a solution of (5-bromo-7-methylfuro[2,3-c]pyridin-2-yl)methoxy-tert-butyl-dimethylsilane (508 mg)

in THF (15 mL) was added 1M TBAF in THF (2.85 mL) at r.t.. The reaction mixture was stirred for 30 min and concentrated. The residue was purified by silica gel column chromatography (AcOEt / Hexane) to afford the desired product (279 mg).

[0279] Reference Example 248: Synthesis of (5-bromo-7-methylfuro[2,3-c]pyridin-2-yl)methoxy-tert-butyl-dimethylsilane

To a mixture of 6-bromo-4-iodo-2-methylpyridin-3-ol (500 mg), bis(triphenylphosphine)palladium (II) chloride (112 mg), CuI (30.3 mg), K_2CO_3 (440 mg) in 1,4-Dioxane (16 mL) was added tert-butyldimethyl(2-propynyloxy)silane (285 μl). The reaction mixture was heated to 70°C for 2 h. TEA and tert-butyldimethyl(2-propynyloxy)silane were added and the mixture was stirred at 70°C for 20 h. The reaction mixture was cooled and diluted with DCM and water. The organic phase was separated by phase separator and concentrated. The residue was purified by silica gel chromatography (AcOEt / Hexane) to afford (5-bromo-7-methylfuro[2,3-c]pyridin-2-yl)methoxy-tert-butyl-dimethylsilane (254 mg).

[0280] Reference Example 249: Synthesis of (5,6-dimethyl-1H-pyrrolo[3,2-b]pyridin-2-yl)methanol

To a solution of 5,6-dimethyl-2-(oxan-2-yloxymethyl)-1H-pyrrolo[3,2-b]pyridine (440 mg) in MeOH (50 mL) was added 5M HCl (2.2 mL) and the reaction mixture was stirred at r.t. for 4 h. 5M NaOH (2.2 mL) was added and the mixture was diluted with water, then extracted with AcOEt. The organic phase was washed with brine, dried over Na_2SO_4, filtered, concentrated and dried to afford the desired product (298 mg).

[0281] Reference Example 250: Synthesis of 5,6-dimethyl-2-(oxan-2-yloxymethyl)-1H-pyrrolo[3,2-b]pyridine

A round-bottom flask charged with 5-bromo-6-methyl-2-(oxan-2-yloxymethyl)-1H-pyrrolo[3,2-b]pyridine (835 mg), $MeB(OH)_2$ (2.3 g), KF (3729 mg, 64.2 mmol), PCy_3 HBF_4 (284 mg), and $Pd_2(dba)_3$ (235 mg) was evacuated and backfilled with N2, then 1,4-dioxane (25 mL) was added. The reaction was stirred at 100°C for 2 h. After cooling, water was added and extracted with AcOEt. The organic phase was washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel column chromatography (AcOEt/Hexane) to afford the desired product (440 mg).

[0282] Reference Example 251: Synthesis of 5-bromo-6-methyl-2-(oxan-2-yloxymethyl)-1H-pyrrolo[3,2-b]pyridine

To a solution of 6-bromo-5-methyl-2-[3-(oxan-2-yloxy)prop-1-ynyl]pyridin-3-amine (367 mg) in DMF (4 ml) was added KOtBu (253 mg), and the reaction mixture was stirred at r.t. for 2 h. sat. NH_4Cl aq. was added and extracted with AcOEt. The organic phase was washed with brine, dried over Na_2SO_4, filtered, and concentrated. The

residue was purified by silica gel column chromatography (AcOEt/Hexane) to afford the desired product (279 mg).

[0283] Reference Example 252: Synthesis of 6-bromo-5-methyl-2-[3-(oxan-2-yloxy)prop-1-ynyl]pyridin-3-amine

A round-bottom flask placed with 2,6-dibromo-5-methylpyridin-3-amine (770 mg), $Pd(PPh_3)_2Cl_2$ (102 mg), and CuI (55.1 mg) was evacuated and backfilled with N_2. 2-Prop-2-ynoxyoxane (487 mg) in THF (15 mL) and 1,1,3,3-Tetramethylguanidine (728 μL) were added, and the reaction mixture was stirred at 70°C for 3 h. The reaction was filtered through celite and concentrated. The residue was purified by silica gel column chromatography (AcOEt/Hexane) to afford the desired product (367 mg).

[0284] Reference Example 253: Synthesis of dibenzyl (3R,5S)-5-tert-butyl-3-(4,4,4-trifluorobutyl)piperidine-1,3-dicarboxylate

1M KHMDS in THF (7.33 mL) in THF (60 mL) was cooled to -78°C under N_2. To the solution was added a solution of dibenzyl (3R,5S)-5-(tert-butyl)piperidine-1,3-dicarboxylate (2.00 g) in THF (10 mL) dropwise and the reaction mixture was stirred at -78°C for 1h. 4,4,4-Trifluoro-1-iodobutane (1.74 g) in THF (10 mL) was added dropwise at -78°C and the reaction mixture was stirred at -78°C for 1 h and at r.t. for 1 h. The reaction mixture was quenched with sat. NH_4Cl aq. and the aqueous phase was extracted with AcOEt washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography (Hexane/AcOEt) to afforded the desired product (2.22 g).

[0285] Reference Example 254: Synthesis of (3-cyclopropyl-2-methylthieno[2,3-b]pyrazin-6-yl)methanol

To a solution of methyl 3-cyclopropyl-2-methylthieno[2,3-b]pyrazine-6-carboxylate (500 mg) in THF (25 mL) was added lithium tri-tert-butoxyaluminohydride (154 mg) at 0°C and the reaction mixture was allowed to warm to r.t. and stirred overnight. Na_2SO_4-$10H_2O$ and Na_2SO_4 were added to the reaction mixture at 0°C. After stirring for a while, the mixture was diluted with AcOEt and filtered through celite. The filtrate was concentrated and the residue was purified by silica gel column chromatography (DCM/AcOEt) to give the desired product (357 mg).

[0286] Reference Example 255: Synthesis of methyl 3-cyclopropyl-2-methylthieno[2,3-b]pyrazine-6-carboxylate

A mixture of methyl 2-chloro-3-cyclopropylthieno[2,3-b]pyrazine-6-carboxylate (1.64 g), dihydroxymethylborane (0.913 g), $Pd(dppf)Cl_2$_DCM (0.748 g), K_3PO_4 (3.24 g) in 1,4-dioxane (40 mL) was degassed, purged with argon and stirred under reflux overnight. The reaction mixture was cooled and diluted with AcOEt. Celite and SiO_2 were added to the mixture and was stirred and filtered through Celite. The filtrate was concentrated and the residue was purified by silica gel column chromatography

(AcOEt/Hexane) to afford the desired product (935 mg).

[0287] Reference Example 256: Synthesis of methyl 2-chloro-3-cyclopropylthieno[2,3-b]pyrazine-6-carboxylate

A mixture of methyl 3-cyclopropyl-2-oxo-1H-thieno[2,3-b]pyrazine-6-carboxylate (1.38 g) and $POCl_3$ (20 mL) was heated and stirred for 1 h. The reaction mixture was concentrated, diluted with DCM, and poured on to iced sat. $NaHCO_3$ aq.. The mixture was extracted with DCM and washed with sat. $NaHCO_3$ aq.. The organic phase was dried over Na_2SO_4, filtered and concentrated to give the desired product (1.64 g).

[0288] Reference Example 257: Synthesis of methyl 3-cyclopropyl-2-oxo-1H-thieno[2,3-b]pyrazine-6-carboxylate

To a solution of methyl 3-cyclopropyl-2-oxo-3,4-dihydro-1H-thieno[2,3-b]pyrazine-6-carboxylate (4.10 g) in THF (160 mL) was added MnO_2 (14.1 g) and the reaction mixture was stirred at r.t. for 30 min. The mixture was filtered through celite and washed with 1,4-dioxane. The filtrate was concentrated to give the desired product (1.39 g).

[0289] Reference Example 258: Synthesis of methyl 3-cyclopropyl-2-oxo-3,4-dihydro-1H-thieno[2,3-b]pyrazine-6-carboxylate

To a solution of methyl 5-[(1-cyclopropyl-2-methoxy-2-oxoethyl)amino]-4-nitrothiophene-2-carboxylate (3.56 g) in AcOH (70 mL) was added Zn (4.44 g). The reaction mixture was heated to 70°C and stirred for 2 h. The mixture was poured on to iced water (200 mL) and stirred for a while, then the suspension was filtered to give the desired product (4.0 g).

[0290] Reference Example 259: Synthesis of methyl 5-[(1-cyclopropyl-2-methoxy-2-oxoethyl)amino]-4-nitrothiophene-2-carboxylate

To a solution of 5-chloro-4-nitrothiophene-2-carboxylic acid methyl ester (3.5 g) in DMF (50 mL) were added methyl 2-amino-2-cyclopropaneacetate hydrochloride (2.88 g) and hunig's base (11.03 mL). The reaction mixture was heated to 70°C and stirred overnight. The reaction mixture was concentrated and the residue was extracted with AcOEt and washed with sat. $NaHCO_3$ aq.. The organic phase was dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography (AcOEt/Hexane) to give the desired product (3.56 g).

[0291] Reference Example 260: Synthesis of [3-methyl-2-(trifluoromethyl)-5H-pyrrolo[2,3-b]pyrazin-6-yl]methanol

A solution of [3-methyl-2-(trifluoromethyl)-5-(2-trimethylsilylethoxymethyl)pyrrolo[2,3-b]pyrazin-6-yl]methanol (1.23 g) in TFA (24 mL) was stirred at r.t. for 4 h. The solvent was evaporated azeotropically with toluene. The residue was dissolved in DMF (24 mL) and treated with 7M NH_3 in MeOH (36 mL), and the mixture was stirred at r.t. for 3 h.

The reaction was diluted with water and extracted with AcOEt. The organic phase was washed with brine, dried over Na_2SO_4, filtered, concentrated and dried to afford the desired product (786 mg).

[0292] Reference Example 261: Synthesis of [3-methyl-2-(trifluoromethyl)-5-(2-trimethylsilylethoxymethyl)pyrrolo[2,3-b]pyrazin-6-yl]methanol

To a solution of trimethyl-[2-[[3-methyl-6-(oxan-2-yloxymethyl)-2-(trifluoromethyl)pyrrolo[2,3-b]pyrazin-5-yl]methoxy]ethyl]silane (1.48 g) in MeOH (60 mL) was added 5M HCl (3 mL), and the reaction mixture was stirred at r.t. for 4 h. The reaction mixture was neutralized by adding 5M NaOH (3 mL), diluted with water, and the MeOH was removed by evaporation, then extracted with AcOEt. The organic phase was washed with brine, dried over Na_2SO_4, filtered, concentrated and dried to afford the desired product (1.23 g).

[0293] Reference Example 262: Synthesis of trimethyl-[2-[[3-methyl-6-(oxan-2-yloxymethyl)-2-(trifluoromethyl)pyrrolo[2,3-b]pyrazin-5-yl]methoxy]ethyl]silane

In a vessel, CuI (1.51 g) and KF (0.46 g) were heated with a burner under reduced pressure with shaking gently until a homogeneous greenish powder was obtained. After the addition of 2-[[2-iodo-3-methyl-6-(oxan-2-yloxymethyl)pyrrolo[2,3-b]pyrazin-5-yl]methoxy]ethyl-trimethylsilane (1.99 g) in NMP (10 mL) and $TMSCF_3$ (1.4 mL), the suspension was vigorously stirred at 80°C for 2 h. 30% NH_3 aq. was added and diluted with water, then extracted with AcOEt. The organic phase was washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel column chromatography (AcOEt/Hexane) to afford the desired product (1.48 g).

[0294] Reference Example 263: Synthesis of 2-[[2-iodo-3-methyl-6-(oxan-2-yloxymethyl)pyrrolo[2,3-b]pyrazin-5-yl]methoxy]ethyl-trimethylsilane

To a solution of 2-[[2-bromo-3-methyl-6-(oxan-2-yloxymethyl)pyrrolo[2,3-b]pyrazin-5-yl]methoxy]ethyl-trimethylsilane (1.84 g) in 1,4-dioxane (18 mL) were added CuI (0.230 g), NaI (3.02 g), and TMEDA (0.183 mL), and the reaction mixture was stirred at 110°C for 9 h. 30% NH_3 aq. was added and diluted with water, extracted with AcOEt. The organic phase was washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel column chromatography (AcOEt/Hexane) to afford the desired product (1.99 g).

[0295] Reference Example 264: Synthesis of

2-[[2-bromo-3-methyl-6-(oxan-2-yloxymethyl)pyrrolo[2,3-b]pyrazin-5-yl]methoxyleth yl-trimethylsilane

To a solution of 2-bromo-3-methyl-6-(oxan-2-yloxymethyl)-5H-pyrrolo[2,3-b]pyrazine (2.55 g) and TEA (10.9 mL) in DMF (25 mL) was added SEMCl (8.3 mL) and the reaction mixture was stirred at 50°C for 22 h. Water was added and extracted with AcOEt. The organic phase was washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel column chromatography (AcOEt/Hexane) to afford the desired product (1.84 g).

[0296] Reference Example 265: Synthesis of 2-bromo-3-methyl-6-(oxan-2-yloxymethyl)-5H-pyrrolo[2,3-b]pyrazine

To a solution of 5-bromo-6-methyl-3-[3-(oxan-2-yloxy)prop-1-ynyl]pyrazin-2-amine (2.23 g) in DMF (22 mL) was added KOtBu (1.53 g), and the reaction mixture was stirred at r.t. for 2 h. Sat. NH_4Cl aq. was added and extracted with AcOEt. The organic phase was washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel column chromatography (AcOEt/Hexane) to afford the desired product (1.18 g).

[0297] Reference Example 266: Synthesis of 5-bromo-6-methyl-3-[3-(oxan-2-yloxy)prop-1-ynyl]pyrazin-2-amine

A round-bottom flask placed with 3,5-dibromo-6-methylpyrazin-2-amine (220 mg), $Pd(PPh_3)_2Cl_2$ (28.9 mg), and CuI (15.7 mg) was evacuated and backfilled with N_2. 2-Prop-2-ynoxyoxane (139 mg) in THF (5 mL) and 1,1,3,3-tetramethylguanidine (207 μL) were added, and the reaction mixture was stirred at 70°C for 3 h. The reaction was filtered through celite and concentrated. The residue was purified by silica gel column chromatography (AcOEt/Hexane) to afford the desired product (199 mg).

[0298] Reference Example 267: Synthesis of [2-[2-(dimethylamino)ethoxy]-3-methylthieno[2,3-b]pyrazin-6-yl]methanol

A solution of methyl 2-[2-(dimethylamino)ethoxy]-3-methylthieno[2,3-b]pyrazine-6-carboxylate (19 g) in DCM (500 ml) was cooled to 0°C and treated dropwise with 1M DIBAL in THF (150 ml). The reaction mixture was stirred at 0°C for 30 min.. Acetone, Na_2SO_4-$10H_2O$ and Na_2SO_4 were added to the reaction mixture and allowed to warm to r.t.. AcOEt was added and stirred at r.t. for 17 h. The mixture was filtered through Celite and concentrated, dried in vacuo to give the desired product (15.3 g).

[0299] Reference Example 268: Synthesis of ethyl 2-[2-(dimethylamino)ethoxy]-3-methylthieno[2,3-b]pyrazine-6-carboxylate

In a 100 mL round-bottom flask, Cs_2CO_3 (7.62 g) was heated in vacuo to remove the residual H_2O. Ethyl 2-chloro-3-methylthieno[2,3-b]pyrazine-6-carboxylate (3.00 g), Pd

$_2$(dba)$_3$ (0.268 g), and BippyPhos (0.296 g) was evacuated and backfilled with N_2, and toluene (20 mL) was added. The mixture was stirred at 85°C for 20 min to activate the catalyst, then N,N-dimethylethanolamine (1.76 mL) was added. The reaction mixture was stirred at 85°C for 3 h. After cooling, a small amount of amino-functionalized silica gel was added, and the mixture was diluted with AcOEt. The mixture was filtered through a pad of amino-functionalized silica gel and the filtrate was concentrated. The residue was purified by amino silica gel column chromatography (AcOEt/Hexane) to afford the desired product (3.22 g).

[0300] Reference Example 269: Synthesis of (2-chloro-3-methylthieno[2,3-b]pyrazin-6-yl)methanol

To a suspension of ethyl 2-chloro-3-methylthieno[2,3-b]pyrazine-6-carboxylate (17.1 g) in DCM (110 ml) was added DIBAL (147 ml) at 0°C. The mixture was stirred at 0°C for 30 min. To the mixture were added acetone (30 ml), Na_2SO_4-10H_2O (23 g) and Na_2SO_4 (90 g), and warm up to rt. To the mixture were added AcOEt (150 ml) amd Celite (60 g) and stirred overnight, then filtered and concentrated to give the desired product (13.2 g).

[0301] Reference Example 270: Synthesis of [2-chloro-3-(trifluoromethyl)thieno[2,3-b]pyrazin-6-yl]methanol

To a stirred solution of ethyl 2-chloro-3-(trifluoromethyl)thieno[2,3-b]pyrazine-6-carboxylate (18.3 mg) in DCM (600 μL) was added DIBAL (1.0 M in DCM, 130 μL) at 0°C, and the mixture was stirred at 0°C for 15 min. After the mixture was warmed to r.t. for 10 min, the reaction was quenched with acetone at 0°C. Na_2SO_4-10H_2O, Na_2SO_4 and EtOAc were added to the mixture, and the mixture was stirred at r.t. for 1 h. The mixture was filtered through a pad of Celite, and the filtrate was concentrated under reduce pressure to give the desired product (15.8 mg).

[0302] Reference Example 271: Synthesis of ethyl 2-chloro-3-(trifluoromethyl)thieno[2,3-b]pyrazine-6-carboxylate

Phosphorus oxychloride (1 mL) was added to ethyl 2-oxo-3-(trifluoromethyl)-1H-thieno[2,3-b]pyrazine-6-carboxylate (367 mg) at 0°C, and the mixture was stirred at 100°C for 48 h. After the mixture was cooled to r.t., it was evaporated and diluted with sat. $NaHCO_3$ aq. The whole was extracted with DCM. The organic layer was washed with H_2O and brine, dried over Na_2SO_4, and concentrated under reduced pressure to give a residue, which was purified by silica gel column chromatography (Hexan/EtOAc) to give the desired product (117 mg).

[0303] Reference Example 272: Synthesis of ethyl 2-oxo-3-(trifluoromethyl)-1H-thieno[2,3-b]pyrazine-6-carboxylate

A mixture of Ethyl 1,2-dihydro-2-oxothieno[2,3-b]pyrazine-6-carboxylate (70.9 mg),

[bis(trifluoroacetoxy)iodo]benzene (272 mg) and Sodium trifluoromethanesulfinate (99 mg) in MeCN (3 mL) was stirred at r.t. for 20 min. The reaction was quenched with sat. $Na_2S_2O_3$ aq., extracted with EtOAc and the organic layer was washed with sat. $NaHCO_3$ aq. and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure.The residue was purified by silica gel column chromatography (Hexane/EtOAc) to give the desired product.

[0304] Reference Example 273: Synthesis of (2,3-dimethylfuro[2,3-b]pyrazin-6-yl)methanol

To a solution of tert-butyl-[(2,3-dimethylfuro[2,3-b]pyrazin-6-yl)methoxy]-dimethylsilane (1.85 g) in THF (30 ml) was added 1M TBAF (6.96 ml) at 0°C. The reaction mixture was allowed to warm to r.t. and stirred for 1 h. The reaction mixture was concentrated and the residue was purified by silica gel column chromatography (AcOEt/Hexane) to give the desired product (1.03 g).

[0305] Reference Example 274: Synthesis of tert-butyl-[(2,3-dimethylfuro[2,3-b]pyrazin-6-yl)methoxy]-dimethylsilane

A mixture of 3-bromo-5,6-dimethyl-2(1H)-pyrazinone (1.43 g), tert-butyldimethyl(2-propynyloxy)silane (1.623 ml), copper (I) iodide (0.134 g), $Pd(dppf)Cl_2$ (0.515 g) and TEA (1.963 ml) in 1,4-dioxane (40 mL) was degassed and purged with argon and stirred at 100°C overnight. The reaction mixture was cooled and diluted with AcOEt. The mixture was filtered through Celite and the filtrate was concentrated. The residue was purified by silica gel column chromatography (AcOEt/Hexane) to afford the desired product (1.86 g).

[0306] Reference Example 275: Synthesis of ethyl 2-chloro-3-methylthieno[2,3-b]pyrazine-6-carboxylate

A mixture of ethyl 3-methyl-2-oxo-1,2-dihydrothieno[2,3-b]pyrazine-6-carboxylate (26 g) and phosphoryl chloride (78 ml) was stirred at 100°C for 5 h. The mixture was poured into 3M AcONa aq. (3 L) and stirred overnight. The suspension was filtered and the solid was diluted with 20% MeOH/DCM, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the desired product (21.0 g).

[0307] Reference Example 276: Synthesis of ethyl 3-methyl-2-oxo-1H-thieno[2,3-b]pyrazine-6-carboxylate

A mixture of ethyl 3-methyl-2-oxo-1,2,3,4-tetrahydrothieno[2,3-b]pyrazine-6-carboxylate (26.4 g) and MnO_2 (47.8 g) in 1,4-dioxane (500 ml) was stirred at 70°C for 1 h. The mixture was filtered and concentrated under reduced pressure. The residue was triturated with IPE to give the desired product (19.6 g).

[0308] Reference Example 277: Synthesis of ethyl 3-methyl-2-oxo-3,4-dihydro-1H-thieno[2,3-b]pyrazine-6-carboxylate

To a suspension of ethyl 5-((1-methoxy-1-oxopropan-2-yl)amino)-4-nitrothiophene-2-carboxylate (33.2 g) in AcOH (300 ml) was carefully added Zinc dust (54.1 g) at r.t. and the mixture was stirred at 70°C for 3 h. The mixture was poured into ice water and stirred for 1 h. The suspension was filtered and the solid was wash with H_2O to give the desired product (60 g) which was used in the next reaction without further purification.

[0309] Reference Example 278: Synthesis of ethyl 5-[(1-methoxy-1-oxopropan-2-yl)amino]-4-nitrothiophene-2-carboxylate

A mixture of ethyl 5-chloro-4-nitrothiophene-2-carboxylate (30.4 g), DL-alanine methyl ester hydrochloride (19.8 g) and DIPEA (90 ml) in DMF (500 ml) was stirred at 50°C overnight. The mixture was poured into ice water and stirred for 1 h. The suspension was filtered and the solid was washed with H_2O to give the desired product (33.3 g).

[0310] Reference Example 279: Synthesis of (2,3-dimethylthieno[2,3-b]pyrazin-6-yl)methanol

To a suspension of $CaCl_2$ (272 mg) in EtOH (2.5 mL) cooled with an ice bath was added $NaBH_4$ (186 mg), and the mixture was stirred at r.t. for 30 min. To the mixture was added a suspension of ethyl 2,3-dimethylthieno[2,3-b]pyrazine-6-carboxylate (232 mg) in EtOH (2.5 mL) over 5 min and the reaction mixture was gradually warmed up to r.t. and stirred for 5 h. H_2O and sat. NH_4Cl aq. were added and stirred for 30min, then extracted with AcOEt. The organic phase was washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was triturated with AcOEt/Hexane, filtered and dried to afford the desired product (154 mg).

[0311] Reference Example 280: Synthesis of ethyl 4,5-diaminothiophene-2-carboxylate

To a solution of ethyl 5-amino-4-nitrothiophene-2-carboxylate (127 mg) in AcOH (2 mL) open to the air was added Zn (288 mg), and the reaction mixture was stirred at r.t. for 30 minutes. The reaction was diluted with AcOEt and the undissolved materials were filtered off through celite. The filtrate was concentrated, and dried to afford ethyl 4,5-diaminothiophene-2-carboxylate (109 mg).

[0312] Reference Example 281: Synthesis of ethyl 5-amino-4-nitrothiophene-2-carboxylate

To a solution of ethyl 5-chloro-4-nitrothiophene-2-carboxylate (500 mg) in EtOH (13 mL) was added 25% aqueous NH_3 (2.4 mL), and the reaction mixture was stirred at 60°C for 5 h. The solvent was concentrated by evaporation. Water was added, and the solids precipitated were collected by filtration to afford ethyl 5-amino-4-nitrothiophene-2-carboxylate (311 mg).

[0313] Reference Example 282: Synthesis of ethyl 2,3-dimethylthieno[2,3-b]pyrazine-6-carboxylate

To a solution of ethyl 4,5-diaminothiophene-2-carboxylate (268 mg) in EtOH (6 mL)

was added diacetyl (0.120 ml), and the reaction mixture was stirred at r.t. for 1 h. The solvent was concentrated by evaporation. Water and sat. $NaHCO_3$ aq. was added, and the aqueous phase was extracted with AcOEt three times. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel column chromatography (AcOEt/Hexane) to afford the desired product (257 mg).

[0314] Reference Example 283: Synthesis of methyl (3S,5S)-5-tert-butyl-1-[(2,3-dimethylquinoxalin-6-yl)methyl]-3-propoxypiperidine-3-carboxylate

To a mixture of methyl (3S,5S)-5-tert-butyl-3-propoxypiperidine-3-carboxylate (35.9 mg) and 2,3-dimethyl-6-quinoxalinecarboxaldehyde (26 mg) in DCM (1.5 mL) was added $NaBH(OAc)_3$ and stirred at r.t. for 18 h. Water was added and organic phase was separated by a phase separator, then concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane) to afford the desired product (46 mg).

[0315] Reference Example 284: Synthesis of 2-(chloromethyl)imidazo[1,2-b]cinnoline

1,3-Dichloropropan-2-one (4.9 g) was added to a solution of cinnolin-3-amine (4.5 g) in THF (100 mL). The reaction was stirred at 80°C for 2.5 h. Additional 1,3-dichloropropan-2-one (4.9 g) was added and the mixture was stirred at 80°C for 3 h. AcONa (9.7 g) was added to the reaction and the resulting mixture was stirred at 80°C for 1.5 h. The crude mixture was partitioned between EtOAc and Na_2CO_3 aq. and the aqueous phase was extracted with EtOAc. The organic phase was concentrated in vacuo and the residue was purified by silica gel column chromatography (EtOAc/hexane) to give the desired product (7.2 g).

[0316] Reference Example 285: Synthesis of methyl (3R,5S)-5-tert-butyl-1-({imidazo[1,2-b]cinnolin-2-yl}methyl)piperidine-3-carboxylate

2,3-Bis(4-methylbenzoyloxy)butanedioic acid; methyl (3R,5S)-5-tert-butylpiperidine-3-carboxylate (150.0 mg) was added to a suspension of 2-(chloromethyl)imidazo[1,2-b]cinnoline (70.0 mg) in MeCN (10 mL) followed by K_2CO_3 (140 mg). The reaction was stirred at 80°C for 24 h. The reaction mixture was partitioned between EtOAc and $NaHCO_3$ aq.. The organic phase was concentrated in vacuo and the residue was purified by silica gel column chromatography (EtOAc/petrol) to give the desired product (150 mg).

[0317] Reference Example 286: Synthesis of methyl (3R,5S)-1-{[5-({[(tert-butoxy)carbonyl]amino}amino)furo[2,3-b]pyridin-2-yl]methyl}-5-tert-butyl-3-propylpiperidine-3-carboxylate

A solution of methyl (3R,5S)-1-({5-bromofuro[2,3-b]pyridin-2-yl}methyl)-5-tert-butyl-3-propylpiperidine-3-carboxylate (241 mg), (tert-butoxy)carbohydrazide (85 mg), tBuXPhos (34 mg) and K

$_2CO_3$ (184 mg) in 1,4-dioxane (5.6 mL) was stirred at r.t. and degassed with N2 before adding $Pd_2(dba)_3$ (24 mg). The resulting mixture was stirred at 100°C for 5 h and then at r.t. for 15 h. (tert-butoxy)carbohydrazide (141 mg), tBuXPhos (34 mg), K_2CO_3 (184 mg) and $Pd_2(dba)_3$ (24 g) were added to the reaction mixture and stirring was continued to 4 h at 100°C. The reaction mixture was filtered through Celite, the filtrate was concentrated in vacuo and the residue was purified by silica gel column chromatography (EtOAc/hexane) to give the desired product (295 mg).

[0318] Reference Example 287: Synthesis of methyl (3R,5S)-5-tert-butyl-3-propyl-1-{[5-(1H-pyrazol-1-yl)furo[2,3-b]pyridin-2-yl]methyl} piperidine-3-carboxylate

Conc. HCl (0.43 mL) was added to a solution of methyl (3R,5S)-1-{[5-({[(tert-butoxy)carbonyl]amino}amino)furo[2,3-b]pyridin-2-yl]methyl} -5-tert-butyl-3-propylpiperidine-3-carboxylate (295 mg) and 1,1,3,3-tetramethoxypropane (0.427 mL) in MeOH (4.4 mL) and the resulting solution was stirred at 70°C for 1 h. The reaction was cooled to r.t., diluted with $NaHCO_3$ aq. (50 mL) and extracted with EtOAc (3 x 35 mL). The crude product was purified by silica gel column chromatography (heptane/EtOAc) to afford the desired product (152 mg).

[0319] Reference Example 288: Synthesis of methyl 2-methyl-4-oxo-3H-thieno[3,2-d]pyrimidine-6-carboxylate

A mixture of dimethyl 3-aminothiophene-2,5-dicarboxylate (500 mg) and MeCN (0.24 mL) in 4M HCl (5.0 mL) was stirred at 100°C for 6 h. The solvent was removed in vacuo and the solid was triturated in Et_2O to give the desired product (672 mg).

[0320] Reference Example 289: Synthesis of methyl 4-chloro-2-2methyl-thieno[3,2-d]pyrimidine-6-carboxylate

A mixture of methyl 2-methyl-4-oxo-3H-thieno[3,2-d]pyrimidine-6-carboxylate (100 mg) and phosphorous (V) oxychloride (0.12 mL) in MeCN (3 mL) was stirred at reflux for 18 h. The reaction was quenched with water and the precipitate was collected by filtration. The solid was washed with water and dried in vacuo to give the desired product (75 mg).

[0321] Reference Example 290: Synthesis of methyl 2-methylthieno[3,2-d]pyrimidine-6-carboxylate

A mixture of methyl 4-chloro-2-2methyl-thieno[3,2-d]pyrimidine-6-carboxylate (4.0 g), sodium formate (2.2 g) and $(PPh_3)_2PdCl_2$ (320 mg) in DMF (10 mL) was degassed with N_2 and stirred at 100°C for 2 h. The reaction mixture was partitioned between EtOAc and water. The organic phase was concentrated in vacuo and the residue was purified by silica gel column chromatography (EtOAc/DCM) to afford the desired product (1.45 g).

[0322] Reference Example 291: Synthesis of {2-methylthieno[3,2-d]pyrimidin-6-yl}methanol

DIBAL (1M in DCM, 7.7 mL) was added to a solution of methyl 2-methylthieno[3,2-d]pyrimidine-6-carboxylate (400 mg) in 2-methyltetrahydrofuran (10 mL) at -78°C. The resulting mixture was allowed to warm to -40°C and stirred for 1 h. The reaction mixture was quenched with Rochelle's salt and extracted with EtOAc. The organic phase was concentrated in vacuo to give the desired product (226 mg) which was used in the next step without further purification.

[0323] Reference Example 292: Synthesis of 2-methylthieno[3,2-d]pyrimidine-6-carbaldehyde

To a solution of {2-methylthieno[3,2-d]pyrimidin-6-yl}methanol (60.0 mg) in DCM (5 mL) was added Dess-Martin periodinane (60.0 mg) and the mixture was stirred at r.t. for 2 h. The reaction was partitioned between $NaHCO_3$ aq. and DCM and the organic phase was concentrated in vacuo to give the desired product (81.0 mg) which was used in the next step without further purification.

[0324] Reference Example 293: Synthesis of 1-benzyl 3-methyl (3R,5S)-5-(tert-butyl)piperidine-1,3-dicarboxylate

In a 3 L round bottom flask, N-(benzyloxycarbonyloxy)succinimide (270 g) was added in one portion to a stirred solution of methyl (3R,5S)-5-(tert-butyl)piperidine-3-carboxylate 2,3-bis((4-methylbenzoyl)oxy)succinate (530 g) and triethylamine (315 mL) in DCM (2750 mL). The solution was stirred at r.t. for 48 h. The reaction mixture was diluted with DCM, washed with sat. $NaHCO_3$, water and brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel pad (1.4 kg silica, EtOAc/cyclohexane) to afford the desired product (288 g).

[0325] Reference Example 294: Synthesis of 1-benzyl 3-methyl (3R,5S)-5-(tert-butyl)-3-(3-methylbut-2-en-1-yl)piperidine-1,3-dicarboxylate

1 M KHMDS (13 mL) in THF was added dropwise to a stirred solution of 1-benzyl 3-methyl (3R,5S)-5-(tert-butyl)piperidine-1,3-dicarboxylate (3.0 g) in anhydrous 2-methyltetrahydrofuran (45 mL) at -75°C. The reaction was stirred at -75°C for 1 h and then a solution of 3,3-dimethylallyl bromide (2.1 mL) was added dropwise. The mixture was stirred at -75°C for 1 h, and then at r.t. for 3 h. The reaction was quenched with NH_4Cl aq. and extracted with EtOAc. The organic phase was concentrated in vacuo and the residue was purified by silica gel column chromatography (cyclohexane/EtOAc) to give the desired product (2.34 g).

[0326] Reference Example 332: Synthesis of methyl (3R,5S)-5-tert-butyl-1-{1-[5-(1H-pyrazol-1-yl)furo[2,3-b]pyridin-2-yl]ethyl}piperidine-3-carboxylate (Isomer 2)

conc. HCl (0.56 mL) was added to a solution of methyl (3R,5S)-1-{1-[5-({[(tert-butoxy)carbonyl]amino}amino)furo[2,3-b]pyridin-2-yl]ethyl}-5-tert-butylpiperidine-3-carboxylate (371.0 mg) and 1,1,3,3-tetramethoxypropane (0.569 mL) in MeOH (8.5 mL). The resulting solution was stirred at 70°C for 2 h. The reaction mixture was poured onto $NaHCO_3$ and extracted into EtOAc. The organic phase was washed with $NaHCO_3$ and brine and concentrated in vacuo. The crude material was purified by column chromatography (SiO_2 EtOAc/DCM) to give the desired product as a diastereomer mixture. The mixture was separated by chiral SFC; Column Lux iA3 (21.2 mm x 250 mm, 5 μm), Mobile phase: 25% isocratic EtOH + 0.2% NH_3) to give the desired product as a single isomer (67 mg) in the 2nd fraction.

[0327] Reference Example 333: Synthesis of methyl (3R,5S)-1-{1-[5-({[(tert-butoxy)carbonyl]amino}amino)furo[2,3-b]pyridin-2-yl]ethyl}-5-tert-butylpiperidine-3-carboxylate

A solution of methyl (3R,5S)-1-(1-{5-bromofuro[2,3-b]pyridin-2-yl}ethyl)-5-tert-butylpiperidine-3-carboxylate (500 mg), Boc-hydrazine (187 mg), tBuXPhos (75.2 mg) and K_2CO_3 (408 mg) in 1,4-dioxane (12.4 mL) was stirred at r.t. and degassed with N2 before adding Pd_2dba_3 (54.1 mg). The resulting mixture was stirred at 100°C overnight. The reaction was diluted in water and extracted with EtOAc. The organic phase was concentrated in vacuo and purified by silica gel column chromatography (EtOAc/hexanes) to give the desired product (371 mg)

[0328] Reference Example 334: Synthesis of methyl (3R,5S)-1-(1-{5-bromofuro[2,3-b]pyridin-2-yl}ethyl)-5-tert-butylpiperidine-3-carboxylate

A solution of 5-bromo-2-(1-bromoethyl)furo[2,3-b]pyridine (2.77 g), 2,3-bis(4-methylbenzoyloxy)butanedioic acid; methyl (3R,5S)-5-tert-butylpiperidine-3-carboxylate (5.3 g) and K_2CO_3 (5.6 g) in DMF (40.0 mL) was stirred at 50°C for 1 h. The reaction was quenched with water and extracted with EtOAc. The organic phase was washed with $NaHCO_3$ and brine and then concentrated in vacuo. The cured material was purified by silica gel column chromatography (EtOAc/heptane) to give the desired product (2.3 g).

[0329] Reference Example 335: Synthesis of 5-bromo-2-(1-bromoethyl)furo[2,3-b]pyridine

To a solution of 1-{5-bromofuro[2,3-b]pyridin-2-yl}ethan-1-ol (2.8 g) in DCM (30.0 mL) was added CBr_4 (5.1 g) and PPh_3 (4.0 g) portion wise. The mixture was stirred at r.t. for 3 h. The reaction mixture was concentrated in vacuo and the crude material was purified by silica gel column chromatography (EtAOc/heptane) to give the desired product (2.8 g).

[0330] Reference Example 343: Synthesis of methyl

(3R,5S)-5-tert-butyl-1-[(1S)-1-{2,3-dimethylthieno[2,3-b]pyrazin-6-yl}ethyl]piperidine-3-carboxylate (Isomer 2)

2,3-Dimethylthieno[2,3-b]pyrazine-6-carboxylic acid (848 mg) and methyl (3R,5S)-5-(tert-butyl)piperidine-3-carboxylate (1055 mg) were dissolved in DCM (25 mL). To the solution were added TEA (2.83 mL) and T3P solution (50%, 3.63 mL) and stirred at r.t. for 4 h. Water was added and extracted with DCM, concentrated and the residue was purified by silica gel column chromatography (Hexane/AcOEt) to afford methyl (3R,5S)-5-(tert-butyl)-1-(2,3-dimethylthieno[2,3-b]pyrazine-6-carbonyl)piperidine-3-carboxylate (1.22 g). The product (500 mg) was dissolved in DCM (10 mL). To the solution were added carbonylchlorobis(triphenylphosphine)iridium(I) (50.1 mg) at r.t., followed by 1,1,3,3-tetramethyldisiloxane (0.681 mL) at 0°C dropwise. After 3 h, 1M dimethylzinc in heptane (2.56 mL) was added at 0°C dropwise. The temperature was allowed warm to r.t. and stirre overnight. sat. NH_4Cl aq. was added and extracted with DCM, concentrated in vacuo and purified by silica gel column chlomatography to afford the desired product as a diastereomer mixture (197 mg). The mixture was purified by SFC; Column YMC Cellulose (20 mm x 250 mm, 5 μm), Mobile phase: 10-90% gradient MeOH + 0.1% DEA) to give the desired product as a single isomer (68 mg) in the 2nd fraction.

[0331] Reference Example 362: Synthesis of (3S,5S)-5-tert-butyl-3-(1-fluoropropyl)piperidine-3-carboxylic acid

conc. HCl (10 mL) was added to a solution of 1-benzyl 3-methyl (3S,5S)-5-tert-butyl-3-(1-fluoropropyl)piperidine-1,3-dicarboxylate (52 mg) in THF (1mL) and the mixture was stirred at 120°C overnight. The reaction was concentrated in vacuo to give the desired product which was used in the next step without further purification (30 mg).

[0332] Reference Example 367: Synthesis of methyl (3S,5S)-5-(tert-butyl)-3-hydroxy-1-tritylpiperidine-3-carboxylate

Triethylamine (1.3 mL) was added to a stirred solution of methyl (3S,5S)-5-tert-butyl-3-hydroxy-piperidine-3-carboxylate (1.00 g) and trityl chloride (1.29 g) in anhydrous DCM (15 mL) was added at r.t.. The resultant solution was stirred at r.t. for 20 h. The reaction was quenched by addition of water, stirred for 15 min and the layers separated. The aqueous phase was extracted with DCM (30 mL), the organics combined, passed through a phase separation cartridge and the solvent evaporated. The residue was purified by silica gel column chromatography (EtOAc/cyclohexane) to afford the desired product (1.67 g).

[0333] Reference Example 372: Synthesis of methyl (3S,5S)-3-(allyloxy)-5-(tert-butyl)-1-tritylpiperidine-3-carboxylate

NaH (60%, 0.247 g) was added portion-wise to a stirred solution of methyl (3S,5S)-5-(tert-butyl)-3-hydroxy-1-tritylpiperidine-3-carboxylate (1.41 g) and allyl bromide (1.1 mL) in anhydrous DMF (25.0 mL) at r.t. under N_2. The reaction was stirred at r.t. for 2.5 h, then diluted with EtOAc (500 mL). The mixture was washed with water, 4% LiCl (100 mL), brine and the organics were evaporated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/cyclohexane) to afford the desired product (1.4 g).

[0334] Reference Example 373: Synthesis of methyl (3S,5S)-5-(tert-butyl)-3-propoxy-1-tritylpiperidine-3-carboxylate

Ammonium formate (1.06 g) was added to a stirred mixture of methyl (3S,5S)-3-(allyloxy)-5-(tert-butyl)-1-tritylpiperidine-3-carboxylate (1.40 g) and palladium (10%, 599 mg) in MeOH (80 mL) and the mixture was heated at 65°C for 3.5 h and then cooled. The mixture was filtered through celite, the filter pad washed with MeOH (50 mL) and the combined filtrate and washings evaporated to afford the desired product (1.34 g).

[0335] Reference Example 374: Synthesis of (3R,5S)-1-((benzyloxy)carbonyl)-5-(tert-butyl)piperidine-3-carboxylic acid

N-(Benzyloxycarbonyloxy)succinimide (18.6) was added to a suspension of (3R,5S)-5-(tert-butyl)piperidine-3-carboxylic acid hydrochloride (15.1 g) and $NaHCO_3$ (18.6 g) in acetonitrile (60 mL) and water (60 mL) and the reaction was stirred at r.t. for 4.5 h. The reaction was diluted with EtOAc and washed with NH_4Cl aq.. The organic phase was concentrated in vacuo to give the desired product (23.5 g) which was used in the next step without further purification.

[0336] Reference Example 375: Synthesis of Methyl (3R,5S)-5-tert-butyl-3-[3-(4,4-difluorocyclohexyl)propyl]-1-[(quinoxalin-6-yl)methyl] piperidine-3-carboxylate

$NaBH(OAc)_3$ (943 mg) was added to a solution of methyl (3R,5S)-5-tert-butyl-3-[3-(4,4-difluorocyclohexyl)propyl]piperidine-3-carboxylate (800 mg) and quinoxaline-6-carbaldehyde (422 mg) in DCE (40 mL) and the mixture was stirred at r.t. overnight. The reaction was quenched with sat. $NaHCO_3$ aq and extracted with DCM. The organic phase was concentrated in vacuo and the residue was purified by silica gel column chromatography (EtOAc/petrol) to give the desired product (900 mg).

[0337] Reference Example 376: Synthesis of Methyl (3R,5S)-5-tert-butyl-3-[3-(4,4-difluorocyclohexyl)propyl]piperidine-3-carboxylate

A suspension of 1-benzyl 3-methyl (3R,5S)-5-tert-butyl-3-[3-(4,4-difluorocyclohexyl)prop-2-en-1-yl]piperidine-1,3-dicarb oxylate (1.8 g) and Pd/C (10% w/w, 180 mg) in EtOH (20 mL) was stirred under H_2 at

r.t. for 3 h. The reaction was filtered through Celite and the filtrate was concentrated in vacuo to give the desired product (950 mg).

[0338] Reference Example 377: Synthesis of 1-Benzyl 3-methyl (3R,5S)-5-tert-butyl-3-[3-(4,4-difluorocyclohexyl)prop-2-en-1-yl]piperidine-1,3-dicarboxylate

KHMDS (1M in THF, 3.60 mL) was added to a solution of 1-benzyl 3-methyl (3R,5S)-5-tert-butylpiperidine-1,3-dicarboxylate (1.0 g) in THF (15.0 mL) at -70°C under N_2. The reaction as stirred for 20 min before adding a solution of 4-[3-bromoprop-1-en-1-yl]-1,1-difluorocyclohexane (789 mg) in THF (5 mL). The reaction was stirred for 1 h at -70°C. The reaction was quenched with NH_4Cl and extracted with EtOAc. The organic phase was concentrated in vacuo and the residue was purified by silica gel column chromatography (EtOAc/petrol) to give the desired product (1.27 g).

[0339] Reference Example 381: Synthesis of Methyl 5-(prop-1-en-2-yl)nicotinate

A mixture of methyl 5-bromonicotinate (50.5 g), isopropenylboronic acid pinacol ester (44.7 g), XPhos Pd G3 (0.570 g, 0.673 mmol) and K_3PO_4 (95 g) in THF:water (5:1, 700 mL) under N_2 was stirred at 60°C for 3 h. Isopropenylboronic acid pinacol ester (5.83 g) and XPhos Pd G3 (0.380 g) were added and the reaction was stirred at 70°C for 1 h. The reaction was quenched with water and extracted with EtOAc. The organic phase was concentrated and the residue was purified by silica gel column chromatography (EtOAc/hexane) to afford the desired product (47g).

[0340] Reference Example 382: Synthesis of Methyl 5-isopropylpiperidine-3-carboxylate

Platinum(IV) oxide (1.10 g) was added to a stirred solution of methyl 5-(prop-1-en-2-yl)nicotinate (12.96 g) in acetic acid (200 mL) under nitrogen. The nitrogen was replaced with hydrogen and the mixture was stirred at r.t. under atmospheric pressure for 48 h. The reaction was filtered through celite and evaporated to afford the desired product (20 g).

[0341] Reference Example 383: Synthesis of 1-Benzyl 3-methyl (3R,5S)-5-(propan-2-yl)piperidine-1,3-dicarboxylate

N-(Benzyloxycarbonyloxy)succinimide (3.81 g) was added in one portion to a stirred solution of (2R,3R)-2,3-bis(4-methylbenzoyloxy)butanedioic acid methyl (3R,5S)-5-(propan-2-yl)piperidine-3-carboxylate (7.00 g) and triethylamine (4.3 mL) in DCM (150 mL) at r.t. for 90 h. The reaction mixture was washed with sat $NaHCO_3$ (300 mL) and extracted with DCM (2 x 200 mL). The organic phase was concentrated and the residue was purified by silica gel column chromatography (Et_2O/cyclohexane) to give the desired product.

[0342] Reference Example 384: Synthesis of 1-Benzyl 3-methyl (3R,5S)-3-allyl-5-isopropylpiperidine-1,3-dicarboxylate

1 M KHMDS in THF (14 mL) in THF (70 mL) was cooled to -78°C under N_2. To the solution was added a solution of 1-benzyl 3-methyl (3R,5S)-5-isopropylpiperidine-1,3-dicarboxylate (3.44 g) in THF (70 mL) over 20 min and the reaction mixture was stirred at -78°C for 1.5 h. 3-Bromopropene (1.49 mL) in THF (30 mL) was added dropwise at -78°C over 10 min and the reaction mixture was stirred at -78°C for 1h. The reaction was allowed to warm to r.t. and quenched with sat. NH_4Cl aq., ten extracted with AcOEt. The organic phase was washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column chromatography (EtOAc/Hexane) to afford the desired product (3.43 g).

[0343] Reference Example 389: Synthesis of 1-benzyl 3-methyl (3S,5S)-5-tert-butyl-3-(1-fluoropropyl)piperidine-1,3-dicarboxylate

Diethylaminosulfur trifluoride (0.43 mL, 3.5 mmol) was added to a solution of 1-benzyl 3-methyl (3R,5S)-5-tert-butyl-3-(1-hydroxypropyl)piperidine-1,3-dicarboxylate (540 mg) in DCM (25 mL) at r.t.. The mixture was stirred overnight at r.t.. The reaction was quenched with $NaHCO_3$ and extracted with DCM. The organic phase was concentrated in vacuo and the residue was purified by silica gel column chromatography (EtOAc/isohexane) to give the desired product (290 mg).

[0344] Reference Example 390: Synthesis of 1-benzyl 3-methyl (3R,5S)-5-tert-butyl-3-(1-hydroxypropyl)piperidine-1,3-dicarboxylate

LiHMDS (2M in THF, 2.0 mL) was added to a solution of 1-benzyl 3-methyl (3R,5S)-5-tert-butylpiperidine-1,3-dicarboxylate (1.0 g) in THF (40 mL) at -78°C under N_2. After 1 h, a solution of propionaldehyde (0.4 mL) in THF (10 mL) was added to the mixture. The reaction was stirred at r.t. overnight. The reaction was quenched with NH_4Cl aq. and extracted with EtOAc. The organic phase was concentrated in vacuo and the residue was purified by silica gel column chromatography (EtOAc/isohexane) to give the desired product (549 mg).

[0345] Reference Example 395: Synthesis of rac-(3R,5S)-5-[1-[tert-butyl(dimethyl)silyl]oxy-2-methylpropan-2-yl]-1-[(2,3-dimethylthieno[2,3-b]pyrazin-6-yl)methyl]-3-propylpiperidine-3-carboxylic acid

To a mixture of rac-(3R,5S)-5-[1-[tert-butyl(dimethyl)silyl]oxy-2-methylpropan-2-yl]-3-propylpiperidine-3-carboxylic acid (146 mg) and 2,3-dimethylthieno[2,3-b]pyrazine-6-carbaldehyde (86 mg) in cyclopentyl methyl ether (3 ml) was added TEA (0.288 mL) and stirred at r.t.. After stirring for 15 min, to the mixture was added $NaBH(OAc)_3$ (217 mg) and stirred at r.t. for 6 h. The reaction mixture was diluted with H_2O at 0°C, and stirred for over night at r.t.. To the reaction mixture was added H_2O and EtOAc. The organic phase was seprated and washed with brine and dried over Na_2SO_4. Then organic phase was

filtered and concentrated under reduced pressure. The residue was purified by GPC (Gel Permeation Chromatography) using $CHCl_3$ and silica gel column chromatography (EtOAc/hexane) to afford the desired product (139 mg).

[0346] Reference Example 396: Synthesis of rac-(3R,5S)-5-[1-[tert-butyl(dimethyl)silyl]oxy-2-methylpropan-2-yl]-3-propylpiperidine-3-carboxylic acid

To a mixture of dibenzyl 5-[1-[tert-butyl(dimethyl)silyl]oxy-2-methylpropan-2-yl]-3-prop-2-enylpiperidine-1,3-dicarboxylate (6.6 g) in EtOH (130 mL) was added Pd/C (10%, wet, 1.35 g) in N_2 atmosphere. Then the reaction mixture atmosphere was exchanged by H_2 gas and stirred vigorously for 1h at r.t.. The reaction mixture was filtered through a pad of Celite, which was then washed with EtOH. The solvent was evaporated in vacuo to give a solid. Then, to the solid was added E_2O and n-hexane to give white solid. The prepicitated solid was filtered and washed with Et_2O and dried in vacuo to give the desired product (2.82 g). Then the filtrate was evaporated in vacuo to desired product (1.32 g).

[0347] Reference Example 397: Synthesis of dibenzyl dibenzyl 5-[1-[tert-butyl(dimethyl)silyl]oxy-2-methylpropan-2-yl]-3-prop-2-enylpiperidine-1,3-dicarboxylate

1M KHMDS in THF (20.6 mL) was cooled to -30°C under N_2. To the solution was added a solution of dibenzyl 5-[1-[tert-butyl(dimethyl)silyl]oxy-2-methylpropan-2-yl]piperidine-1,3-dicarboxylate (7.43 g) in THF (20 mL) over 10 min and the reaction mixture was stirred at -30°C for 30 min. Then, 3-bromopropene (2.38 mL) in THF (20 mL) was added dropwise at -30°C over 10 min and the reaction mixture was stirred at -30°C for 2h. The reaction was quenched with sat. NH_4Cl aq. at -30°C and allowed to warm to r.t.. Then the mixture was diluted H_2O and AcOEt, and separated organic phase. The organic phase was washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography (EtOAc/Hexane) twice to afford the desired product (6.61 g).

[0348] Reference Example 398: Synthesis of dibenzyl dibenzyl 5-[1-[tert-butyl(dimethyl)silyl]oxy-2-methylpropan-2-yl]piperidine-1,3-dicarboxylate

To a mixture of 5-[1-[tert-butyl(dimethyl)silyl]oxy-2-methylpropan-2-yl]-1-phenylmethoxycarbonylpiperidine-3-carboxylic acid (7.16 g) in DMF (90 mL) was added K_2CO_3 (2.77 g) and benzyl bromide (1.95 mL), and stirred at r.t.. After stirring for 3 days, to the mixture was added to H_2O and AcOEt at 0°C. The organic phase was seprated and washed with brine and dried over Na_2SO_4. Then organic phase was filtered and concentrated under

reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/hexane) to afford the desired product (7.72 g).

[0349] Reference Example 399: Synthesis of 5-[1-[tert-butyl(dimethyl)silyl]oxy-2-methylpropan-2-yl]-1-phenylmethoxycarbonylpiperidine-3-carboxylic acid

To a mixture of 1-O-benzyl 3-O-ethyl 5-[1-[tert-butyl(dimethyl)silyl]oxy-2-methylpropan-2-yl]piperidine-1,3-dicarboxylate (11.30 g) in THF (150 mL) was added potassium trimethylsilanolate (4.05 g) and stirred at r.t. After stirring for over night, to the mixture was added Potassium trimethylsilanolate (2.02 g) and stirred for 3 h at r.t.. To the mixture was added to 5N HCl (90 ml), and H_2O and AcOEt was added at 0°C and separated. The resulting water phase was extraced with AcOEt twice and all organic phase was gathered. The organic phase was dried over Na_2SO_4. Then organic phase was filtered and concentrated in vacuo to afford the desired product (9.30 g).

[0350] Reference Example 400: Synthesis of 1-O-benzyl 3-O-ethyl 5-[1-[tert-butyl(dimethyl)silyl]oxy-2-methylpropan-2-yl]piperidine-1,3-dicarboxylate

To a mixture of ethyl 5-[1-[tert-butyl(dimethyl)silyl]oxy-2-methylpropan-2-yl]piperidine-3-carboxylate (8.40 g) in DCM (175 mL) was added TEA (5.11 mL) and N-(benzyloxycarbonyloxy)succinimide (7.46 g) at 0°C, and stirred for 1 h at r.t.. To the mixture was added sat. $NaHCO_3$ and AcOEt at 0°C. The organic phase was separated and washed with brine and dried over Na_2SO_4. Then organic phase was filtered and concentrated in vacuo to crude mixture. The mixture was purified by silica gel columun chromatography (hexane/AcOEt) to give the desired product (10.91 g).

[0351] Reference Example 401: Synthesis of ethyl 5-[1-[tert-butyl(dimethyl)silyl]oxy-2-methylpropan-2-yl]piperidine-3-carboxylate

To a mixture of PtO_2 (0.267 g) in AcOH (150 mL) was added ethyl 5-[1-[tert-butyl(dimethyl)silyl]oxy-2-methylpropan-2-yl]pyridine-3-carboxylate (7.94 g) in AcOH (50 mL) under N_2. Then the reaction mixture atmosphere was exchanged by H_2 gas and stirred vigorously for 4h at r.t.. The reaction mixture was filtered through a pad of Celite, which was then washed with AcOEt. The solvent was evaporated in vacuo to give crude mixture. Then, to the mixture was added sat. $NaHCO_3$ and AcOEt, and the organic phase was separated. Then, the resulting H_2O phase was extracted with AcOEt twice and all organic phase were gathered. The organic phase was dried over Na_2SO_4 and filterd, and evaporated in vacuo to give the desired product (8.06 g).

[0352] Reference Example 402: Synthesis of ethyl 5-[1-[tert-butyl(dimethyl)silyl]oxy-2-methylpropan-2-yl]pyridine-3-carboxylate

To a mixture of [2-(5-bromo-3-pyridinyl)-2-methylpropoxy]-tert-butyl-dimethylsilane (8.43 g) in EtOH (200 mL) was added $Pd(dtbpf)Cl_2$ (1.00 g) and KOAc (7.21 g) at r.t. Then the reaction mixture atmosphere was exchaneged by carbon monooxide gas and stirred vigorously for over night at 70°C. The reaction mixture was cooled to r.t. and diluted with H_2O and AcOEt. The organic phase was separated and the resulting H_2O phase was AcOEt again. The obtained all organic phase was gathered and washed with brine and dried over Na_2SO_4. Then mixture was filetered and was evaporated in vacuo to give crude mixture. The crude mixture was purified by silica gel columun chromatography (hexane/AcOEt) twice to give the desired product (7.94 g).

[0353] Reference Example 403: Synthesis of [2-(5-bromo-3-pyridinyl)-2-methylpropoxy]-tert-butyl-dimethylsilane

To a mixture of 2-(5-bromopyridin-3-yl)-2-methylpropan-1-ol (5.92 g) in DCM (60 mL) were added DIPEA (6.74 mL) and t-butyldimethylsilyltrifluoromethanesulfonate (7.09 mL) at 0°C. The reaction mixture was stirred for 2h at r.t.. The reaction mixture was diluted with H_2O and AcOEt at 0°C. The mixture was separated to the organic phase and H_2O phase. The obtained H_2O phase was extracted with AcOEt twice. Then, all organic phase were gathered and washed with brine, and dried over Na_2SO_4. The organic phase was filterd and evaporated in vacuo. The crude mixture was purified by silica gel column chromatography (hexane/AcOEt) to give the desired product (7.97 g).

[0354] Reference Example 404: Synthesis of (2R,6S)-6-tert-butyl-2-propylmorpholine-2-carboxylic acid;hydrochloride

To a stirred solution of 2-O-benzyl 4-O-tert-butyl (2R,6S)-6-tert-butyl-2-prop-2-enylmorpholine-2,4-dicarboxylate (810 mg) in EtOH (6 mL) was added Pd/C (100 mg) at rt. H_2 gas was charged. The mixture was stirred at rt for 1 h. It was filtered through celite with EtOH. The filtrate was concentrated in vacuo. To the residue was added 1,4-dioxane (1 mL) and 4 M HCl-1,4-dioxane (6 mL). The mixture was stirred at rt for 30 min. It was concentrated with toluene to give the desired compound (520 mg).

[0355] Reference Example 405: Synthesis of 2-O-benzyl 4-O-tert-butyl (2R,6S)-6-tert-butyl-2-prop-2-enylmorpholine-2,4-dicarboxylate

To a solution of 2-O-benzyl 4-O-tert-butyl (2R,6S)-6-tert-butylmorpholine-2,4-dicarboxylate (1.35 g) in THF (20 mL) was added KHMDS (1M THF solution) (3.93 mL) at -78°C and it was stirred for 30 min. A solution of allyl bromide (0.464 mL) in THF (10 mL) was added and it was slowly warmed to 0°C for 3 h. It was stirred at 0°C for 30 min. It was quenched with water and sat. NH_4Claq at 0°C and extracted with AcOEt. The organic layer was washed with brine, dried over Na_2SO_4 and cencentrated in vacuo. The residue was purified by

column chromatography (hexane/AcOEt) to give the desired compound (1.19 g).

[0356] Reference Example 406: Synthesis of 2-O-benzyl 4-O-tert-butyl (2R,6S)-6-tert-butylmorpholine-2,4-dicarboxylate

To a suspension of (2R,6S)-6-tert-butyl-4-[(2-methylpropan-2-yl)oxycarbonyl]morpholine-2-carboxylic acid (1.54 g) and Cs_2CO_3 (2.095 g) in DMF (15 mL) was added benzyl bromide (0.669 mL) and the mixture was stirred at rt for 2 h. It was quenched with water and extracted with AcOEt. The organic layer was washed with water and brine, dried over Na_2SO_4 and cencentrated in vacuo. The residue was purified by column chromatography (hexane/AcOEt) to give the desired compound (1.99 g).

[0357] Reference Example 407: Synthesis of (2R,6S)-6-tert-butyl-4-[(2-methylpropan-2-yl)oxycarbonyl]morpholine-2-carboxylic acid

To a solution of ((2R,6S)-4-benzyl-6-(tert-butyl)morpholin-2-yl)methanol (2.80 g) in THF (50 ml) were added di-tert-butyl dicarbonate (2.69 mL) and Pd/C (2.00 g). H_2 gas was charged and the mixture was stirred at rt for 3 h. It was filtered with celite. The filtrate was concentrated in vacuo. To the residue were added DCM/H_2O(2:1) (45 mL), 2,2,6,6-Tetramethylpiperidinyloxy (0.498 g) and Iodobenzene diacetate (4.45 g) at 0°C. It was stirred at rt for 15 h. Iodobenzene diacetate (1.03 g) and 2,2,6,6-tetramethylpiperidinyloxy (0.100 g) were added and the mixture was stirred at rt for 1 h. It was quenched with sat. $Na_2S_2O_3$aq and extracted with DCM. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. To the residue was added 10% Na_2CO_3aq. and washed with AcOEt. The aqueous layer was acidified by 5 M HClaq. It was extracted with AcOEt. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The product was triturated with hexane to give the desired compound (1.54 g).

[0358] Reference Example 408: Synthesis of [(2R,6S)-4-benzyl-6-tert-butylmorpholin-2-yl]methanol

A mixture of (S)-2-(chloromethyl)oxirane (2.83 mL), 1-(benzylamino)-3,3-dimethylbutan-2-ol (5.00 g) and lithium perchlorate (2.57 g) in toluene (25 ml) was heated at 50°C for 2 h. It was quenched with water. It was extrated with AcOEt. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated in vacuo. It was dissolved to THF (100 mL) and KOtBu (4.87 g) was added at 0°C and the mixture was stirred at 0°C for 1 h. It was stirred at rt for 10 h. It was quenched with sat. NH_4Claq and water and extracted with AcOEt. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography (hexane/AcOEt) to give the desired compound (2.94 g).

[0359] Reference Example 409: Synthesis of methyl 5-(1-hydroxy-1-methyl-ethyl)piperidine-3-carboxylate acetate

A mixture of methyl 5-(1-hydroxy-1-methyl-ethyl)pyridine-3-carboxylate (1.4 g) and Pt_2O (1.92 g) in Acetic acid (23.9 mL) was stirred for 8 hours under atmospheric pressure of hydrogen at r.t.. The reaction mixture was filtered, washing with AcOEt and the solvent was evaporated under reduced pressure to afford the desired compound (1.8 g).

[0360] Reference Example 410: Synthesis of O1-benzyl O3-methyl 5-(1-hydroxy-1-methyl-ethyl)piperidine-1,3-dicarboxylate

Methyl 5-(1-hydroxy-1-methyl-ethyl)piperidine-3-carboxylate acetate (1.8 g) was dissolved in DCM (27.77 mL), then triethylamine (2.42 mL) and carbonic acid (2,5-dioxo-1-pyrrolidinyl) (phenylmethyl) ester (1.04 g) were added. The reaction solution was stirred at r.t. overnight. Water was added and extracted with DCM, dried over Na_2SO_4, filtered and concentrated. The residue was purified by FC C18 cartridge (60 G using a gradient from 3% to 60% of MeCN in water +0.1% HCOOH). To aqueous phase was added an aqueous saturated $NaHCO_3$ solution and extracted with AcOEt (x3), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford the desired compound (1.05 g).

[0361] Reference Example 411: Synthesis of O1-benzyl O3-methyl 5-(1-fluoro-1-methyl-ethyl)piperidine-1,3-dicarboxylate and

Reference Example 412: Synthesis of O1-benzyl O3-methyl 5-(1-fluoro-1-methyl-ethyl)piperidine-1,3-dicarboxylate

A mixture of O1-benzyl O3-methyl 5-(1-hydroxy-1-methyl-ethyl)piperidine-1,3-dicarboxylate (250 mg) and deoxofluor 1M solution in o-xylene (2.24 mL) in DCM (8.945 mL) was stirred at 0°C for 1h and r.t. overnight. The mixture was diluted with DCM then washed with a saturated solution of $NaHCO_3$, and then with brine. The organic phase was dried over Na_2SO_4, filtered and then concentrated to dryness under reduced pressure obtaining the crude target material, which was purified by FC (Biotage, SFAR, cyclohexane/AcOEt) to afford O1-benzyl O3-methyl 5-(1-fluoro-1-methyl-ethyl)piperidine-1,3-dicarboxylate (product 1: 21 mg) and then O1-benzyl O3-methyl 5-(1-fluoro-1-methyl-ethyl)piperidine-1,3-dicarboxylate (product 2: 150 mg).

[0362] Reference Example 413: Synthesis of methyl 5-(1-fluoro-1-methyl-ethyl)piperidine-3-carboxylate

To a solution of O1-benzyl O3-methyl 5-(1-fluoro-1-methyl-ethyl)piperidine-1,3-dicarboxylate (400 mg) in ethanol (11.86 mL), Pd/C (126 mg) was added and then N_2 was replaced with H_2 gas. The reaction was stirred vigorously at rt for 2 hours. The reaction was filtered through a pad of

celite and the filtrate was evaporated and dried in vacuo to afford methyl 5-(1-fluoro-1-methyl-ethyl)piperidine-3-carboxylate (210 mg).

[0363] Reference Example 414: Synthesis of O1-tert-butyl O3-methyl 5-(1-fluoro-1-methyl-ethyl)piperidine-1,3-dicarboxylate

To a stirred solution of methyl 5-(1-fluoro-1-methyl-ethyl)piperidine-3-carboxylate (210 mg) in DCM (5.17 mL) at r.t., di-tert-butyl dicarbonate (451 mg) was added (portion-wise) and the resulting reaction mixture was stirred for 2 hours at r.t.. The mixture was diluted with DCM then washed with a saturated solution of $NaHCO_3$, and then with brine. The organic phase was dried over Na_2SO_4, filtered and then concentrated to dryness under reduced pressure obtaining the crude target material, which was purified by FC (Biotage, SFAR, Cyclohexane/AcOEt) to afford O1-tert-butyl O3-methyl 5-(1-fluoro-1-methyl-ethyl)piperidine-1,3-dicarboxylate (275 mg).

[0364] Reference Example 415: Synthesis of O1-tert-butyl O3-methyl 3-allyl-5-(1-fluoro-1-methyl-ethyl)piperidine-1,3-dicarboxylate

To a solution of O1-tert-butyl O3-methyl 5-(1-fluoro-1-methyl-ethyl)piperidine-1,3-dicarboxylate (275 mg) in THF (4.53 mL) under a N_2 atmosphere at -78°C KHMDS (1 M in THF) (1.18 mL) was added slowly via syringe. After completion of the addition the reaction mixture was stirred at this temperature for 15 minutes, then a solution of 3-bromo-1-propene (0.13 mL) in THF (4.532 mL) was slowly added and the mixture was stirred at the same temperature for 1.5 hours then the mixture was let reaching r.t. and stirred for 2 hours. UPLC/MS check showed product formation. Saturated aq. NH_4Cl was added slowly, the mixture was stirred then diluted with water and the layers separated. The aqueous layer was extracted with EtOAc (2x) and the combined organic layers were dried, filtered and concentrated. The crude residue was purified by FC (25 g Biotage Sfar Silica D 60 μm cartridge, Cyclohexane/AcOEt) to provide O1-tert-butyl O3-methyl 3-allyl-5-(1-fluoro-1-methyl-ethyl)piperidine-1,3-dicarboxylate (244 mg).

[0365] Reference Example 416: Synthesis of O1-tert-butyl O3-methyl 5-(1-fluoro-1-methyl-ethyl)-3-propyl-piperidine-1,3-dicarboxylate

To a solution of O1-tert-butyl O3-methyl 3-allyl-5-(1-fluoro-1-methyl-ethyl)piperidine-1,3-dicarboxylate (244 mg) in EtOH (7.11 mL), Pd/C (75.61 mgl) was added and then N_2 was replaced with H_2 gas. The reaction was stirred vigorously at r.t. for 2 hours. The reaction was filtered through a pad of celite and the filtrate was evaporated and dried in vacuo to afford O1-tert-butyl O3-methyl 5-(1-fluoro-1-methyl-ethyl)-3-propyl-piperidine-1,3-dicarboxylate (245 mg).

[0366] Reference Example 417: Synthesis of methyl 5-(1-fluoro-1-methyl-ethyl)-3-propyl-piperidine-3-carboxylate

To a solution of O1-tert-butyl O3-methyl 5-(1-fluoro-1-methyl-ethyl)-3-propyl-piperidine-1,3-dicarboxylate (65.0 mg) in DCM (3.55 mL), trifluoroacetic acid (0.14 mL) was added. The mixture was stirred at r.t. for 2 hours. Then the mixture was concentrated in vacuo and the crude was dissolved in MeOH, loaded on a SCX, washed with MeOH and eluted with ammonia solution 2N in MeOH. Volatiles were removed to afford methyl 5-(1-fluoro-1-methyl-ethyl)-3-propyl-piperidine-3-carboxylate (40 mg).

[0367] Reference Example 418: Synthesis of methyl 1-[(2,3-dimethylquinoxalin-6-yl)methyl]-5-(1-fluoro-1-methyl-ethyl)-3-propyl-piperidine-3-carboxylate

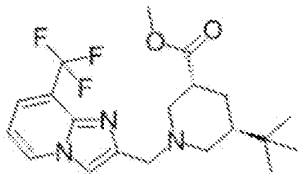
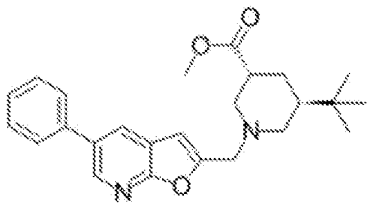
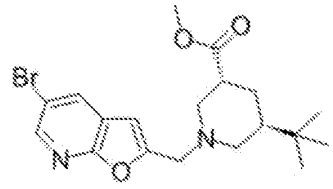
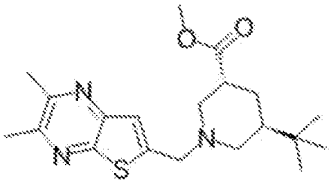
A solution of methyl 5-(1-fluoro-1-methyl-ethyl)-3-propyl-piperidine-3-carboxylate (40.0 mg), 2,3-dimethylquinoxaline-6-carbaldehyde (30.98 mg) and Na_2SO_4 in DCM (1.63 mL) was stirred at r.t. for 1 h. Then $NaBH(OAc)_3$ (86.39 mg) was added and the mixture was stirred at r.t. for 2 h. Water was added, the layers were separated and the organic phase was dried. The crude material was purified by FC on silica (Sfar silica D 5g, Cyclohexane/AcOEt), to afford methyl 1-[(2,3-dimethylquinoxalin-6-yl)methyl]-5-(1-fluoro-1-methyl-ethyl)-3-propyl-piperidine-3-carboxylate (60 mg).

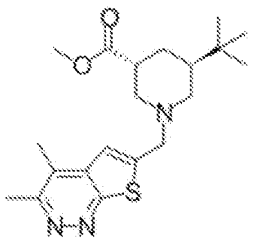
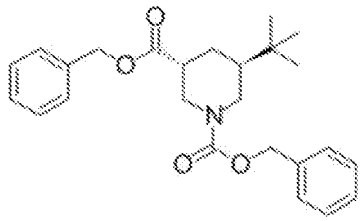
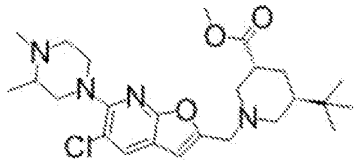
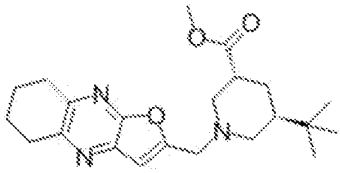
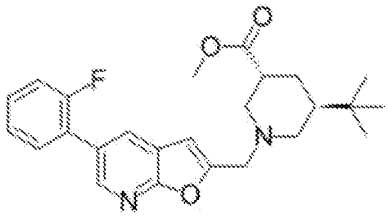
[0368] The compounds of Reference Examples were manufactured in the same manner as in any of the above Reference Examples. Structural formulae and physicochemical data of the compounds of Reference Examples are shown in the following table.

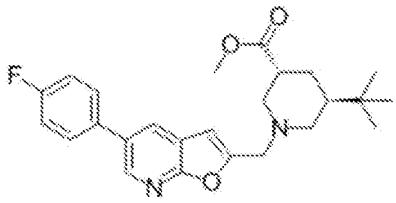
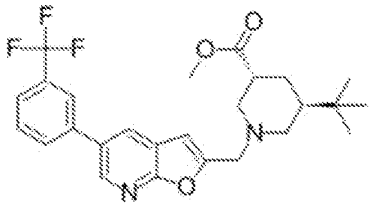
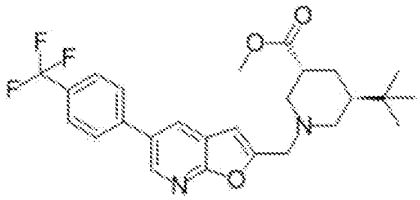
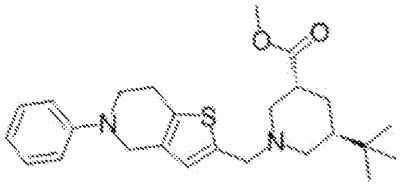
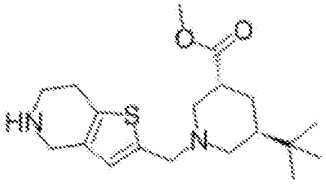
[0369]

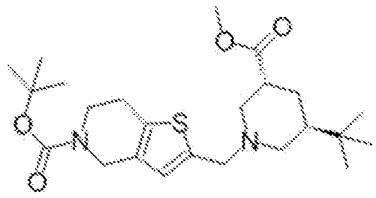
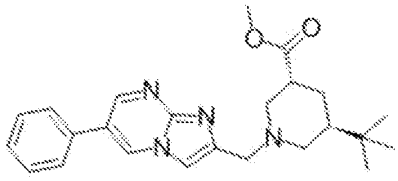
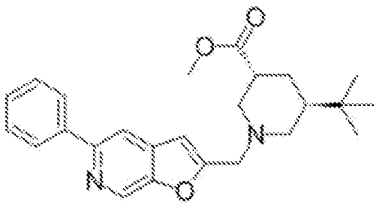
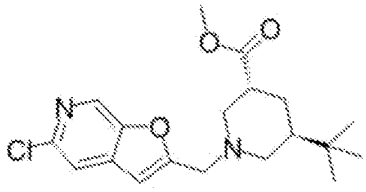
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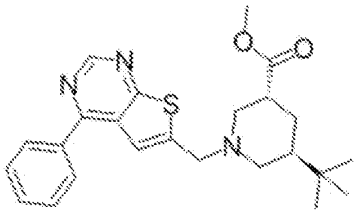
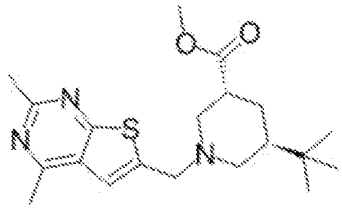
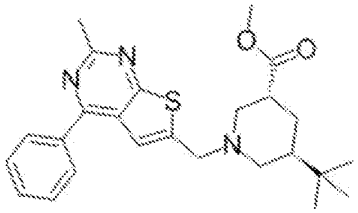
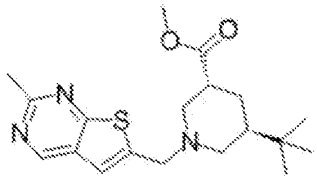
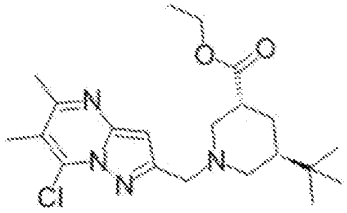
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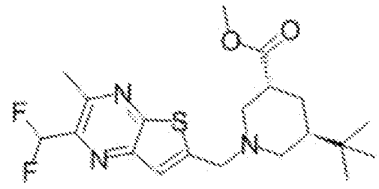
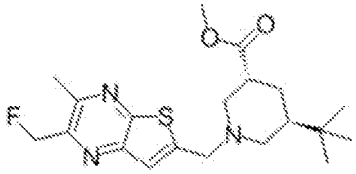
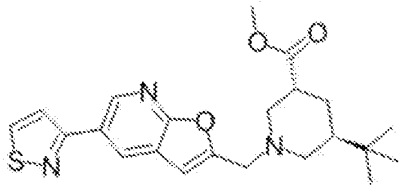
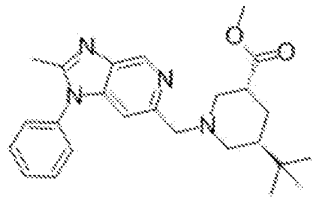
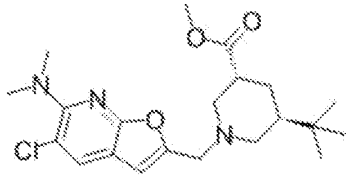
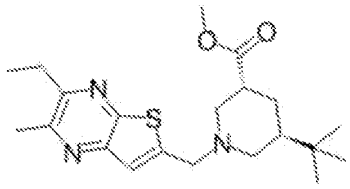
REX	STR	Physicochemical Data
1		NMR2; 8.26 (d, J = 6.8 Hz, 1H), 7.82 (s, 1H), 7.48 (d, J = 7.1 Hz, 1H), 6.81 (t, J = 7.0 Hz, 1H), 3.91 (dd, J = 15.4, 1.1 Hz, 1H), 3.75 (s, 3H), 3.72 (dd, J = 7.0 Hz, 1H), 3.54 (d, J = 10.6 Hz, 1H), 3.06 (d, J = 10.0 Hz, 1H), 2.71 (s, 1H), 2.31 (d, J = 13.1 Hz, 1H), 2.09 – 2.01 (m, 1H), 1.94 (t, J = 11.0 Hz, 1H), 1.62 (s, 1H), 1.30 – 1.14 (m, 1H), 0.90 (s, 9H).
2		NMR2; 8.47 (d, J = 2.3 Hz, 1H), 8.05 – 7.95 (m, 1H), 7.63 – 7.57 (m, 2H), 7.48 (dd, J = 8.4, 6.8 Hz, 2H), 7.44 – 7.36 (m, 1H), 6.70 (s, 1H), 3.92 – 3.84 (d, J = 5.2 Hz, 1H), 3.73 (s, 3H), 3.73 (d, J = 5.2 Hz, 1H), 3.48 (d, J = 11.4 Hz, 1H), 3.04 (d, J = 10.9 Hz, 1H), 2.70 (bxs, 1H), 2.29 (d, J = 13.3 Hz, 1H), 2.18 (dd, J = 11.4, 3.6 Hz, 1H), 1.98 (t, J = 11.0 Hz, 1H), 1.65 (s, 1H), 1.15 (td, J = 12.9, 5.0 Hz, 1H), 0.90 (s, 9H).
3		NMR2; 8.29 (d, J = 2.2 Hz, 1H), 7.97 (d, J = 2.3 Hz, 1H), 6.63 (d, J = 1.0 Hz, 1H), 3.83 (dd, J = 15.6, 1.1 Hz, 1H), 3.72 (s, 3H), 3.66 (d, J = 15.6 Hz, 1H), 3.48 – 3.40 (m, 1H), 3.00 (d, J = 10.7 Hz, 1H), 2.69 (d, J = 4.4 Hz, 1H), 2.28 (d, J = 13.0 Hz, 1H), 2.15 (dd, J = 11.2, 3.5 Hz, 1H), 1.95 (t, J = 10.9 Hz, 1H), 1.70 – 1.57 (m, 1H), 1.14 (td, J = 12.8, 5.0 Hz, 1H), 0.89 (s, 9H).
4		[M+H]+ 376.3

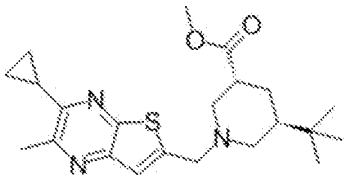
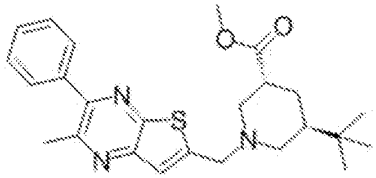
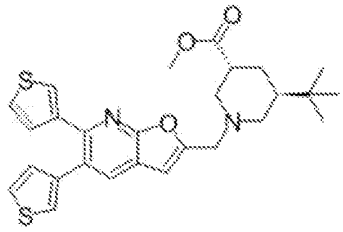
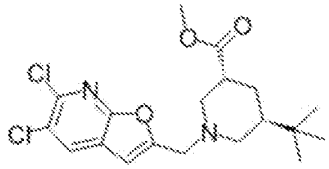
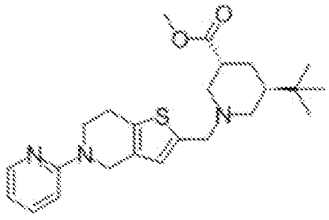
5		[M+H]+ 376.4
6		NMR2; 7.34 - 7.27 (m, 10H), 5.13 (d, J=12.1 Hz, 3H), 4.98 - 4.97 (m, 1H), 4.65 (d, J=13.4 Hz, 1H), 4.28 - 4.27 (m, 1H), 2.89 (dd, J=3.9, 13.5 Hz, 1H), 2.78 - 2.70 (m, 1H), 2.46 - 2.46 (m, 1H), 2.28 (d, J=11.6 Hz, 1H), 1.52 - 1.44 (m, 1H), 1.40 - 1.30 (m, 1H), 0.87 (s, 9H).
7		[M+H]+ 477.5 Epimer mixture
8		[M+H]+ 386.1
9		NMR2; 8.44 – 8.39 (m, 1H), 8.03 (t, J = 1.9 Hz, 1H), 7.47 (td, J = 7.7, 1.8 Hz, 1H), 7.37 (ddd, J = 9.9, 5.0, 1.9 Hz, 1H), 7.30 – 7.15 (m, 2H), 6.69 (t, J = 0.9 Hz, 1H), 3.89 (d, J = 15.6 Hz, 1H), 3.73 (s, 3H), 3.70 (d, J = 15.6 Hz, 1H), 3.48 (d, J = 10.7 Hz, 1H), 3.04 (d, J = 10.1 Hz, 1H), 2.70 (s, 1H), 2.29 (d, J = 13.3 Hz, 1H), 2.19 (dd, J = 11.3, 3.5 Hz, 1H), 1.98 (t, J = 11.0 Hz, 1H), 1.68 – 1.63 (m, 1H), 1.15 (td, J = 12.9, 5.0 Hz, 1H), 0.90 (s, 9H).

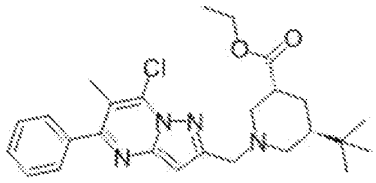
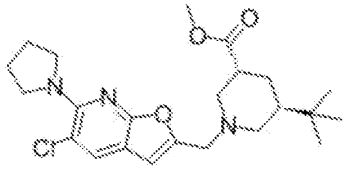
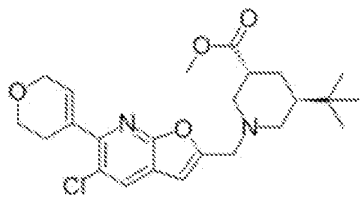
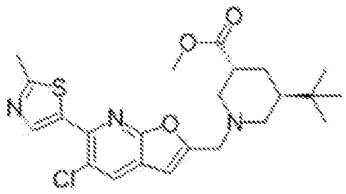
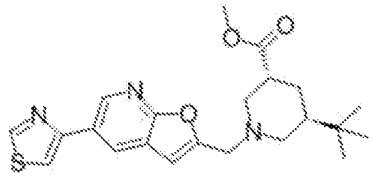
10		NMR2; 8.42 (d, J = 2.2 Hz, 1H), 7.97 (d, J = 2.2 Hz, 1H), 7.60 – 7.51 (m, 2H), 7.22 – 7.12 (m, 2H), 6.70 (d, J = 1.0 Hz, 1H), 4.12 (q, J = 7.1 Hz, 1H), 3.88 (dd, J = 15.4, 1.1 Hz, 1H), 3.76 – 3.66 (m, 4H), 3.48 (d, J = 11.3 Hz, 1H), 3.03 (d, J = 10.6 Hz, 1H), 2.70 (s, 1H), 2.29 (d, J = 13.2 Hz, 1H), 2.18 (dd, J = 11.3, 3.5 Hz, 1H), 1.97 (t, J = 10.9 Hz, 1H), 1.15 (td, J = 12.9, 5.0 Hz, 1H), 0.90 (s, 9H).
11		NMR2; 8.47 (d, J = 2.3 Hz, 1H), 8.04 (d, J = 2.2 Hz, 1H), 7.84 (d, J = 1.9 Hz, 1H), 7.78 (d, J = 7.5 Hz, 1H), 7.63 (dt, J = 15.4, 7.8 Hz, 2H), 6.73 (d, J = 1.0 Hz, 1H), 3.89 (dd, J = 15.5, 1.1 Hz, 1H), 3.76 – 3.67 (m, 4H), 3.49 (d, J = 11.5 Hz, 1H), 3.07 – 3.00 (m, 1H), 2.71 (d, J = 4.5 Hz, 1H), 2.29 (d, J = 13.2 Hz, 1H), 2.18 (dd, J = 11.3, 3.5 Hz, 1H), 1.98 (t, J = 11.0 Hz, 1H), 1.72 – 1.59 (m, 1H), 1.16 (td, J = 12.9, 4.9 Hz, 1H), 0.90 (s, 9H).
12		NMR2; 8.48 (s, 1H), 8.05 (s, 1H), 7.78 – 7.68 (m, 4H), 6.74 (s, 1H), 3.87 (m, 1H), 3.77 – 3.72 (m, 4H), 3.50 (m, 1H), 3.04 (m, 1H), 2.71 (s, 1H), 2.31 (m, 1H), 2.19 (m, 1H), 1.98 (m, 1H), 1.64 (m, 1H), 1.16 (s, 1H), 0.91 (s, 9H).
13		$[M+H]^+$ 427.2
14		NMR2; 6.51 (s, 1H), 3.87 (t, J = 1.9 Hz, 2H), 3.74 (d, J = 14.1 Hz, 1H), 3.70 (s, 3H), 3.54 (d, J = 14.1 Hz, 1H), 3.31 (dq, J = 11.2, 2.0 Hz, 1H), 3.16 (t, J = 6.0 Hz, 2H), 2.94 (ddt, J = 10.6, 3.7, 1.8 Hz, 1H), 2.77 (t, J = 5.9 Hz, 2H), 2.66 (dt, J = 5.5, 2.7 Hz, 1H), 2.23 (ddd, J = 13.0, 3.9, 2.1 Hz, 1H), 2.06 – 1.97 (m, 1H), 1.81

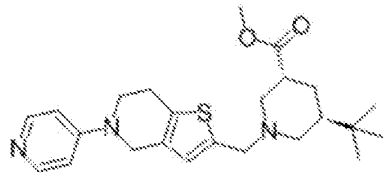
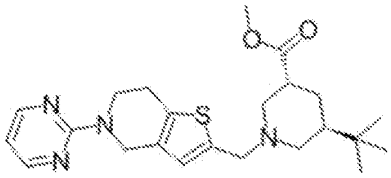
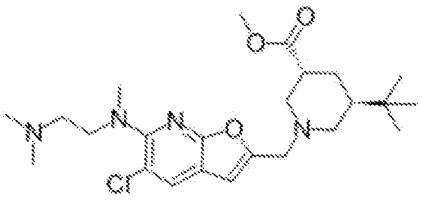
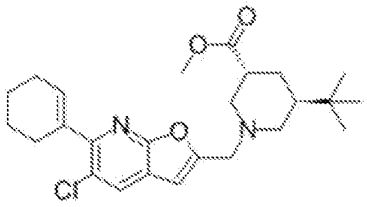
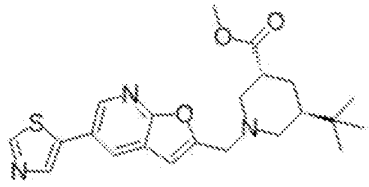
		(m, 2H), 1.72 – 1.62 (m, 1H), 1.11 (td, *J* = 12.8, 5.0 Hz, 1H), 0.88 (s, 9H).
15		NMR2, 6.55 (s, 1H), 4.42 (s, 2H), 3.73-3.69 (m, 6H), 3.53 (d, *J* = 14.1 Hz, 1H), 3.32 (d, *J* = 11.2 Hz, 1H), 2.94 (d, *J* = 10.6 Hz, 1H), 2.78 (s, 2H), 2.66 (s, 1H), 2.23 (d, *J* = 13.2 Hz, 1H), 1.99 (m, 1H), 1.81 (t, *J* = 10.9 Hz, 1H), 1.73 – 1.62 (m, 1H), 1.48 (s, 9H), 1.12 (td, *J* = 12.8, 5.0 Hz, 1H), 0.89 (s, 9H).
16		[M+H]+ 407.4
17		NMR2; 8.87 (t, *J* = 1.0 Hz, 1H), 8.03 – 7.95 (m, 2H), 7.89 (d, *J* = 1.0 Hz, 1H), 7.52 – 7.43 (m, 2H), 7.43 – 7.34 (m, 1H), 6.72 (d, *J* = 0.9 Hz, 1H), 3.87 (dd, *J* = 15.2, 1.1 Hz, 1H), 3.72 – 3.61 (m, 4H), 3.44 (d, *J* = 11.2 Hz, 1H), 3.04 (d, *J* = 10.9 Hz, 1H), 2.70 (s, 1H), 2.30 (d, *J* = 13.2 Hz, 1H), 2.13 (dd, *J* = 11.3, 3.5 Hz, 1H), 1.95 (t, *J* = 11.0 Hz, 1H), 1.73 – 1.63 (m, 1H), 1.20 – 1.10 (m, 1H), 0.90 (s, 9H).
18		NMR2; 8.55 (t, *J* = 0.9 Hz, 1H), 7.49 (d, *J* = 0.9 Hz, 1H), 6.67 (q, *J* = 0.9 Hz, 1H), 3.83 (dd, *J* = 15.4, 1.1 Hz, 1H), 3.71 (s, 3H), 3.63 (dd, *J* = 15.4, 0.8 Hz, 1H), 3.41 (dd, *J* = 11.2, 2.1 Hz, 1H), 3.05 – 2.96 (m, 1H), 2.70 (dd, *J* = 5.4, 2.7 Hz, 1H), 2.30 (d, *J* = 13.3 Hz, 1H), 2.18 – 2.07 (m, 1H), 1.93 (t, *J* = 10.9 Hz, 1H), 1.71 – 1.55 (m, 1H), 1.16 (td, *J* = 12.9, 5.0 Hz, 1H), 0.89 (s, 9H).

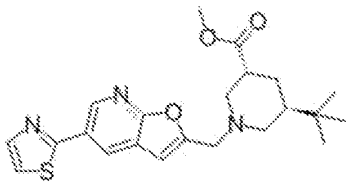
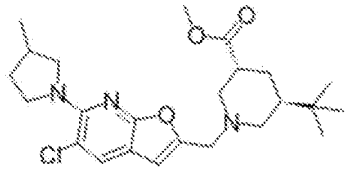
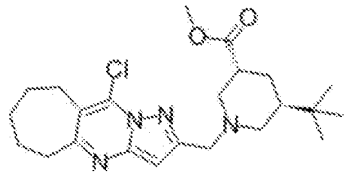
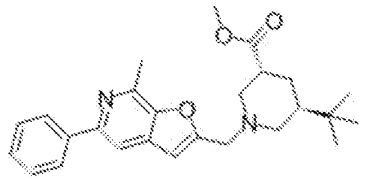
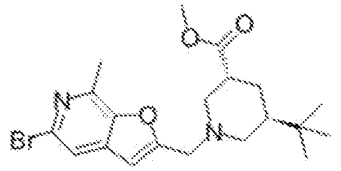
19		[M+H]$^+$ 424.3
20		[M+H]$^+$ 376.4
21		[M+H]$^+$ 438.4 NMR2, 7.97 – 7.85 (m, 2H), 7.59 – 7.49 (m, 3H), 7.31 (s, 1H), 3.84 (dd, *J* = 1.1, 14.5 Hz, 1H), 3.66 (s, 3H), 3.64 (dd, *J* = 1.1, 14.5 Hz, 1H), 3.41 – 3.29 (m, 1H), 3.04 – 2.94 (m, 1H), 2.88 (s, 3H), 2.72 – 2.62 (m, 1H), 2.31 – 2.21 (m, 1H), 2.06 (dd, *J* = 3.3, 11.0 Hz, 1H), 1.87 (t, *J* = 11.0 Hz, 1H), 1.77 – 1.65 (m, 1H), 1.18 – 1.09 (m, 1H), 0.89 (s, 9H).
22		[M+H]$^+$ 362.4
23		[M+H]$^+$ 407.4

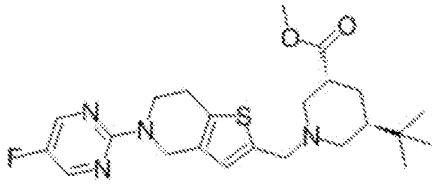
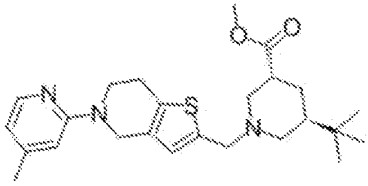
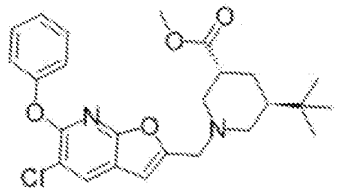
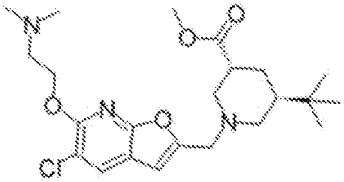
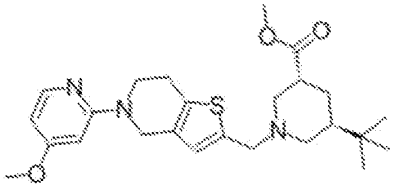
24		[M+H]+ 412.4
25		[M+H]+ 394.5
26		NMR2; 8.84 (d, *J* = 2.1 Hz, 1H), 8.78 (d, *J* = 4.7 Hz, 1H), 8.49 (d, *J* = 2.2 Hz, 1H), 7.67 (d, *J* = 4.7 Hz, 1H), 6.73 (d, *J* = 1.0 Hz, 1H), 3.87 (dd, *J* = 15.5, 1.1 Hz, 1H), 3.77 – 3.65 (m, 4H), 3.48 (dd, *J* = 11.3, 2.0 Hz, 1H), 3.07 – 2.99 (m, 1H), 2.74 – 2.67 (m, 1H), 2.29 (d, *J* = 13.2 Hz, 1H), 2.18 (dd, *J* = 11.3, 3.5 Hz, 1H), 1.97 (t, *J* = 11.0 Hz, 1H), 1.66 (tt, *J* = 11.4, 3.6 Hz, 1H), 1.15 (td, *J* = 12.9, 5.0 Hz, 1H), 0.90 (s, 9H).
27		[M+H]+ 421.5
28		[M+H]+ 408.5
29		[M+H]+ 390.4

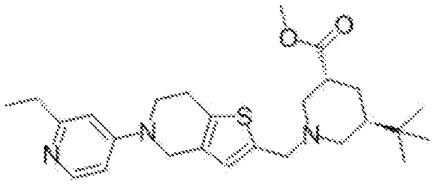
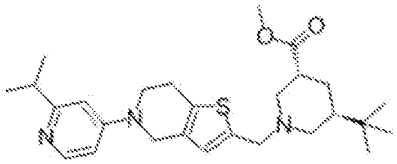
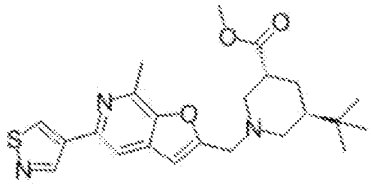
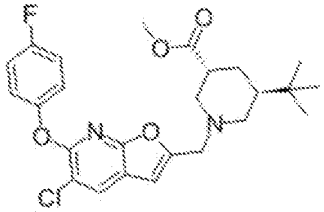
30		[M+H]+ 402.4
31		[M+H]+ 438.4
32		[M+H]+ 495.3
33		[M+H]+ 309.2 NMR2: 7.94 (1H, s), 6.66 (1H, s), 3.82 (1H, d, J=15.7 Hz), 3.73 (3H, s), 3.65 (1H, d, J=15.7 Hz), 3.44 (1H, d, J=11.2 Hz), 3.03 – 2.94 (1H, m), 2.74 – 2.66 (1H, m), 2.33 – 2.24 (1H, m), 2.15 (1H, dd, J=11.3, 3.5 Hz), 1.95 (1H, t, J=10.9 Hz), 1.68 – 1.56 (1H, m), 1.14 (1H, td, J=12.9, 5.0 Hz), 0.88 (9H, s)
34		NMR2: 8.20 (ddd, J = 5.0, 2.0, 0.9 Hz, 1H), 7.49 (ddd, J = 8.9, 7.1, 2.0 Hz, 1H), 6.69 (dt, J = 8.7, 0.9 Hz, 1H), 6.65 – 6.55 (m, 2H), 4.52 (q, J = 1.7 Hz, 2H), 4.05 – 3.90 (m, 2H), 3.75 (dd, J = 14.1, 1.0 Hz, 1H), 3.70 (s, 3H), 3.55 (d, J = 14.2 Hz, 1H), 3.37 – 3.29 (m, 1H), 3.00 – 2.87 (m, 3H), 2.66 (dt, J = 5.3, 2.7 Hz, 1H), 2.28 – 2.19 (m, 1H), 2.01 (dd, J = 11.2, 3.6 Hz, 1H), 1.82 (t, J = 10.9 Hz, 1H), 1.67 (tt, J = 11.4, 3.5 Hz, 1H), 1.12 (ddd, J = 13.1, 12.3, 5.0 Hz, 1H), 0.89 (s, 9H).

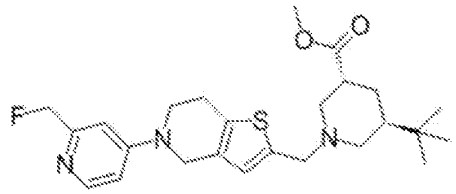
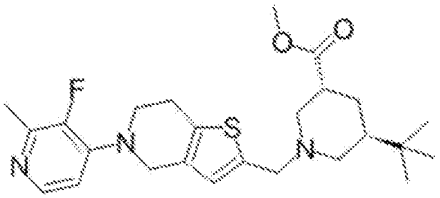
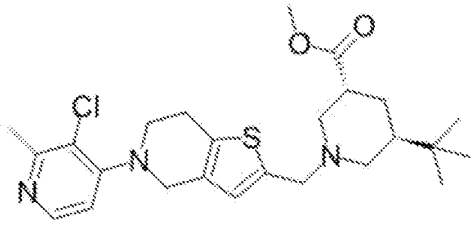
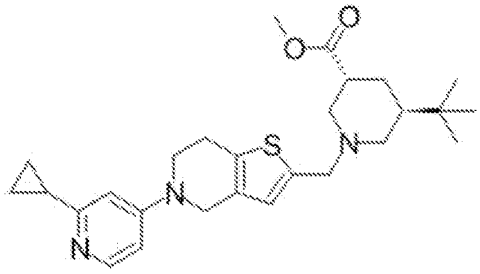
35		[M+H]+ 469.5
36		[M+H]+ 434.5 NMR2; 7.65 (1H, s), 6.41 (1H, s), 3.76 (1H, dd, J=15.1, 1.0 Hz), 3.71 (3H, s), 3.74 – 3.63 (4H, m), 3.58 (1H, d, J=15.1 Hz), 3.42 (1H, d, J=11.3 Hz), 2.98 (1H, d, J=10.7 Hz), 2.71 – 2.63 (1H, m), 2.26 (1H, d, J=13.1 Hz), 2.12 (1H, dd, J=11.3, 3.6 Hz), 2.00 – 1.84 (5H, m), 1.72 – 1.56 (1H, m), 1.11 (1H, td, J=12.8, 5.0 Hz), 0.88 (9H, s)
37		[M+H]+ 447.2
38		[M+H]+ 462.1
39		NMR2; δ 8.93 (d, J = 2.0 Hz, 1H), 8.81 (d, J = 2.2 Hz, 1H), 8.42 (d, J = 2.2 Hz, 1H), 7.60 (d, J = 1.9 Hz, 1H), 6.73 – 6.67 (m, 1H), 3.87 (dd, J = 15.4, 1.1 Hz, 1H), 3.73 (s, 3H), 3.69 (dd, J = 15.4, 0.9 Hz, 1H), 3.48 (dq, J = 11.3, 1.9 Hz, 1H), 3.03 (ddt, J = 10.7, 3.7, 1.8 Hz, 1H), 2.70 (dq, J = 5.3, 2.6 Hz, 1H), 2.34 – 2.23 (m, 1H), 2.18 (dd, J = 11.3, 3.5 Hz, 1H), 1.97 (t, J = 11.0 Hz, 1H), 1.66 (ddt, J = 12.4, 11.2, 3.5 Hz, 1H), 1.15 (td, J = 12.9, 5.0 Hz, 1H), 0.89 (s, 9H).

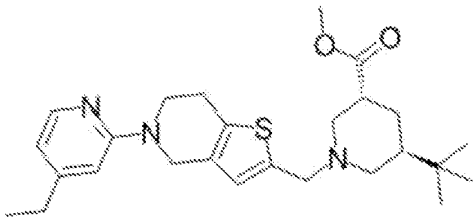
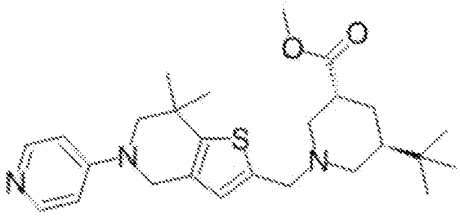
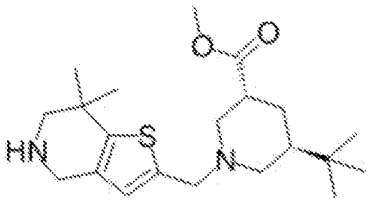
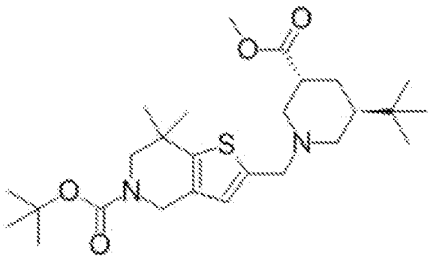
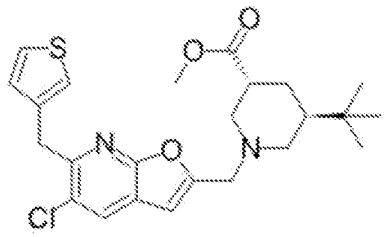
40		NMR2: 8.29 – 8.25 (m, 2H), 6.75 – 6.69 (m, 2H), 6.63 (s, 1H), 4.35 (q, J = 1.5 Hz, 2H), 3.80 – 3.71 (m, 3H), 3.70 (s, 3H), 3.56 (d, J = 14.2 Hz, 1H), 3.33 (dd, J = 11.2, 2.1 Hz, 1H), 2.99 – 2.89 (m, 3H), 2.70 – 2.64 (m, 1H), 2.28 – 2.20 (m, 1H), 2.02 (dd, J = 11.2, 3.6 Hz, 1H), 1.81 (t, J = 10.9 Hz, 1H), 1.67 (tt, J = 11.6, 3.5 Hz, 1H), 1.13 (td, J = 12.8, 5.0 Hz, 1H), 0.89 (s, 9H).
41		NMR2: 8.34 (d, J = 4.7 Hz, 2H), 6.62 (s, 1H), 6.50 (t, J = 4.7 Hz, 1H), 4.77 (q, J = 1.9 Hz, 2H), 4.25 – 4.07 (m, 2H), 3.75 (d, J = 14.0 Hz, 1H), 3.70 (s, 3H), 3.54 (d, J = 14.1 Hz, 1H), 3.33 (dd, J = 11.2, 2.1 Hz, 1H), 2.99 – 2.92 (m, 1H), 2.91 – 2.85 (m, 2H), 2.69 – 2.63 (m, 1H), 2.23 (d, J = 13.0 Hz, 1H), 2.01 (dd, J = 11.2, 3.6 Hz, 1H), 1.82 (t, J = 10.9 Hz, 1H), 1.69 (dt, J = 12.1, 3.5 Hz, 1H), 1.12 (td, J = 12.8, 5.0 Hz, 1H), 0.89 (s, 9H).
42		[M+H]+ 465.4
43		[M+H]+ 445.3
44		NMR2: 8.82 (d, J = 0.7 Hz, 1H), 8.49 (d, J = 2.2 Hz, 1H), 8.09 (d, J = 0.8 Hz, 1H), 8.03 (d, J = 2.2 Hz, 1H), 6.72 (d, J = 1.0 Hz, 1H), 3.87 (d, J = 15.2 Hz, 1H), 3.74 (s, 3H), 3.73 – 3.65 (m, 1H), 3.48 (d, J = 11.6 Hz, 1H), 3.03 (d, J = 10.8 Hz, 1H), 2.71 (s, 1H), 2.29 (d, J = 13.1 Hz, 1H), 2.17 (dd, J = 11.2, 3.5 Hz, 1H), 1.97 (t, J = 11.0 Hz, 1H), 1.67 – 1.62 (m, 1H), 1.15

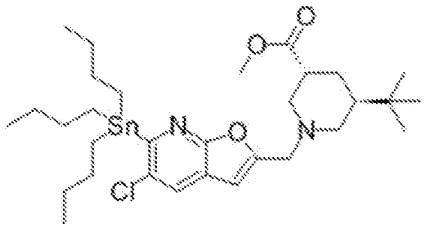
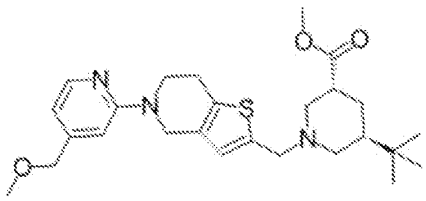
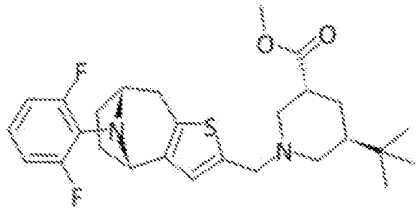
		(td, *J* = 12.9, 5.0 Hz, 1H), 0.90 (s, 9H).
45		NMR2, 8.85 (d, *J* = 2.2 Hz, 1H), 8.44 (d, *J* = 2.2 Hz, 1H), 7.91 (d, *J* = 3.3 Hz, 1H), 7.38 (d, *J* = 3.3 Hz, 1H), 6.73 (d, *J* = 1.0 Hz, 1H), 3.87 (dd, *J* = 15.5, 1.1 Hz, 1H), 3.76 – 3.65 (m, 4H), 3.48 (d, *J* = 11.2 Hz, 1H), 3.03 (d, *J* = 10.8 Hz, 1H), 2.70 (s, 1H), 2.29 (d, *J* = 13.2 Hz, 1H), 2.18 (dd, *J* = 11.3, 3.5 Hz, 1H), 1.97 (t, *J* = 10.9 Hz, 1H), 1.68 – 1.63 (m, 1H), 1.41 – 1.30 (m, 1H), 1.15 (td, *J* = 12.8, 5.1 Hz, 1H), 0.90 (s, 9H).
46		$[M+H]^+$ 448.4
47		$[M+H]^+$ 433.4
48		$[M+H]^+$ 421
49		NMR2, 7.47 (s, 1H), 6.63 (s, 1H), 3.83 (dd, *J* = 15.5, 1.1 Hz, 1H), 3.71 (s, 3H), 3.64 (dd, *J* = 15.5, 0.8 Hz, 1H), 3.43 (dq, *J* = 11.2, 2.0 Hz, 1H), 3.01 (ddt, *J* = 10.8, 3.7, 1.8 Hz, 1H), 2.74 – 2.66 (m, 4H), 2.29 (ddt, *J* = 15.1, 3.3, 1.8 Hz, 1H), 2.12 (dd, *J* = 11.2, 3.5 Hz, 1H), 1.93 (d, *J* = 10.9 Hz, 1H), 1.65 (ddt, *J* = 12.4, 11.2, 3.5 Hz, 1H), 1.15 (td, *J* = 12.9, 5.0 Hz, 1H), 0.89 (s, 9H).

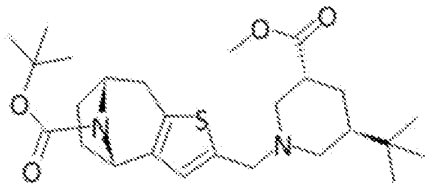
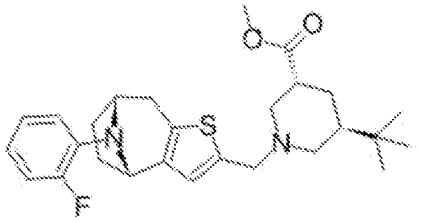
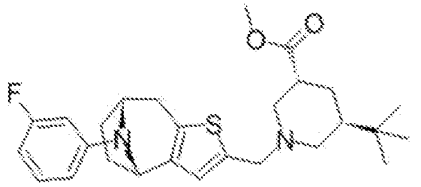
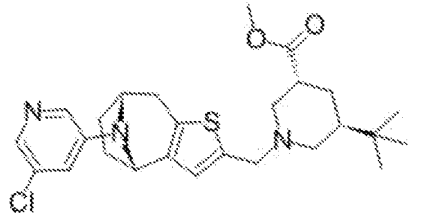
50		[M+H]+ 447.3
51		[M+H]+ 442.4
52		[M+H]+ 457.4
53		[M+H]+ 452.4
54		[M+H]+ 458.3

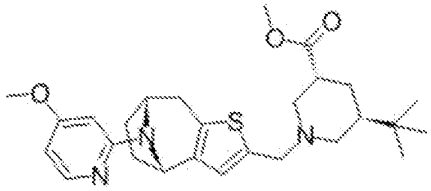
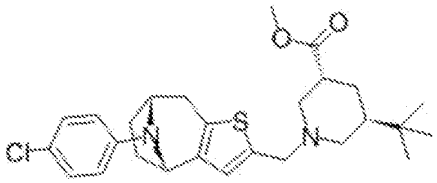
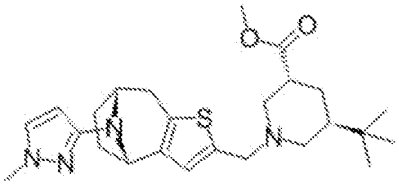
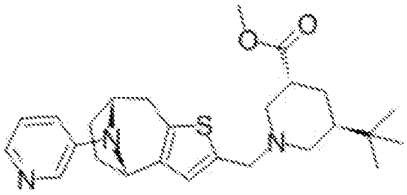
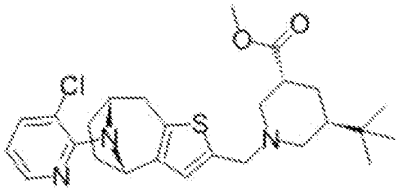
S5		NMR2; 8.22 (d, *J* = 5.9 Hz, 1H), 6.66 – 6.58 (m, 2H), 6.56 (dd, *J* = 6.0, 2.6 Hz, 1H), 4.34 (q, *J* = 1.6 Hz, 2H), 3.79 – 3.62 (m, 3H), 3.70 (s, 3H), 3.59 – 3.52 (m, 1H), 3.33 (dq, *J* = 11.1, 1.9 Hz, 1H), 2.99 – 2.88 (m, 3H), 2.73 (q, *J* = 7.6 Hz, 2H), 2.66 (dt, *J* = 5.3, 2.8 Hz, 1H), 2.28 – 2.20 (m, 1H), 2.02 (dd, *J* = 11.2, 3.5 Hz, 1H), 1.82 (t, *J* = 10.9 Hz, 1H), 1.67 (tt, *J* = 11.4, 3.5 Hz, 1H), 1.30 (t, *J* = 7.6 Hz, 3H), 1.13 (td, *J* = 12.8, 4.9 Hz, 1H), 0.89 (s, 9H).
S6		NMR2; 8.24 (d, *J* = 5.9 Hz, 1H), 6.63 (s, 1H), 6.59 (d, *J* = 2.6 Hz, 1H), 6.56 (dd, *J* = 5.9, 2.6 Hz, 1H), 4.34 (q, *J* = 1.6 Hz, 2H), 3.79 – 3.67 (m, 3H), 3.70 (s, 3H), 3.56 (d, *J* = 14.2 Hz, 1H), 3.33 (dq, *J* = 11.1, 1.9 Hz, 1H), 3.00 – 2.88 (m, 4H), 2.67 (dq, *J* = 5.3, 2.7 Hz, 1H), 2.24 (ddt, *J* = 13.1, 3.3, 1.8 Hz, 1H), 2.02 (dd, *J* = 11.2, 3.6 Hz, 1H), 1.82 (t, *J* = 10.9 Hz, 1H), 1.67 (tt, *J* = 11.5, 3.5 Hz, 1H), 1.30 (d, *J* = 6.9 Hz, 6H), 1.13 (td, *J* = 12.8, 5.0 Hz, 1H), 0.89 (s, 9H).
S7		$[M+H]^+$ 428
S8		$[M+H]^+$ 475.3

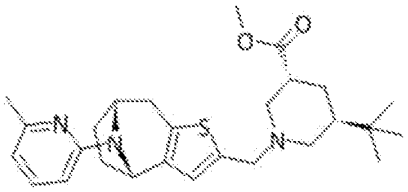
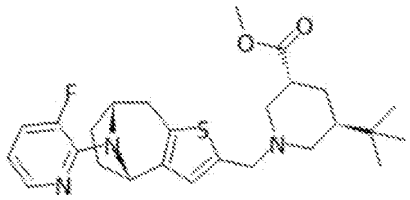
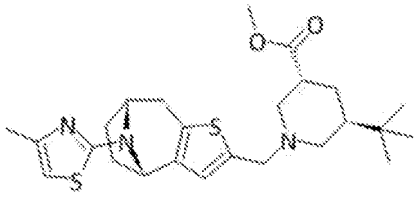
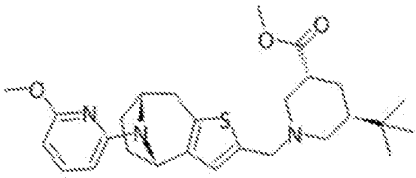
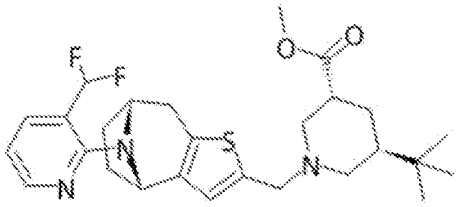
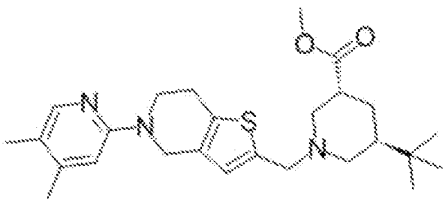
59		NMR2; 8.23 (d, J = 5.9 Hz, 1H), 6.88 (d, J = 2.7 Hz, 1H), 6.67 – 6.64 (m, 1H), 6.63 (s, 1H), 5.47 (s, 1H), 5.35 (s, 1H), 4.38 (t, J = 1.4 Hz, 2H), 3.73 (d, J = 22.4 Hz, 6H), 3.56 (d, J = 14.2 Hz, 1H), 3.33 (d, J = 11.2 Hz, 1H), 2.99 – 2.92 (m, 2H), 2.67 (s, 1H), 2.24 (d, J = 13.0 Hz, 1H), 2.04 – 1.97 (m, 1H), 1.82 (t, J = 10.9 Hz, 1H), 1.72 – 1.62 (m, 2H), 1.13 (td, J = 12.8, 5.0 Hz, 1H), 0.89 (s, 9H).
60		NMR2; 8.04 (d, J = 5.6 Hz, 1H), 6.70 – 6.63 (m, 1H), 6.60 (s, 1H), 4.30 (s, 2H), 3.75 (d, J = 14.2 Hz, 1H), 3.70 (s, 3H), 3.68 (t, J = 5.6 Hz, 2H), 3.56 (d, J = 14.1 Hz, 1H), 3.34 (d, J = 11.3 Hz, 1H), 2.97 – 2.92 (m, 3H), 2.67 (s, 1H), 2.47 (d, J = 3.9 Hz, 3H), 2.24 (d, J = 13.1 Hz, 1H), 2.07 – 1.99 (m, 1H), 1.82 (t, J = 10.9 Hz, 1H), 1.69 (d, J = 12.2 Hz, 1H), 1.13 (td, J = 12.8, 5.0 Hz, 1H), 0.89 (s, 9H).
61		[M+H]+ 476.3
62		NMR2; 8.14 (d, J = 5.9 Hz, 1H), 6.62 (s, 1H), 6.59 (d, J = 2.6 Hz, 1H), 6.52 (dd, J = 6.0, 2.6 Hz, 1H), 4.40 – 4.27 (m, 2H), 3.78 – 3.65 (m, 3H), 3.70 (s, 3H), 3.56 (d, J = 14.2 Hz, 1H), 3.37 – 3.29 (m, 1H), 2.99 – 2.88 (m, 3H), 2.69 – 2.65 (m, 1H), 2.07 – 1.99 (m, 2H), 1.93 (tt, J = 8.2, 4.9 Hz, 1H), 1.82 (t, J = 10.9 Hz, 1H), 1.67 (tt, J = 11.4, 3.5 Hz, 1H), 1.13 (td, J = 12.8, 5.0 Hz, 1H), 1.05 – 0.97 (m, 2H), 0.97 – 0.90 (m, 2H), 0.89 (s, 9H).

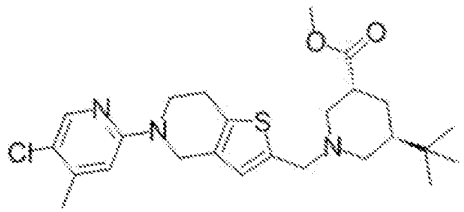
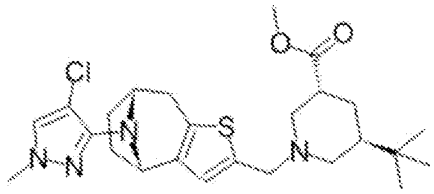
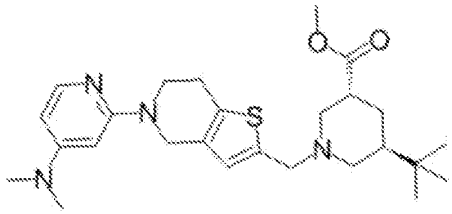
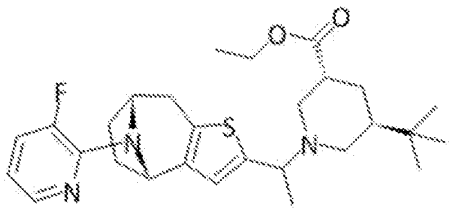
63		[M+H]+ 456.3
64		[M+H]+ 456.3
65		[M+H]+ 379.3
66		[M+H]+ 479.3
67		[M+H]+ 461.5, 463.2

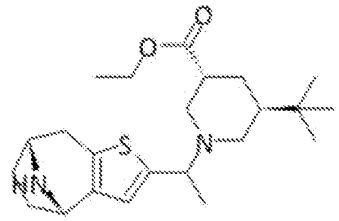
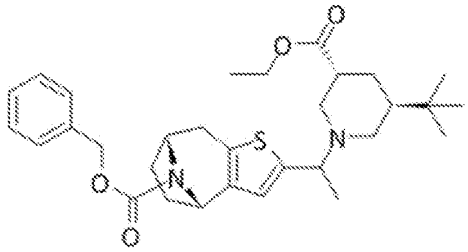
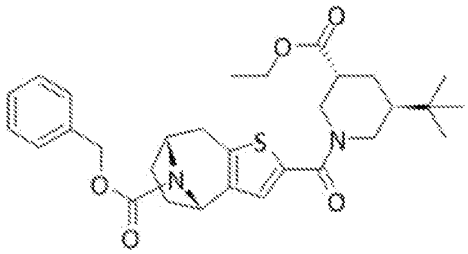
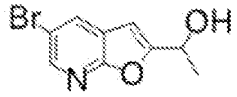
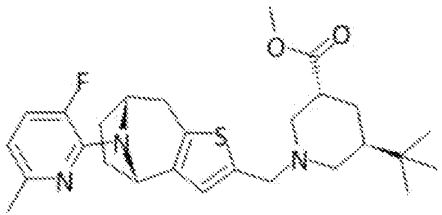
68		[M+H]+ 653.3, 655.4
69		[M+H]+ 472.3
70		[M+H]+ 489.6, 490.2
71		NMR2 6.55 (s, 1H), 4.57 (d, J = 5.1 Hz, 1H), 4.31 – 4.23 (m, 1H), 3.75 – 3.60 (m, 4H), 3.51 (d, J = 14.3 Hz, 1H), 3.43 (dd, J = 16.8, 4.5 Hz, 1H), 3.30 (d, J = 11.1 Hz, 1H), 2.93 (d, J = 10.5 Hz, 1H), 2.71 (d, J = 16.7 Hz, 1H), 2.65 (brs, 1H), 2.43 – 2.19 (m, 3H), 2.12 – 2.06 (m, 1H), 1.99 (dd, J = 11.2, 3.6 Hz, 1H), 1.81 (t, J = 10.9 Hz, 1H), 1.73 – 1.58 (m, 1H), 1.12 (td, J = 12.8, 4.9 Hz, 1H), 0.88 (s, 9H).

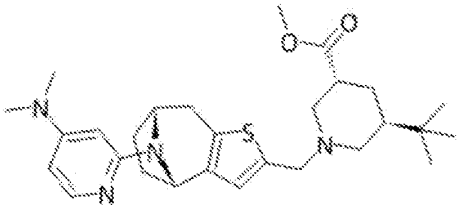
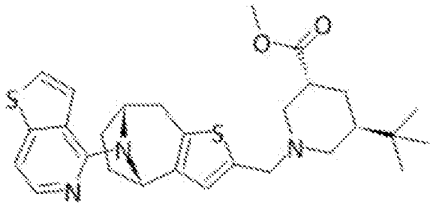
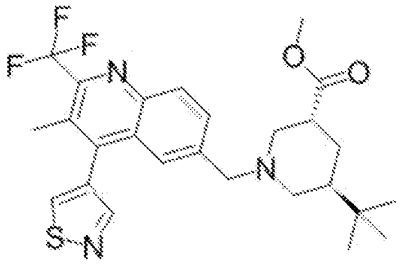
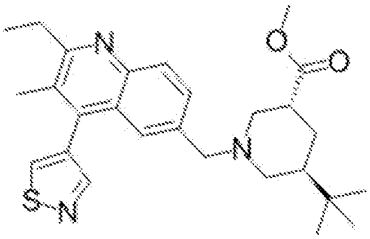
72		NMR2, 6.56 (s, 1H), 4.88 (d, *J* = 40.0 Hz, 1H), 4.54 (d, *J* = 30.6 Hz, 1H), 3.71 (d, *J* = 14.1 Hz, 1H), 3.66 (s, 3H), 3.49 (d, *J* = 14.3 Hz, 1H), 3.45 – 3.17 (m, 2H), 2.93 (d, *J* = 10.5 Hz, 1H), 2.65 (d, *J* = 5.0 Hz, 1H), 2.49 (d, *J* = 16.1 Hz, 1H), 2.22 (d, *J* = 12.6 Hz, 2H), 2.07 (m, *J* = 11.7, 6.4 Hz, 1H), 1.97 (dd, *J* = 11.2, 3.5 Hz, 1H), 1.83 (dt, *J* = 21.7, 10.3 Hz, 2H), 1.68 (t, *J* = 10.3 Hz, 2H), 1.41 (bra, 9H), 1.11 (td, *J* = 12.7, 5.0 Hz, 1H), 0.88 (s, 9H).
73		$[M+H]^+$ 471.6, 472.3
74		$[M+H]^+$ 471.6, 472.3
75		$[M+H]^+$ 488.3

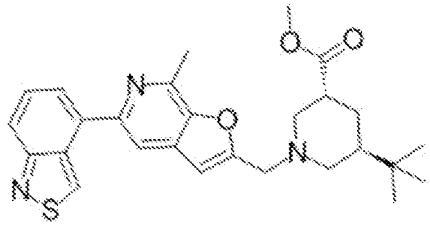
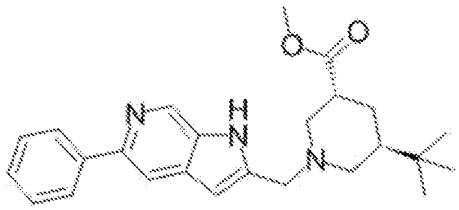
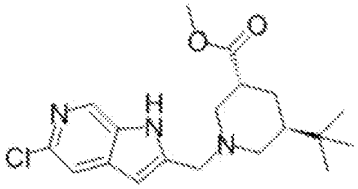
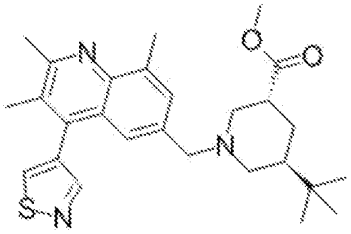
76		[M+H]+ 484.4 NMR2; 7.99 (1H, d, J=5.8 Hz), 6.66 (1H, s), 6.19 (1H, dd, J=5.8, 2.2 Hz), 6.05 (1H, d, J=2.1 Hz), 4.98 (1H, d, J=5.6 Hz), 4.86 (1H, dd, J=7.9, 4.4 Hz), 3.74 (3H, s), 3.68 (1H, d, J=14.2 Hz), 3.57 (3H, s), 3.50 (1H, d, J=14.2 Hz), 3.36 (1H, dd, J=16.2, 4.5 Hz), 3.32 – 3.23 (1H, m), 2.97 – 2.87 (1H, m), 2.66 – 2.58 (1H, m), 2.46 (1H, dd, J=16.3, 1.3 Hz), 2.42 – 2.29 (1H, m), 2.29 – 2.16 (2H, m), 2.03 – 1.93 (2H, m), 1.86 – 1.73 (2H, m), 1.72 – 1.59 (1H, m), 1.10 (1H, td, J=12.8, 5.0 Hz), 0.87 (9H, s)
77		[M+H]+ 487.3
78		[M+H]+ 457.3
79		[M+H]+ 454.4
80		[M+H]+ 488.3

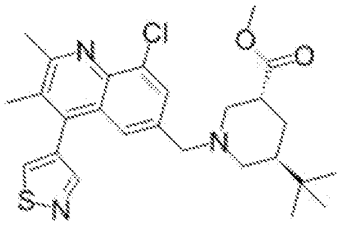
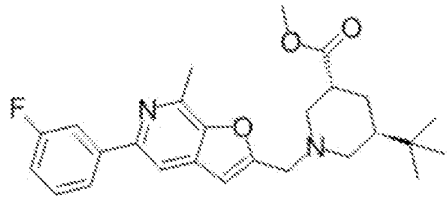
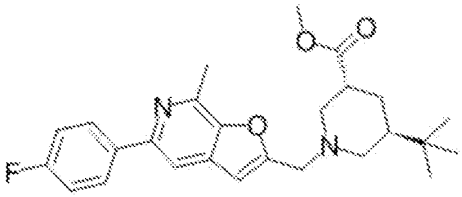
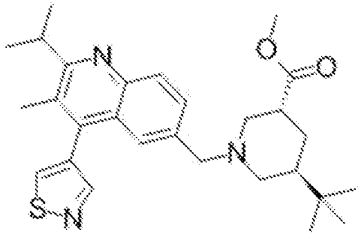
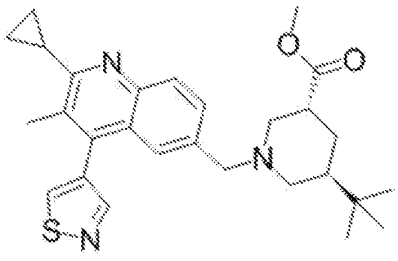
81		[M+H]+ 468.4
82		[M+H]+ 473.3
83		[M+H]+ 474.4
84		[M+H]+ 484.5, 485.2
85		[M+H]+ 504.3
86		[M+H]+ 456

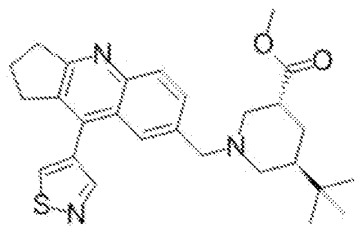
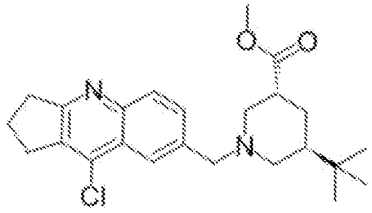
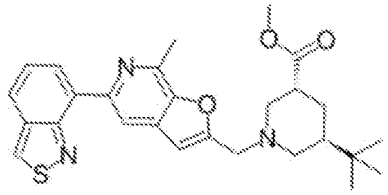
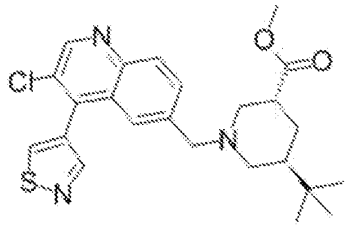
87		[M+H]+ 476
88		[M+H]+ 491.2
89		NMR2; 7.92 (d, *J* = 6.0 Hz, 1H), 6.62 (s, 1H), 6.05 (dd, *J* = 6.0, 2.2 Hz, 1H), 5.79 (d, *J* = 2.2 Hz, 1H), 4.49 (d, *J* = 15.8 Hz, 1H), 4.45 (d, *J* = 15.8 Hz, 1H), 4.03 – 3.87 (m, 2H), 3.75 (d, *J* = 14.2 Hz, 1H), 3.69 (s, 3H), 3.55 (d, *J* = 14.2 Hz, 1H), 3.37 – 3.28 (m, 1H), 2.99 (s, 6H), 2.99 – 2.91 (m, 1H), 2.93 – 2.87 (m, 2H), 2.69 – 2.63 (m, 1H), 2.28 – 2.19 (m, 1H), 2.03 – 1.97 (m, 1H), 1.89 – 1.75 (m, 1H), 1.68 (tt, *J* = 11.5, 3.5 Hz, 1H), 1.16 – 1.05 (m, 1H), 0.88 (s, 9H).
90		[M+H]+ 500.4 NMR2; 7.90 (dq, *J* = 5.0, 1.7 Hz, 1H), 7.18 – 7.08 (m, 1H), 6.62 – 6.53 (m, 2H), 5.36 – 5.29 (m, 1H), 4.98 – 4.90 (m, 1H), 4.19 – 4.07 (m, 1H), 4.07 – 3.95 (m, 1H), 3.95 – 3.81 (m, 1H), 3.42 – 3.12 (m, 2H), 2.85 (d, *J* = 10.7 Hz, 1H), 2.62 – 2.45 (m, 2H), 2.32 (q, *J* = 10.8 Hz, 1H), 2.24 – 1.88 (m, 4H), 1.85 – 1.66 (m, 1H), 1.62 – 1.57 (m, 1H), 1.40 – 1.17 (m, 4H), 1.04 (td, *J* = 12.7, 5.0 Hz, 1H), 0.94 – 0.83 (m, 12H). Epimer mixture

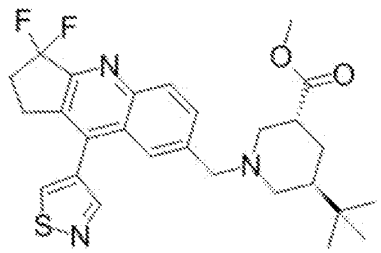
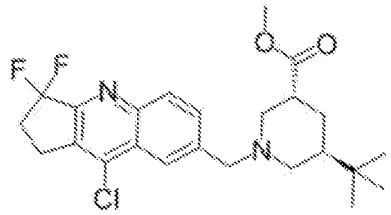
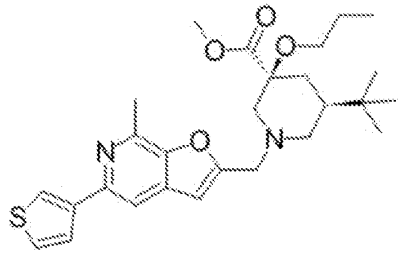
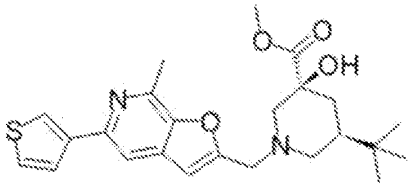
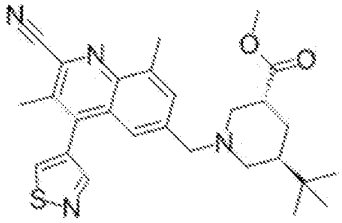
91		NMR2; 6.50 – 6.42 (m, 1H), 4.24 – 4.01 (m, 4H), 3.96 – 3.78 (m, 2H), 3.35-3.20 (m, 1H), 3.09 (ddd, J = 16.9, 12.7, 4.6 Hz, 1H), 2.90-2.74 (m, 1H), 2.66 – 2.57 (m, 1H), 2.51 (d, J = 16.3 Hz, 1H), 2.26 – 1.81 (m, 6H), 1.77 – 1.55 (m, 1H), 1.42 – 1.24 (m, 6H), 1.07 (t, J = 12.8, 4.3 Hz, 1H), 0.87 (d, J = 6.2 Hz, 9H). Epimer mixture
92		[M+H]+ 539.4 Epimer mixture
93		NMR2; 7.36 – 7.21 (m, 5H), 7.02 (s, 1H), 5.25 – 4.93 (m, 3H), 4.85 (d, J = 13.5 Hz, 1H), 4.76 – 4.34 (m, 2H), 4.23 – 3.95 (m, 1H), 3.57 – 3.21 (m, 1H), 3.05 (s, 1H), 2.77 – 2.51 (m, 2H), 2.30 (dt, J = 32.4, 11.6 Hz, 2H), 2.05 (brs, 1H), 1.96 – 1.81 (m, 1H), 1.74 – 1.62 (m, 1H), 1.62 – 1.37 (m, 5H), 1.16 (t, J = 7.2 Hz, 2H), 0.96 – 0.87 (m, 9H).
94		NMR2; 8.34 (s, 1H), 8.01 (d, J = 2.2 Hz, 1H), 6.62 (d, J = 1.0 Hz, 1H), 5.06 (qd, J = 6.6, 1.0 Hz, 1H), 1.67 (d, J = 6.6 Hz, 3H).
95		[M+H]+ 486.4

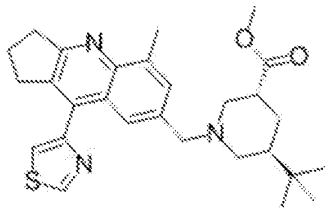
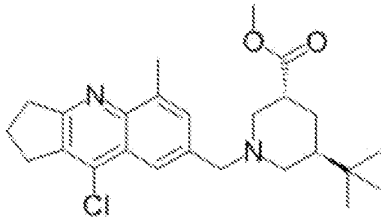
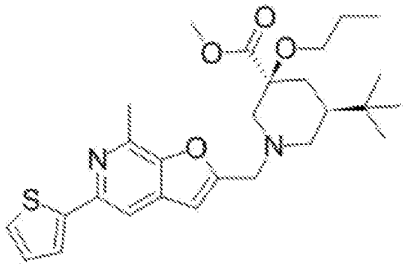
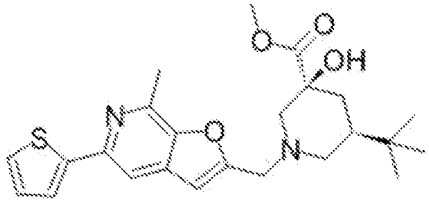
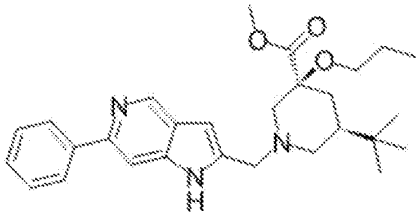
96		[M+H]+ 497.4
97		[M+H]+ 510.3
98		NMR2: 8.70 (s, 1H), 8.51 (s, 1H), 8.17 (d, *J* = 8.7 Hz, 1H), 7.80 (dd, *J* = 8.7, 1.8 Hz, 1H), 7.22 (s, 1H), 3.66 (s, 3H), 3.63 (s, 1H), 3.44 (d, *J* = 14.1 Hz, 1H), 3.14 (d, *J* = 11.1 Hz, 1H), 2.86 (d, *J* = 10.6 Hz, 1H), 2.61 (s, 1H), 2.38 (q, *J* = 1.7 Hz, 3H), 2.24 (d, *J* = 13.2 Hz, 1H), 1.97 (dd, *J* = 11.2, 3.5 Hz, 1H), 1.76 (t, *J* = 10.9 Hz, 1H), 1.60 (s, 1H), 1.13 (td, *J* = 12.8, 5.0 Hz, 1H), 0.85 (s, 9H).
99		NMR2: 8.62 (s, 1H), 8.49 (s, 1H), 8.01 (d, *J* = 8.6 Hz, 1H), 7.66 (dd, *J* = 8.6, 1.9 Hz, 1H), 7.13 – 7.08 (m, 1H), 3.69 (s, 3H), 3.61 (d, *J* = 13.7 Hz, 1H), 3.39 (d, *J* = 13.7 Hz, 1H), 3.14 (d, *J* = 11.6 Hz, 1H), 3.06 (q, *J* = 7.5 Hz, 2H), 2.87 (d, *J* = 10.5 Hz, 1H), 2.60 (s, 1H), 2.25 (s, 3H), 2.21 (s, 1H), 1.93 (dd, *J* = 11.3, 3.5 Hz, 1H), 1.73 (t, *J* = 10.8 Hz, 1H), 1.41 (t, *J* = 7.5 Hz, 3H), 1.11 (td, *J* = 12.7, 4.9 Hz, 1H), 0.85 (s, 9H).

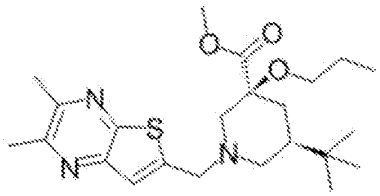
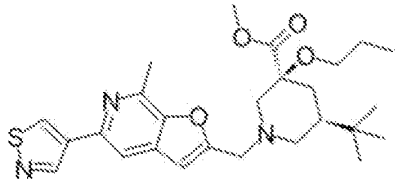
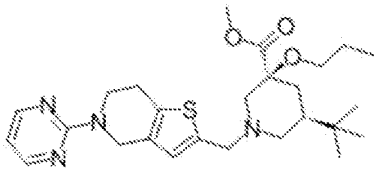
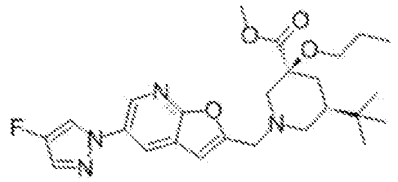
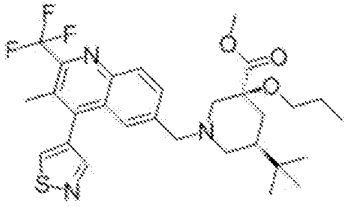
100		[M+H]+ 478 NMR2: 9.93 (d, J = 1.1 Hz, 1H), 7.94 – 7.84 (m, 1H), 7.76 (s, 1H), 7.59 – 7.48 (m, 2H), 6.75 (s, 1H), 3.89 (dd, J = 15.3, 1.0 Hz, 1H), 3.76 – 3.65 (m, 4H), 3.48 (dq, J = 11.2, 1.9 Hz, 1H), 3.06 (ddt, J = 10.7, 3.6, 1.7 Hz, 1H), 2.86 (s, 3H), 2.72 (dq, J = 5.4, 2.6 Hz, 1H), 2.31 (ddt, J = 13.2, 3.3, 1.8 Hz, 1H), 2.15 (dd, J = 11.3, 3.5 Hz, 1H), 1.98 (t, J = 10.9 Hz, 1H), 1.68 (ddt, J = 12.5, 11.2, 3.5 Hz, 1H), 1.17 (td, J = 12.9, 5.0 Hz, 1H), 0.91 (s, 9H).
101		NMR2: 10.17 (brs, 1H), 8.90 (s, 1H), 8.04 – 7.96 (m, 2H), 7.87 (d, J = 1.0 Hz, 1H), 7.50 – 7.43 (m, 2H), 7.38 – 7.31 (m, 1H), 6.37 (s, 1H), 3.89 (d, J = 15.3 Hz, 1H), 3.80 (s, 3H), 3.67 (d, J = 15.3 Hz, 1H), 3.31 – 3.22 (m, 1H), 3.05 – 2.96 (m, 1H), 2.76 – 2.68 (m, 1H), 2.38 – 2.30 (m, 1H), 2.03 – 1.96 (m, 1H), 1.79 - 1.67 (m, 1H), 1.58 – 1.46 (m, 1H), 1.34 – 1.22 (m, 1H), 0.90 (s, 9H).
102		[M+H]+ 364.4
103		NMR2: 8.59 (s, 1H), 8.46 (s, 1H), 7.31 (s, 1H), 6.94 (s, 1H), 3.67 – 3.57 (m, 4H), 3.30 (d, J = 13.5 Hz, 1H), 3.14 (d, J = 11.1 Hz, 1H), 2.88 (d, J = 10.6 Hz, 1H), 2.81 (s, 3H), 2.76 (s, 3H), 2.59 (brs, 1H), 2.24 (brs, 1H), 2.20 (s, 3H), 1.89 (dd, J = 11.3, 3.6 Hz, 1H), 1.78 – 1.62 (m, 2H), 1.16 – 1.04 (m, 1H), 0.86 (s, 9H).

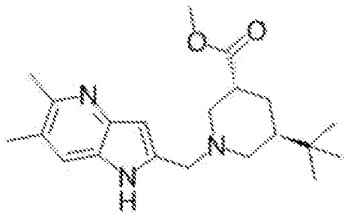
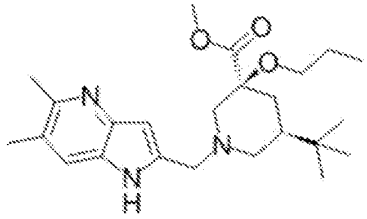
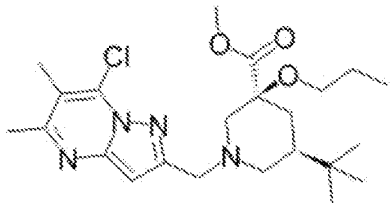
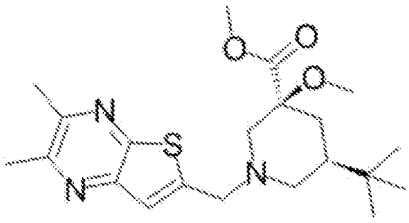
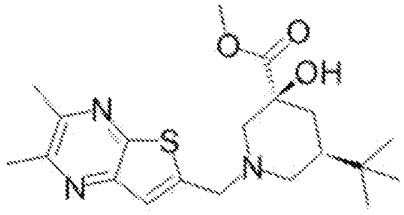
104		NMR2: 8.63 (s, 1H), 8.47 (s, 1H), 7.84 (d, J = 1.7 Hz, 1H), 7.03 (s, 1H), 3.71 (s, 3H), 3.63 (d, J = 13.7 Hz, 1H), 3.28 (d, J = 13.8 Hz, 1H), 3.12 (d, J = 11.2 Hz, 1H), 2.92 – 2.84 (m, 1H), 2.82 (s, 3H), 2.62 – 2.56 (m, 1H), 2.25 – 2.20 (m, 4H), 1.90 (dd, J = 11.2, 3.5 Hz, 1H), 1.78 (t, J = 10.9 Hz, 1H), 1.71 – 1.59 (m, 1H), 1.11 (td, J = 12.8, 4.9 Hz, 1H), 0.87 (s, 9H).
105		[M+H]+ 440
106		[M+H]+ 440
107		NMR2: 8.61 (s, 1H), 8.48 (s, 1H), 8.01 (d, J = 8.8 Hz, 1H), 7.64 (dd, J = 8.7, 1.9 Hz, 1H), 7.08 (s, 1H), 3.71 – 3.59 (m, 4H), 3.47 (h, J = 6.6 Hz, 1H), 3.38 (d, J = 13.6 Hz, 1H), 3.15 (d, J = 11.1 Hz, 1H), 2.88 (d, J = 10.3 Hz, 1H), 2.66 – 2.57 (m, 1H), 2.28 – 2.18 (m, 4H), 1.92 (dd, J = 11.2, 3.5 Hz, 1H), 1.78 – 1.57 (m, 2H), 1.41 (d, J = 6.7 Hz, 6H), 1.10 (td, J = 12.7, 5.0 Hz, 1H), 0.85 (s, 9H).
108		[M+H]+ 478.4 NMR2: 8.62 (s, 1H), 8.49 (s, 1H), 7.91 (d, J = 8.6 Hz, 1H), 7.61 (dd, J = 8.7, 1.9 Hz, 1H), 7.08 (s, 1H), 3.65 (s, 4H), 3.37 (d, J = 13.5 Hz, 1H), 3.14 (d, J = 11.3 Hz, 1H), 2.86 (d, J = 10.5 Hz, 1H), 2.59 (brs, 1H), 2.36 (s, 3H), 2.35 – 2.18 (m, 2H), 1.92 (dd, J = 11.3, 3.5 Hz, 1H), 1.72 (t, J = 10.8 Hz, 1H), 1.70-1.55 (m, 1H), 1.32 – 1.22 (m, 2H), 1.16 – 1.01 (m, 3H), 0.84 (s, 9H).

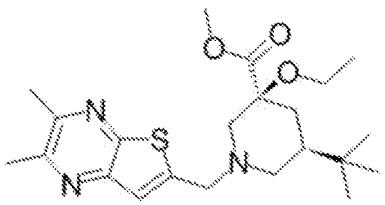
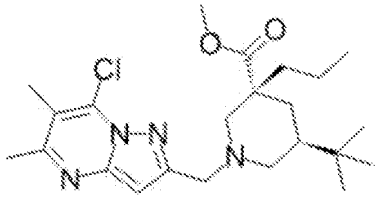
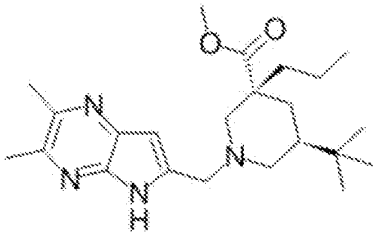
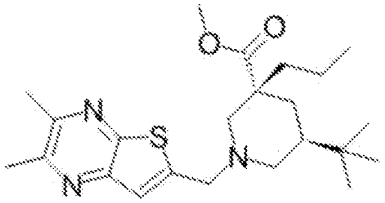
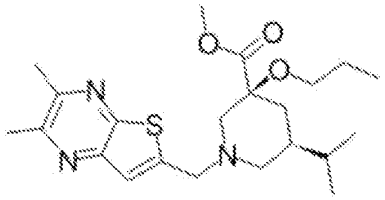
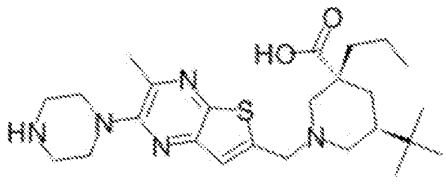
109		NMR2: 8.77 (s, 1H), 8.65 (s, 1H), 8.01 (d, J = 8.6 Hz, 1H), 7.67 (dd, J = 8.6, 1.9 Hz, 1H), 7.50 (s, 1H), 3.68 (d, J = 13.6 Hz, 1H), 3.64 (s, 3H), 3.44 (d, J = 13.6 Hz, 1H), 3.23 (t, J = 7.7 Hz, 2H), 3.18 (d, J = 11.2 Hz, 1H), 2.99 – 2.87 (m, 3H), 2.61 (s, 1H), 2.27 – 2.14 (m, 3H), 2.09 – 1.89 (m, 1H), 1.76 (t, J = 10.9 Hz, 1H), 1.69 – 1.58 (m, 1H), 1.12 (td, J = 12.7, 4.9 Hz, 1H), 0.86 (s, 9H).
110		NMR2: 8.00 (t, J = 1.3 Hz, 1H), 7.95 (d, J = 8.6 Hz, 1H), 7.68 (dd, J = 8.6, 1.9 Hz, 1H), 3.80 (d, J = 13.6 Hz, 1H), 3.65 (s, 3H), 3.54 (d, J = 13.6 Hz, 1H), 3.20 (dt, J = 22.5, 7.6 Hz, 5H), 3.02 – 2.94 (m, 1H), 2.64 (t, J = 2.8 Hz, 1H), 2.24 (p, J = 7.6 Hz, 3H), 2.07 – 1.97 (m, 1H), 1.85 (t, J = 10.9 Hz, 1H), 1.73 (m, J = 11.4, 3.4 Hz, 1H), 1.15 (td, J = 12.8, 5.0 Hz, 1H), 0.89 (s, 9H).
111		NMR2: 9.30 (s, 1H), 8.65 (d, J = 0.6 Hz, 1H), 8.18 (dd, J = 6.9, 1.2 Hz, 1H), 7.81 (dd, J = 8.6, 1.2 Hz, 1H), 7.40 (dd, J = 8.6, 6.9 Hz, 1H), 6.73 (d, J = 0.8 Hz, 1H), 3.89 (d, J = 15.6 Hz, 1H), 3.72 (s, 3H), 3.71 (d, J = 15.6 Hz, 1H), 3.45 (d, J = 11.2 Hz, 1H), 3.08 – 3.01 (m, 1H), 2.84 (d, J = 0.5 Hz, 3H), 2.71 (s, 1H), 2.28 (d, J = 13.2 Hz, 1H), 2.15 (dd, J = 11.3, 3.5 Hz, 1H), 1.96 (t, J = 11.0 Hz, 1H), 1.73 – 1.64 (m, 1H), 1.14 (td, J = 12.9, 5.0 Hz, 1H), 0.91 (s, 9H).
112		NMR2: 8.91 (s, 1H), 8.86 (s, 1H), 8.64 (s, 1H), 8.09 (d, J = 8.7 Hz, 1H), 7.77 (dd, J = 8.7, 1.8 Hz, 1H), 7.43 (s, 1H), 3.72 – 3.62 (m, 4H), 3.45 (d, J = 13.9 Hz, 1H), 3.16 (d, J = 11.3 Hz, 1H), 2.88 (d, J = 9.9 Hz, 1H), 2.62 (s, 1H), 2.25 (d, J = 13.7 Hz, 1H), 1.97 (dd, J = 11.2, 3.5 Hz, 1H), 1.78 (t, J = 10.9 Hz, 1H), 1.69-1.50 (m, 1H), 1.14 (td, J = 12.8, 5.0 Hz, 1H), 0.86 (s, 9H).

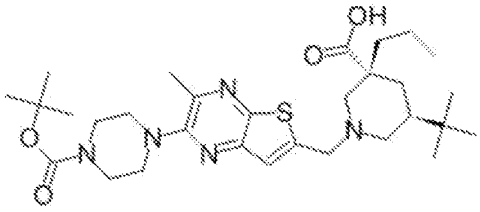
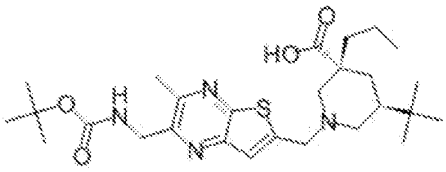
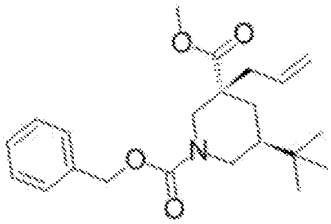
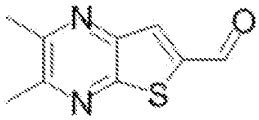
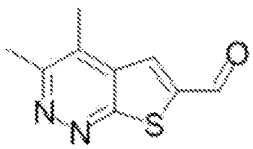
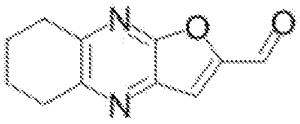
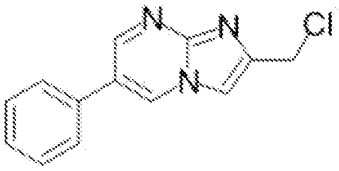
113		NMR2; 8.85 (s, 1H), 8.67 (s, 1H), 8.26 (d, *J* = 8.7 Hz, 1H), 7.80 (dd, *J* = 8.8, 1.9 Hz, 1H), 7.63 (s, 1H), 3.75 – 3.67 (m, 1H), 3.65 (s, 3H), 3.48 (d, *J* = 13.9 Hz, 1H), 3.17 (d, *J* = 11.2 Hz, 1H), 3.04 (t, *J* = 7.0 Hz, 2H), 2.93 – 2.86 (m, 1H), 2.79 – 2.64 (m, 2H), 2.62 (s, 1H), 2.25 (d, *J* = 13.3 Hz, 1H), 2.03 – 1.91 (m, 1H), 1.79 (t, *J* = 10.9 Hz, 1H), 1.64 – 1.60 (m, 1H), 1.14 (td, *J* = 12.9, 5.0 Hz, 1H), 0.86 (s, 9H).
114		NMR2; 8.29 (d, *J* = 8.8 Hz, 1H), 8.11 (s, 1H), 7.82 (dd, *J* = 8.7, 1.8 Hz, 1H), 3.82 (d, *J* = 13.9 Hz, 1H), 3.66 (s, 3H), 3.59 (d, *J* = 13.9 Hz, 1H), 3.27 – 3.19 (m, 3H), 2.97 (d, *J* = 12.3 Hz, 1H), 2.84 – 2.69 (m, 2H), 2.65 (brs, 1H), 2.28 (d, *J* = 13.2 Hz, 1H), 2.09 – 2.00 (m, 1H), 1.87 (t, *J* = 10.9 Hz, 1H), 1.79 – 1.67 (m, 1H), 1.17 (td, *J* = 12.7, 4.9 Hz, 1H), 0.89 (s, 9H).
115		$[M+H]^+$ 485.4
116		$[M+H]^+$ 443.4
117		NMR2; 8.69 (s, 1H), 8.49 (s, 1H), 7.65 (s, 1H), 7.11 (s, 1H), 3.68-3.60 (m, 4H), 3.35 (d, *J* = 14.0 Hz, 1H), 3.15-3.10 (m, 1H), 2.90-2.82 (m, 1H), 2.82 (s, 3H), 2.61 (brs, 1H), 2.48 (s, 3H), 2.27-2.21 (m, 1H), 1.96-1.91 (m, 1H), 1.76 (t, *J* = 10.9 Hz, 1H), 1.65-1.55 (m, 1H), 1.18-1.06 (m, 1H), 0.86 (s, 9H).

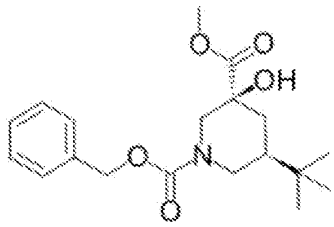
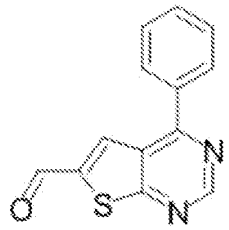
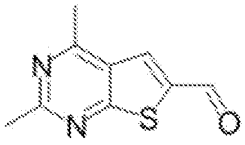
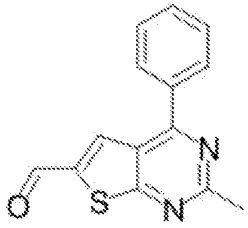
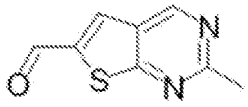
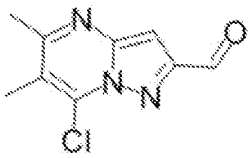
118		[M+H]+ 478.4
119		[M+H]+ 439.4
120		[M+H]+ 485.4
121		[M+H]+ 443.3
122		[M+H]+ 464.5

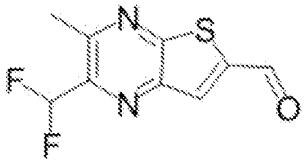
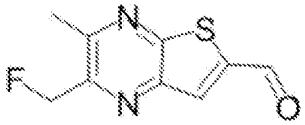
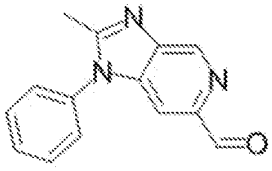
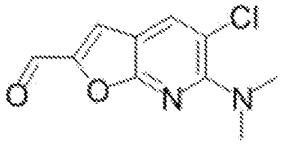
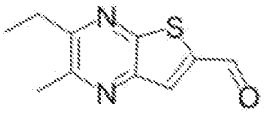
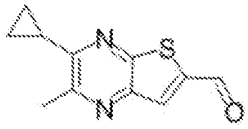
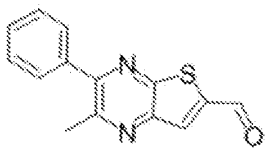
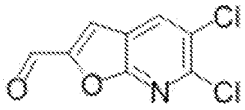
123		[M+H]+ 434.8
124		[M+H]+ 487
125		NMR2: 8.34 (d, J = 4.7 Hz, 2H), 6.61 (s, 1H), 6.50 (t, J = 4.7 Hz, 1H), 4.76 (t, J = 1.7 Hz, 2H), 4.16 (t, J = 5.7 Hz, 2H), 3.78 (d, J = 14.0 Hz, 1H), 3.74 (s, 3H), 3.57 (d, J = 14.1 Hz, 1H), 3.47 – 3.36 (m, 2H), 3.16 (dt, J = 8.7, 6.7 Hz, 1H), 2.96 – 2.83 (m, 3H), 2.59 – 2.49 (m, 1H), 1.85 (dd, J = 22.2, 10.7 Hz, 2H), 1.71 – 1.58 (m, 1H), 1.50 (p, J = 7.1 Hz, 2H), 1.00 (t, J = 12.4 Hz, 1H), 0.90 (s, 9H), 0.86 (t, J = 7.4 Hz, 3H).
126		[M+H]+ 473.5
127		NMR2: 8.69 (s, 1H), 8.51 (s, 1H), 8.16 (d, J = 8.7 Hz, 1H), 7.75 (dd, J = 8.7, 1.8 Hz, 1H), 7.19 (s, 1H), 3.71 (d, J = 13.8 Hz, 1H), 3.68 (s, 3H), 3.47 – 3.33 (m, 2H), 3.19 (d, J = 10.3 Hz, 1H), 3.09 (dt, J = 8.6, 6.7 Hz, 1H), 2.85 (d, J = 8.6 Hz, 1H), 2.54 (d, J = 12.0 Hz, 1H), 2.38 (s, 3H), 1.87 – 1.75 (m, 2H), 1.65 – 1.53 (m, 1H), 1.46 (h, J = 7.1 Hz, 2H), 1.01 (t, J = 12.4 Hz, 1H), 0.90 – 0.79 (m, 12H).

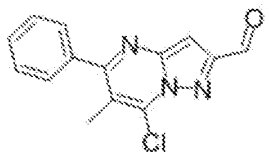
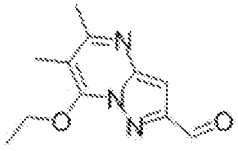
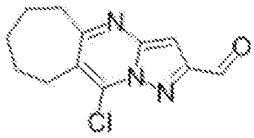
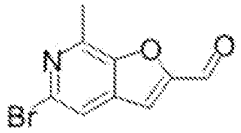
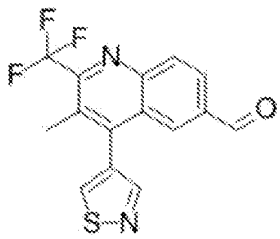
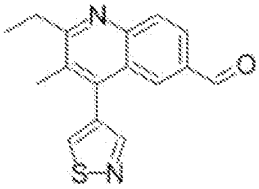
128		[M+H]+ 358.4
129		NMR2; 9.11 (brs, 1H), 7.40 (s, 1H), 6.39 (s, 1H), 3.91 (d, J = 14.7 Hz, 1H), 3.81 (s, 3H), 3.65 (d, J = 14.7 Hz, 1H), 3.45 – 3.36 (m, 1H), 3.24 – 3.14 (m, 2H), 2.97 – 2.88 (m, 1H), 2.57 (s, 3H), 2.55 – 2.47 (m, 1H), 2.37 (s, 3H), 1.97 (t, J = 11.0 Hz, 1H), 1.82 (d, J = 10.7 Hz, 1H), 1.50 – 1.38 (m, 3H), 1.22 - 1.14 (m, 1H), 0.90 (s, 9H), 0.82 (t, J = 7.4 Hz, 3H).
130		[M+H]+ 451.4, 453.4 NMR2; 6.57 (s, 1H), 3.92 (d, J = 14.2 Hz, 1H), 3.75 (s, 3H), 3.74 (d, J = 14.2 Hz, 1H), 3.45 – 3.34 (m, 2H), 3.16 (dt, J = 8.6, 6.7 Hz, 1H), 3.03 – 2.94 (m, 1H), 2.59 (s, 3H), 2.58 – 2.49 (m, 1H), 2.42 (s, 3H), 1.93 (d, J = 10.5 Hz, 1H), 1.91 (t, J = 11.1 Hz, 1H), 1.69 – 1.57 (m, 1H), 1.55 – 1.42 (m, 2H), 1.08 – 0.97 (m, 1H), 0.90 (s, 9H), 0.84 (t, J = 7.4 Hz, 3H).
131		[M+H]+ 406.8
132		[M+H]+ 392.7

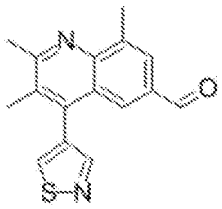
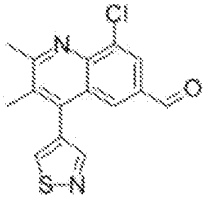
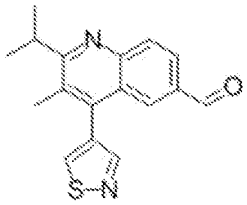
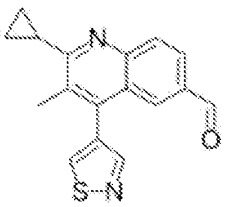
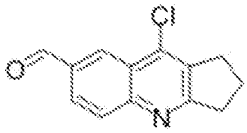
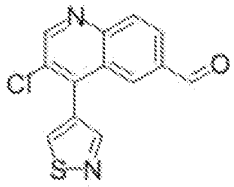
133		[M+H]+ 420.8
134		[M+H]+ 435.4, 437.4
135		[M+H]+ 401.5
136		[M+H]+ 418.8
137		[M+H]+ 420.4
138		[M+H]+ 474.4

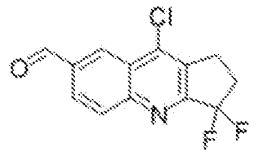
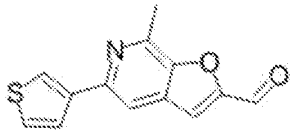
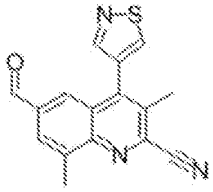
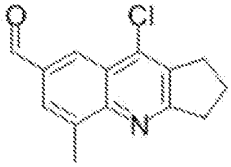
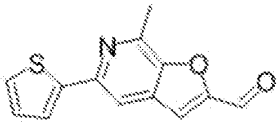
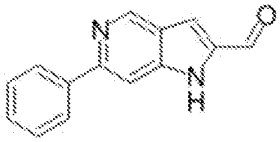
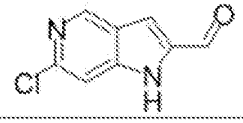
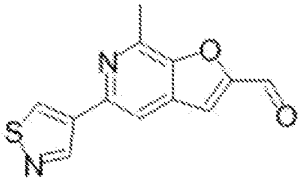
139		[M+H]+ 574.5
140		[M+H]+ 519.4
141		NMR2; 7.42 - 7.28 (m, 5H), 5.75 - 5.62 (m, 1H), 5.16 - 5.01 (m, 4H), 4.65 (d, J=11.6 Hz, 1H), 4.29 - 4.28 (m, 1H), 3.63 - 3.51 (m, 3H), 2.47 (d, J=12.6 Hz, 1H), 2.37 - 2.19 (m, 4H), 1.40 - 1.29 (m, 1H), 0.99 (t, J=14.5 Hz, 1H), 0.90 (s, 9H).
142		NMR2; 10.16 (s, 1H), 8.07 (s, 1H), 2.71 (s, 3H), 2.70 (s, 3H).
143		[M+H]+ 193.1
144		NMR2; 9.97 (s, 1H), 7.63 (s, 1H), 3.16 – 3.09 (m, 4H), 2.07 – 1.94 (m, 4H).
145		NMR2; 8.82 (d, J = 2.52 Hz, 1H), 8.52 (d, J = 2.52 Hz, 1H), 7.65 (s, 1H), 7.66 – 7.46 (m, 5H), 4.83 (d, J = 0.64Hz, 2H).

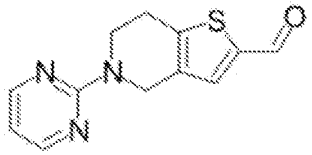
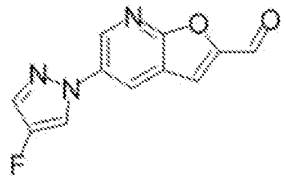
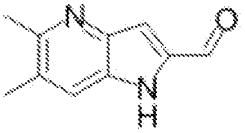
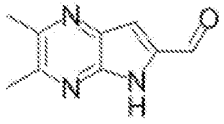
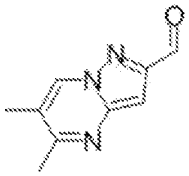
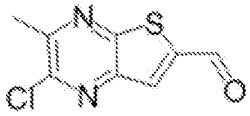
146		NMR1; 7.45 - 7.35 (m, 5H), 6.01 (s, 1H), 5.11 (s, 2H), 4.47 (d, J=13.1 Hz, 1H), 4.14 - 4.05 (m, 1H), 3.58 (s, 3H), 2.74 - 2.64 (m, 1H), 2.51 - 2.45 (m, 1H), 2.30 (d, J=11.1 Hz, 1H), 1.28 - 1.21 (m, 2H), 0.92 (s, 9H).
147		[M+H]+ 241.1
148		[M+H]+ 193.0
149		[M+H]+ 255.2 NMR2; 10.09 (s, 1H), 8.21 (s, 1H), 7.99 ~ 7.88 (m, 2H), 7.65 ~ 7.55 (m, 3H), 2.93 (s, 3H).
150		[M+H]+ 179.1
151		[M+H]+ 210.2, 212.1 NMR2; 10.22 (s, 1H), 7.13 (s, 1H), 2.66 (s, 3H), 2.49 (s, 3H).

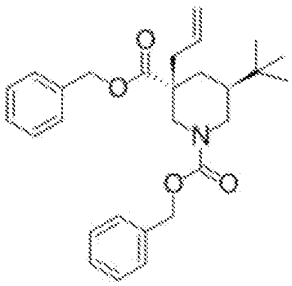
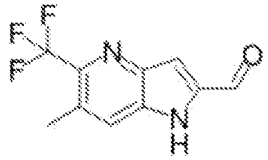
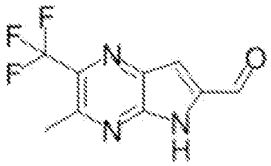
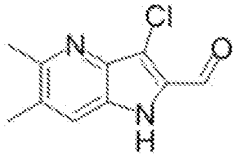
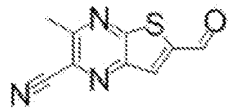
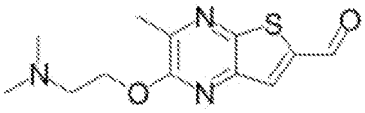
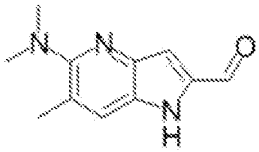
152		[M+H]+ 229.2 NMR2: 10.21 (s, 1H), 8.17 (s, 1H), 6.82 (t, J = 54.1 Hz, 1H), 2.92 (s, 3H).
153		[M+H]+ 211.2
154		[M+H]+ 238.3
155		[M+H]+ 225.2
156		[M+H]+ 207.2
157		[M+H]+ 219.2 NMR2: 10.13 (s, 1H), 8.04 (s, 1H), 2.83 (s, 3H), 2.31 – 2.21 (m, 1H), 1.31 – 1.25 (m, 2H), 1.21 – 1.13 (m, 2H).
158		NMR2: 10.21 (s, 1H), 8.15 (s, 1H), 7.72 – 7.62 (m, 2H), 7.58 – 7.48 (m, 3H), 2.79 (s, 3H).
159		[M+H]+ 216.1, 218.0 NMR2, 9.94 (1H, s), 8.22 (1H, s), 7.49 (1H, s)

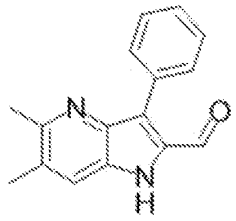
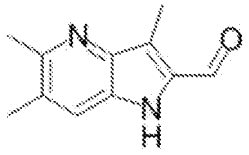
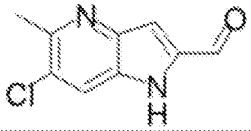
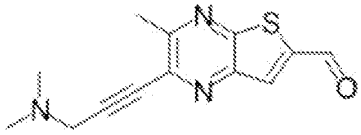
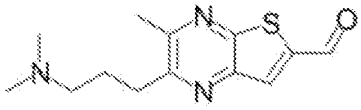
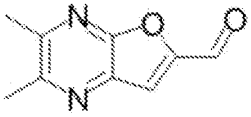
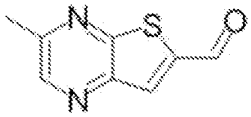
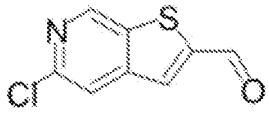
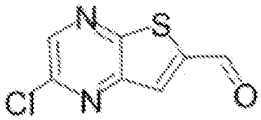
160		[M+H]+ 272.2
161		[M+H]+ 220.2
162		[M+H]+ 250.2
163		NMR2; 9.99 (s, 1H), 7.71 (s, 1H), 7.47 (s, 1H), 2.82 (s, 3H).
164		NMR2; 9.80 (s, 1H), 7.48 (s, 1H), 5.05 (br, 1H), 4.56 (br, 1H), 3.41 (br, 1H), 2.66 (d, J = 17.4 Hz, 1H), 2.30 (br, 1H), 2.15 (tt, J = 11.8, 6.4 Hz, 1H), 1.94 – 1.83 (m, 1H), 1.62 (br, 1H), 1.41 (s, 9H).
165		NMR2; 10.07 (s, 1H), 8.76 (s, 1H), 8.55 (s, 1H), 8.36 (d, J = 8.7 Hz, 1H), 8.24 (dd, J = 8.8, 1.7 Hz, 1H), 7.90 (d, J = 1.7 Hz, 1H), 2.44 (q, J = 1.8 Hz, 3H).
166		NMR2; 10.01 (s, 1H), 8.68 (s, 1H), 8.52 (s, 1H), 8.21 – 8.09 (m, 2H), 7.82 (dd, J = 1.7, 0.6 Hz, 1H), 3.10 (q, J = 7.5 Hz, 2H), 2.30 (s, 3H), 1.45 (t, J = 7.5 Hz, 3H).

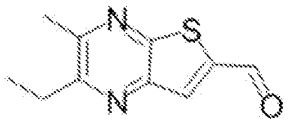
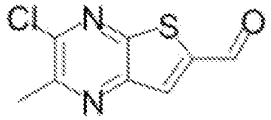
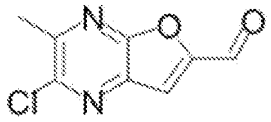
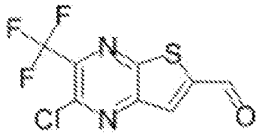
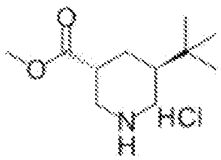
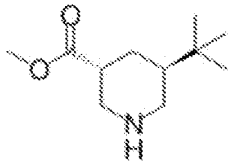
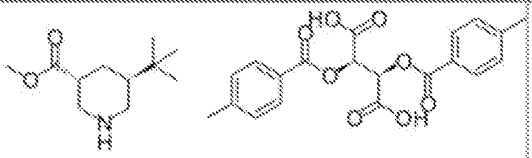
167		NMR2: 9.95 (s, 1H), 8.66 (s, 1H), 8.50 (s, 1H), 7.97 (s, 1H), 7.65 (s, 1H), 2.88 (s, 3H), 2.82 (s, 3H), 2.25 (s, 3H).
168		NMR2: 9.94 (s, 1H), 8.69 (s, 1H), 8.51 (s, 1H), 8.25 (d, J = 1.7 Hz, 1H), 7.74 (d, J = 1.7 Hz, 1H), 2.88 (s, 3H), 2.28 (s, 3H).
169		NMR2: 10.00 (s, 1H), 8.67 (s, 1H), 8.52 (s, 1H), 8.18 (d, J = 8.7 Hz, 1H), 8.11 (dd, J = 8.7, 1.8 Hz, 1H), 7.79 (s, 1H), 3.52 (p, J = 6.7 Hz, 1H), 2.31 (s, 3H), 1.43 (d, J = 6.7 Hz, 6H).
170		NMR2: 9.98 (s, 1H), 8.68 (s, 1H), 8.52 (s, 1H), 8.11 – 8.01 (m, 2H), 7.78 (dd, J = 1.8, 0.7 Hz, 1H), 2.41 (s, 3H), 2.40 – 2.31 (m, 1H), 1.40-1.36 (m, 2H), 1.19 – 1.10 (m, 2H).
171		NMR2 10.22 (s, 1H), 8.70 – 8.65 (m, 1H), 8.20 – 8.08 (m, 2H), 3.32 – 3.16 (m, 4H), 2.30 (p, J = 7.7 Hz, 2H).
172		$[M+H]^+$ 275.2

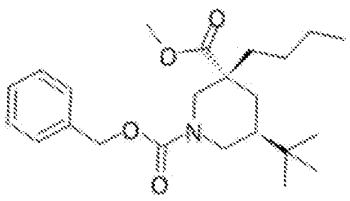
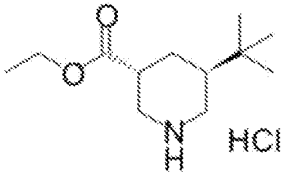
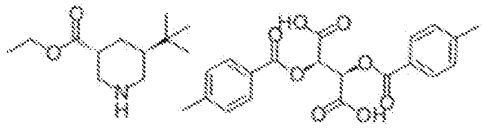
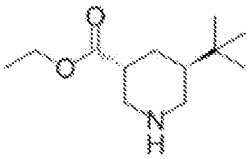
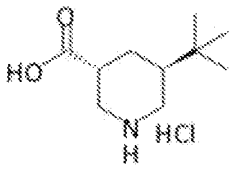
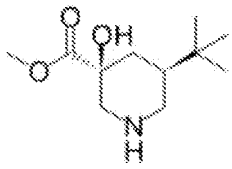
173		NMR2: 10.28 (s, 1H), 8.78 (d, J = 1.8 Hz, 1H), 8.39 (d, J = 8.7 Hz, 1H), 8.28 (dd, J = 8.7, 1.8 Hz, 1H), 3.29 (t, J = 7.2 Hz, 2H), 2.88 – 2.73 (m, 2H).
174		[M+H]+ 244.2
175		NMR2: 10.02 (s, 1H), 8.76 (s, 1H), 8.54 (s, 1H), 8.08 (dd, J = 1.8, 1.1 Hz, 1H), 7.77 (dd, J = 1.8, 0.8 Hz, 1H), 2.89 (s, 3H), 2.55 (s, 3H).
176		NMR2: 10.16 (s, 1H), 8.53 (s, 1H), 8.01 (s, 1H), 3.28 (t, J = 7.7 Hz, 2H), 3.20 (t, J = 7.5 Hz, 2H), 2.83 (s, 3H), 2.28 (p, J = 7.7 Hz, 2H).
177		[M+H]+ 244.1
178		[M+H]+ 223.2
179		[M+H]+ 181.1
180		[M+H]+ 245

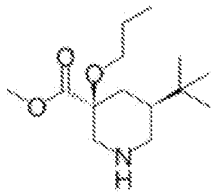
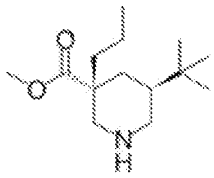
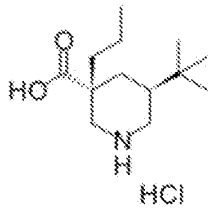
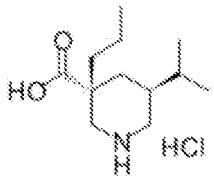
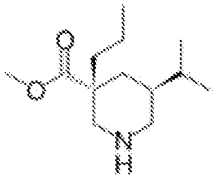
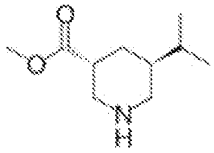
181		NMR2: 9.85 (s, 1H), 8.36 (d, J = 4.8 Hz, 2H), 7.54 (s, 1H), 6.86 (t, J = 4.8 Hz, 1H), 4.90 (t, J = 1.6 Hz, 2H), 4.20 (t, J = 5.7 Hz, 2H), 3.02 (tt, J = 5.8, 1.7 Hz, 2H).
182		[M+H]+ 232.2
183		[M+H]+ 175.1 NMR2: 9.89 (s, 1H), 9.00 (brs, 1H), 7.52 (t, J = 1.0 Hz, 1H), 7.35 (dd, J = 2.2, 1.0 Hz, 1H), 2.62 (s, 3H), 2.43 (s, 3H).
184		[M+H]+ 176.1
185		[M+H]+ 176.1
186		[M+H]+ 213.1 NMR2; 10.17 (1H, s), 8.07 (1H, s), 2.83 (3H, s)
187		[M+H]+ 209.1
188		[M+H]+ 175.1

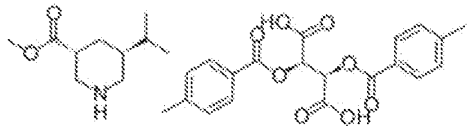
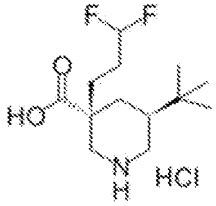
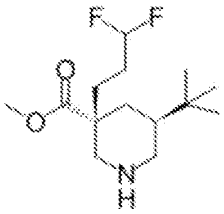
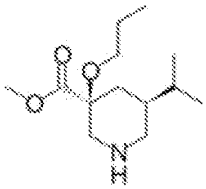
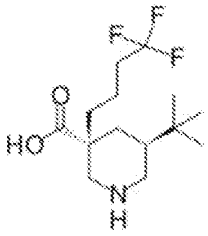
189		[M+H]+ 450.3 NMR2: 7.20 - 7.12 (m, 10H), 5.55 - 5.44 (m, 1H), 5.01 - 4.94 (m, 2H), 4.90 - 4.73 (m, 3H), 4.57 - 4.50 (m, 1H), 4.13 (bs, 1H), 3.79 - 3.52 (m, 1H), 2.36 - 2.15 (m, 2H), 2.08 (d, *J* = 7.3 Hz, 1H), 1.88 - 1.60 (m, 2H), 0.87 - 0.73 (m, 1H), 0.70 (s, 9H), 0.69 - 0.67 (m, 1H).
190		[M+H]+ 229.0
191		[M+H]+ 230.0 NMR2: 10.04 (s, 1H), 9.52 (brs, 1H), 7.49 (d, *J* = 2.0 Hz, 1H), 2.87 (q, *J* = 1.8 Hz, 3H).
192		[M+H]+ 209.0
193		NMR2: 10.23 (s, 1H), 8.17 (s, 1H), 2.96 (s, 3H).
194		NMR2: 10.10 (s, 1H), 7.95 (s, 1H), 4.55 (t, *J* = 5.8 Hz, 2H), 2.81 (t, *J* = 5.7 Hz, 2H), 2.63 (s, 3H), 2.38 (s, 6H).
195		[M+H]+ 204.1

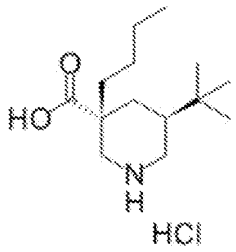
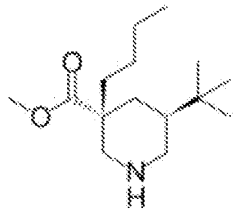
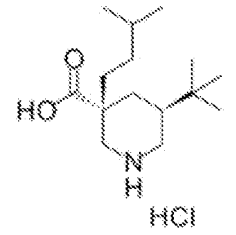
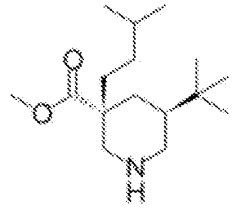
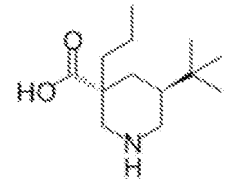
196		[M+H]+ 251.2
197		[M+H]+ 189.1
198		[M+H]+ 195.1
199		[M+H]+ 260.2
200		[M+H]+ 264.1
201		[M+H]+ 177.1 NMR2; 9.96 (s, 1H), 7.65 (s, 1H), 2.70 (s, 6H).
202		NMR2; 10.19 (s, 1H), 8.66 (s, 1H), 8.15 (s, 1H), 2.75 (s, 3H).
203		[M+H]+ 198.0
204		[M+H]+ 199.0

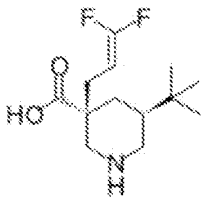
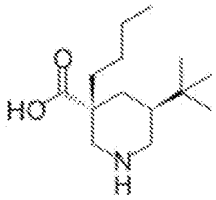
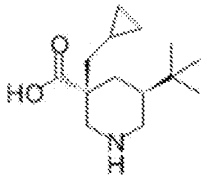
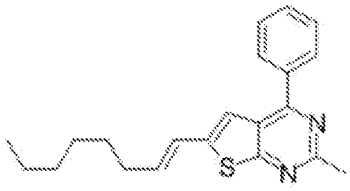
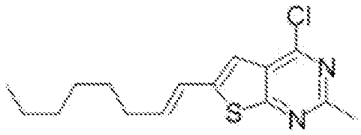
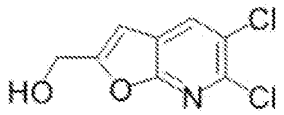
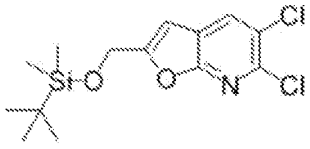
205		[M+H]+ 207.2 NMR2: 10.16 (s, 1H), 8.11 (s, 1H), 3.00 (q, J = 7.5 Hz, 2H), 2.73 (s, 3H), 1.39 (t, J = 7.5 Hz, 3H).
206		NMR2: 10.18 (s, 1H), 8.10 (s, 1H), 2.81 (s, 3H).
207		NMR2: 9.99 (s, 1H), 7.64 (s, 1H), 2.82 (s, 3H).
208		NMR2: 10.26 (s, 1H), 8.18(s, 1H).
209	AND Enantiomer 	NMR1: 9.52 - 9.27 (brs, 1H), 8.13 - 7.93 (brs, 1H), 3.69 (s, 3H), 3.49 (d, J = 12.7 Hz, 1H), 3.17 (d, J = 12.4 Hz, 1H), 3.13 - 3.08 (m, 1H), 3.12 - 2.96 (m, 1H), 2.69 - 2.56 (m, 1H), 2.13 (d, J = 13.0 Hz, 1H), 1.50 (dt, J = 5.0, 13.1 Hz, 1H), 1.40 - 1.31 (m, 1H), 0.85 (s, 9H). Trans racemic
210		NMR2: 3.72 (s, 3H), 3.40 (d, J=12.1 Hz, 1H), 3.10 (d, J=12.6 Hz, 1H), 2.66 - 2.59 (m, 2H), 2.36 - 2.22 (m, 2H), 1.45 - 1.35 (m, 1H), 1.28 - 1.19 (m, 1H), 0.85 (s, 9H).
211		[M+H]- 200.3 NMR1: 7.80 (d, J = 7.9 Hz, 4H), 7.29 (d, J = 7.9 Hz, 4H), 5.60 (s, 2H), 3.68 (s, 3H), 3.47 (d, J = 14.5 Hz, 2H), 3.13 (d, J = 12.1 Hz, 1H), 3.06 (s, 1H), 2.97 (dd, J = 13.0, 4.4 Hz, 1H), 2.35 (s, 6H), 2.12 (d, J = 13.6 Hz, 1H), 1.52-1.40 (m, 1H), 1.40-1.17 (m, 1H), 0.83 (s, 9H).

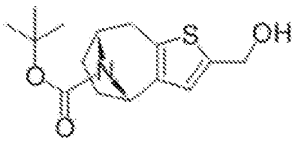
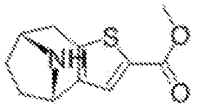
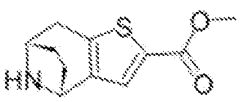
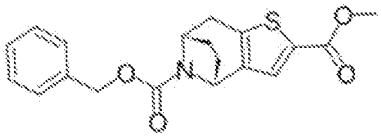
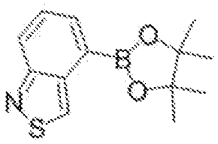
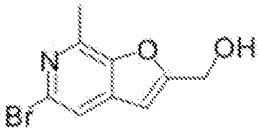
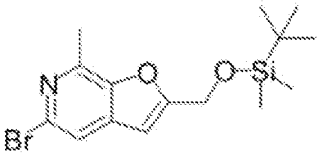
212		[M+H]+ 390.4 NMR2: 7.40 – 7.26 (m, 5H), 5.17 – 5.11 (m, 2H), 4.69 – 4.61 (m, 1H), 4.33 – 4.20 (m, 1H), 3.65 – 3.51 (m, 3H), 2.48 – 2.40 (m, 1H), 2.35 (dq, J = 13.1, 2.5 Hz, 2H), 1.54 – 1.38 (m, 2H), 1.34 (ddd, J = 12.2, 4.1, 3.0 Hz, 1H), 1.31 – 1.08 (m, 4H), 0.98 – 0.84 (m, 13H).
213		[M+H]+ 214.1
214		NMR1: 7.79 (d, J = 8.0 Hz, 4H), 7.28 (d, J = 8.0 Hz, 4H), 5.58 (s, 2H), 4.27 - 4.18 (dq, J = 10.8, 7.1 Hz, 1H), 4.11 - 4.02 (dq, J = 10.8, 7.1 Hz, 1H), 3.18 - 3.10 (m, 2H), 3.06 - 3.01 (m, 1H), 2.95 (dd, J = 12.9, 4.3 Hz, 1H), 2.57 (dd, J = 6.0, 6.0 Hz, 1H), 2.34 (S, 6H), 2.13 (d, J = 13.5 Hz, 1H), 1.48 (ddd, J = 6.6, 6.6, 5.2 Hz, 1H), 1.33 - 1.24 (m, 1H), 1.21 (t, J = 7.1 Hz, 3H), 0.83 (s, 9H).
215	AND Enantiomer 	[M+H]+ 214.3 Trans racemic
216		NMR1: 10.22 - 10.17 (m, 1H), 7.88 - 7.83 (m, 1H), 3.45 (d, J=12.6 Hz, 1H), 3.17 (d, J=11.6 Hz, 1H), 3.04 - 2.91 (m, 2H), 2.66 - 2.59 (m, 1H), 2.17 (d, J=13.1 Hz, 1H), 1.60 - 1.37 (m, 2H), 0.88 (s, 9H).
217		[M+H]+ 216.4 NMR2: 5.57 (s, 1H), 3.64 (s, 3H), 3.28 - 3.21 (m, 1H), 2.88 - 2.84 (m, 1H), 2.25 (dq, J=2.3, 5.5 Hz, 1H), 2.17 (d, J=11.9 Hz, 1H), 2.06 (dd, J=11.6, 11.6 Hz, 1H), 1.21 - 1.11 (m, 1H), 1.05 (dd, J=12.4, 12.4 Hz, 1H), 0.84 (s, 9H).

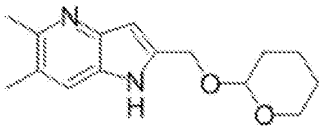
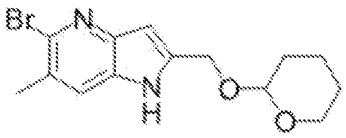
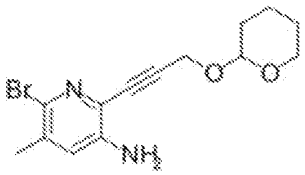
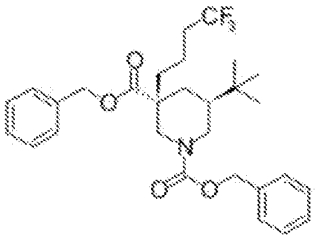
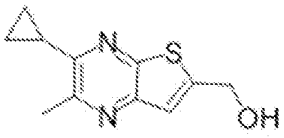
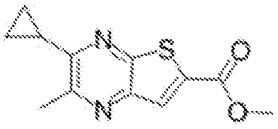
218		[M+H]+ 258.3 NMR2: 3.78 (s, 3H), 3.61 (dd, J=2.3, 12.6 Hz, 1H), 3.38 - 3.33 (m, 1H), 3.30 - 3.24 (m, 1H), 3.06 - 3.03 (m, 1H), 2.44 - 2.40 (m, 2H), 2.28 - 2.22 (m, 1H), 1.59 - 1.50 (m, 2H), 1.31 - 1.25 (m, 1H), 1.17 - 1.09 (m, 1H), 0.90 (t, J=7.4 Hz, 3H), 0.87 (s, 9H)
219		[M+H]+ 242.3 NMR2: 3.71 (s, 3H), 3.47 (dd, J=2.0, 12.9 Hz, 1H), 3.10 - 3.04 (m, 1H), 2.30 - 2.19 (m, 3H), 1.49 - 1.40 (m, 1H), 1.39 - 1.30 (m, 1H), 1.29 - 1.13 (m, 2H), 1.11 - 1.05 (m, 1H), 0.99 (t, J=12.4 Hz, 1H), 0.80 (t, J=7.1 Hz, 3H), 0.85 (s, 9H).
220		NMR1: 13.12 - 13.07 (m, 1H), 10.16 (d, J=9.7 Hz, 1H), 7.66 (d, J=9.7 Hz, 1H), 3.42 (d, J=12.4 Hz, 1H), 3.14 (d, J=11.3 Hz, 1H), 2.67 (dd, J=11.9, 11.9 Hz, 1H), 2.57 (t, J=10.7 Hz, 1H), 2.12 (d, J=11.4 Hz, 1H), 1.58 - 1.13 (m, 6H), 0.86 (m, 12H).
221		[M+H]+ 214.4
222		[M+H]+ 228.3
223		NMR2; 3.71 (s, 3H), 3.37 – 3.27 (m, 1H), 3.06 – 2.97 (m, 1H), 2.72 (dd, J = 13.0, 3.7 Hz, 1H), 2.63 – 2.55 (m, 1H), 2.37 (dd, J = 12.7, 10.1 Hz, 1H), 2.22 – 2.11 (m, 1H), 1.50 – 1.34 (m, 2H), 1.32 – 1.19 (m, 1H), 0.88 (dd, J = 6.8, 5.1 Hz, 6H).

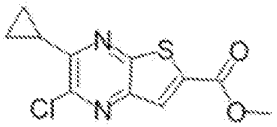
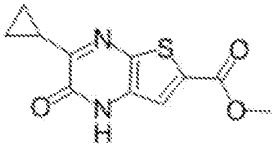
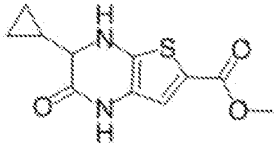
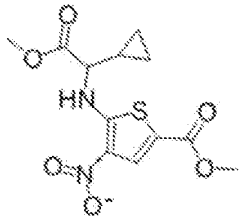
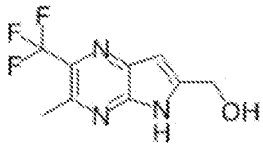
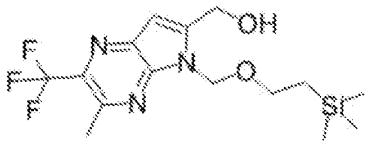
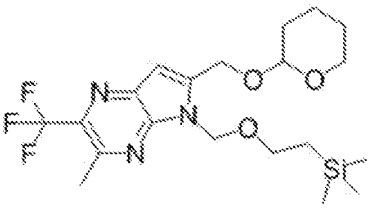
224		NMR1; 7.84 – 7.76 (m, 4H), 7.28 (d, *J* = 8.0 Hz, 4H), 5.59 (s, 2H), 3.67 (s, 3H), 3.44 – 3.35 (m, 1H), 3.04 (d, *J* = 12.3 Hz, 1H), 3.01 – 2.94 (m, 2H), 2.61 (dd, *J* = 12.3, 10.9 Hz, 1H), 2.35 (s, 6H), 2.00 (d, *J* = 13.3 Hz, 1H), 1.55 – 1.41 (m, 2H), 1.40 – 1.35 (m, 1H), 0.82 (dd, *J* = 6.8, 4.6 Hz, 6H).
225		[M+H]$^+$ 264.3
226		[M+H]$^+$ 278.3, 279.3
227		[M+H]$^+$ 244.7
228		[M+H]$^+$ 296.2 NMR2; 12.42 (s, 1H), 8.27 – 8.23 (m, 1H), 7.26 (s, 1H), 3.47 (d, *J* = 12.0 Hz, 1H), 3.36 (d, *J* = 12.3 Hz, 1H), 2.61 (t, *J* = 12.5 Hz, 1H), 2.41 (d, *J* = 12.0 Hz, 1H), 2.13 – 1.99 (m, 3H), 1.94 – 1.83 (m, 1H), 1.68 – 1.57 (m, 1H), 1.58 – 1.41 (m, 1H), 1.32 – 1.20 (m, 1H), 1.08 (t, *J* = 12.9 Hz, 1H), 0.97 – 0.77 (m, 10H).

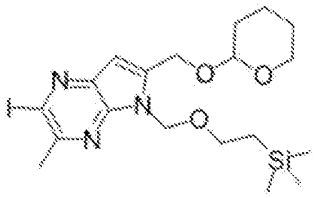
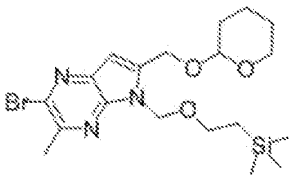
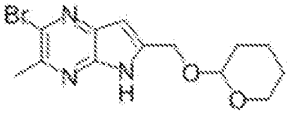
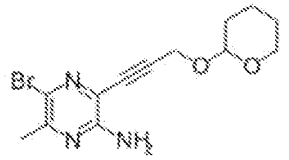
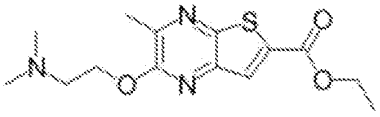
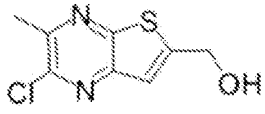
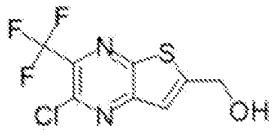
229		[M+H]+ 242.2 NMR1: 12.99 (brs, 1H), 9.74 (brs, 1H), 7.62 (brs, 1H), 3.45 (d, J = 12.5 Hz, 1H), 3.14 (d, J = 11.5 Hz, 1H), 2.68 (d, J = 12.5 Hz, 1H), 2.56 (t, J = 11.4 Hz, 1H), 2.11 (d, J = 11.3 Hz, 1H), 1.63 – 1.50 (m, 1H), 1.50 – 1.38 (m, 1H), 1.36 – 1.01 (m, 6H), 0.93 – 0.79 (m, 12H).
230		[M+H]+ 256.2 NMR2; 3.74 (s, 3H), 3.75 – 3.66 (m, 1H), 3.57 – 3.49 (m, 1H), 3.17 (dddd, J = 12.5, 3.4, 2.3, 1.0 Hz, 1H), 2.37 – 2.23 (m, 3H), 1.57 – 1.44 (m, 1H), 1.43 – 0.97 (m, 7H), 0.92 – 0.83 (m, 12H).
231		[M+H]+ 256.2 NMR2; 13.15 (bws, 1H), 10.10 (br s, 1H), 7.69 (br s, 1H), 3.48 (d, J=12.4 Hz, 1H), 3.19 (d, J=11.4 Hz, 1H), 2.73 - 2.72 (m, 1H), 2.65 - 2.59 (m, 1H), 2.17 (d, J=10.6 Hz, 1H), 1.69 - 1.58 (m, 1H), 1.55 - 1.45 (m, 2H), 1.39 - 1.27 (m, 2H), 1.23 - 1.11 (m, 1H), 1.10 - 0.99 (m, 1H), 0.93 - 0.88 (m, 15H).
232		[M+H]+ 270.3 NMR2; 3.74 (s, 3H), 3.55 - 3.50 (m, 1H), 3.17 (d, J=12.6 Hz, 1H), 2.76 - 2.66 (m, 1H), 2.36 - 2.24 (m, 3H), 1.58 - 1.27 (m, 3H), 1.20 - 0.96 (m, 3H), 0.93 - 0.89 (m, 1H), 0.88 - 0.84 (m, 15H).
233		[M+H]+ 228.4 NMR2; 12.53 (brs, 1H), 8.19 (brs, 1H), 3.48 (d, J = 12.1 Hz, 1H), 3.34 (d, J = 12.4 Hz, 1H), 2.60 (t, J = 12.6 Hz, 1H), 2.44 (d, J = 12.1 Hz, 1H), 2.08 (d, J = 12.9 Hz, 1H), 1.90 – 1.79 (m, 1H), 1.65 – 1.53 (m, 1H), 1.35 – 1.14 (m, 3H), 1.08 (t, J = 13.0 Hz, 1H), 0.91 (t, J = 6.9 Hz, 3H), 0.88 (s, 9H).

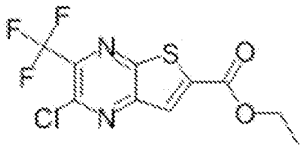
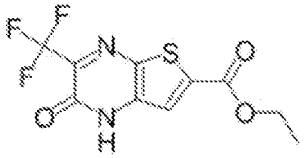
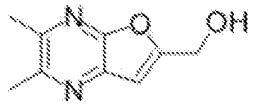
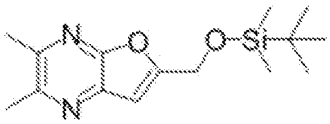
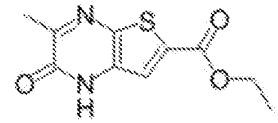
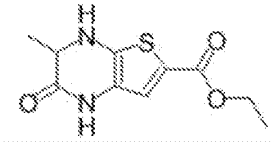
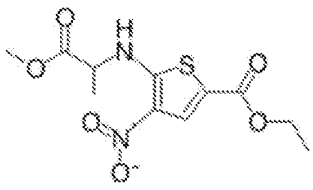
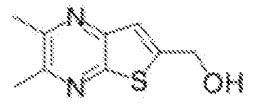
234		[M+H]+ 262.1
235		[M+H]+ 242.3
236		NMR2; 7.36 – 7.27 (m, 10H), 5.19 – 5.09 (m, 2H), 5.04 – 4.75 (m, 3H), 4.31 – 4.26 (m, 1H), 2.52 – 2.35 (m, 3H), 1.51 – 1.38 (m, 2H), 1.30 – 1.25 (m, 1H), 1.00 (t, J = 12.8 Hz, 1H), 0.86 (s, 9H), 0.69 – 0.57 (m, 1H), 0.43 – 0.35 (m, 2H), -0.03 – -0.08 (m, 2H).
237		[M+H]+ 337.3 NMR2; 7.94 – 7.85 (m, 2H), 7.58 – 7.49 (m, 3H), 7.19 (s, 1H), 6.57 (d, J = 15.6 Hz, 1H), 6.24 (dt, J = 15.6, 6.9 Hz, 1H), 2.86 (s, 3H), 2.29 – 2.20 (m, 2H), 1.54 – 1.44 (m, 2H), 1.39 – 1.26 (m, 6H), 0.89 (t, J = 6.9 Hz, 3H).
238		[M+H]+ 295.3, 297.2 NMR2; 7.03 (s, 1H), 6.58 (d, J = 15.7 Hz, 1H), 6.27 (dt, J = 15.7, 7.0 Hz, 1H), 2.78 (s, 3H), 2.30 – 2.21 (m, 2H), 1.54 – 1.45 (m, 2H), 1.40 – 1.23 (m, 6H), 0.90 (t, J = 7.0 Hz, 3H).
239		[M+H]+ 218.1, 220.1 NMR2; 7.97 (1H, s), 6.67 (0H, d, J=1.8 Hz), 4.80 (2H, s), 2.05 (0H, s)
240		[M+H]+ 332.3, 334.2 NMR2; 7.79 (1H, s), 6.45 (1H, s), 4.66 (2H, s), 0.85 – 0.68 (15H, m)

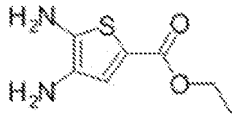
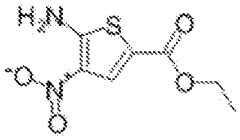
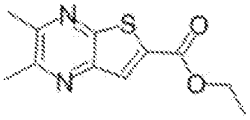
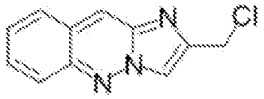
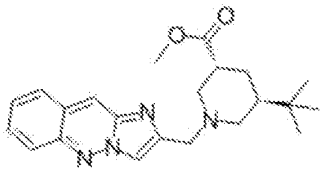
241		NMR2 6.71 (s, 1H), 4.98-4.80 (br, 1H), 4.73 (s, 2H), 4.64-4.42 (br, 1H), 3.44-3.23 (br, 1H), 2.52 (d, J = 16.4 Hz, 1H), 2.24 (brs, 1H), 2.06 (m, 2H), 1.87 (m, 1H), 1.78-1.60 (bc, 1H), 1.42 (s, 9H).
242		NMR2 7.50 (s, 1H), 4.96 (d, J = 33.9 Hz, 1H), 4.60 (s, 1H), 3.85 (s, 3H), 3.45 (br, 1H), 2.59 (d, J = 16.9 Hz, 1H), 2.31 – 2.21 (m, 1H), 2.19 – 2.02 (m, 1H), 1.91 - 1.81 (m, 1H), 1.70 - 1.60 (m, 1H), 1.40 (s, 9H).
243		NMR2 7.45 (s, 1H), 4.29 (d, J = 5.6 Hz, 1H), 3.98 (ddt, J = 7.6, 4.7, 1.4 Hz, 1H), 3.85 (s, 3H), 3.24 – 3.14 (m, 1H), 2.62 (dd, J = 17.1, 1.3 Hz, 1H), 2.21 – 2.08 (m, 1H), 2.13 – 1.86 (m, 4H), 1.61 (dddd, J = 12.6, 8.4, 6.7, 1.3 Hz, 1H).
244	AND Enantiomer 	NMR2 7.46 (s, 1H), 4.31 (d, J = 5.6 Hz, 1H), 3.99 (ddt, J = 7.6, 4.9, 1.4 Hz, 1H), 3.85 (s, 3H), 3.25 – 3.15 (m, 1H), 2.67 – 2.58 (m, 1H), 2.22 – 1.87 (m, 3H), 1.68 – 1.56 (m, 1H).
245	AND Enantiomer 	NMR2 7.52 (br, 1H), 7.50 - 7.20 (m, 5H), 5.17 - 5.01 (m, 3H), 4.68 - 4.54 (m, 1H), 3.86 (s, 3H), 3.59 - 3.24 (m ,1H), 2.61 (d, J = 16.8 Hz, 1H), 2.40 - 2.09 (m, 2H), 1.96 - 1.85 (m, 1H), 1.75 - 1.58 (m ,1H).
246		NMR2; 9.78 (d, J = 1.1 Hz, 1H), 7.95 (dt, J = 8.9, 1.1 Hz, 1H), 7.89 – 7.73 (m, 1H), 7.44 (dd, J = 8.9, 6.4 Hz, 1H), 1.40 (s, 12H).
247		NMR2; 7.50 (s, 1H), 6.65 (s, 1H), 4.83 (s, 2H), 2.71 (s, 3H), 2.19 (s, 1H).
248		NMR2; δ 7.47 (d, J = 0.8 Hz, 1H), 6.58 (t, J = 1.0 Hz, 1H), 4.83 (d, J = 1.1 Hz, 2H), 2.69 (s, 3H), 0.95 (s, 9H), 0.15 (s, 6H).

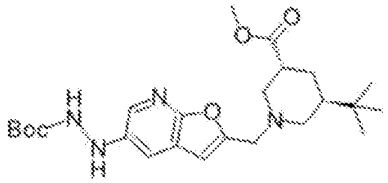
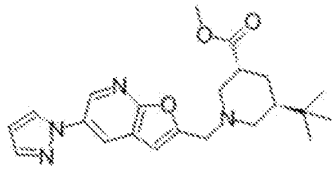
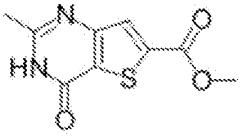
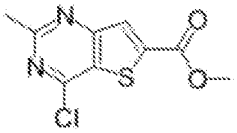
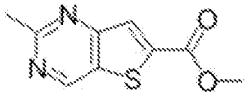
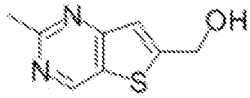
249		[M+H]+ 177.2 NMR1: 10.93 (brs, 1H), 7.40 (s, 1H), 6.24 (s, 1H), 5.33 (t, J = 5.4 Hz, 1H), 4.60 (d, J = 5.4 Hz, 2H), 2.43 (s, 3H), 2.30 (s, 3H).
250		[M+H]+ 261.2 NMR2: 8.45 (brs, 1H),7.38 (s, 1H), 6.51 (dd, J = 2.1, 0.9 Hz, 1H), 4.87 (dd, J = 13.2, 0.9 Hz, 1H), 4.80 (d, J = 13.2 Hz, 1H), 4.69 (dd, J = 5.1, 2.6 Hz, 1H), 4.00 – 3.90 (m, 1H), 3.62 – 3.52 (m, 1H), 2.57 (s, 3H), 2.37 (s, 3H), 1.96 – 1.35 (m, 6H).
251		[M+H]+ 325.2, 327.2 NMR2: 8.70 (brs, 1H), 7.51 - 7.48 (m, 1H), 6.51 (dd, J = 2.0, 0.9 Hz, 1H), 4.87 (dd, J = 13.6, 0.9 Hz, 1H), 4.82 (d, J = 13.6 Hz, 1H), 4.69 (dd, J = 5.3, 2.5 Hz, 1H), 4.01 – 3.92 (m, 1H), 3.64 – 3.53 (m, 1H), 2.47 (d, J = 0.8 Hz, 3H), 1.91 – 1.49 (m, 6H).
252		[M+H]+ 325.3, 327.3 NMR2: 6.87 (q, J = 0.8 Hz, 1H), 4.88 (dd, J = 3.9, 2.9 Hz, 1H), 4.56 (d, J = 16.0 Hz, 1H), 4.52 (d, J = 16.0 Hz, 1H), 4.23 (brs, 2H), 3.93 – 3.82 (m, 1H), 3.62 – 3.50 (m, 1H), 2.29 (d, J = 0.8 Hz, 3H), 1.91 – 1.41 (m, 6H).
253		[M+H]+ 520.9 NMR2: 7.43 – 7.26 (m, 10H), 5.18 – 5.09 (m, 2H), 5.06 – 4.84 (m, 2H), 4.79 – 4.61 (m, 1H), 4.37 – 4.16 (m, 1H), 2.48 – 2.28 (m, 3H), 1.98 – 1.85 (m, 1H), 1.56 – 1.38 (m, 5H), 1.35 – 1.26 (m, 1H), 0.99 – 0.87 (m, 1H), 0.86 (s, 9H).
254		[M+H]+ 221.2 NMR2: 7.24 (t, J = 1.0 Hz, 1H), 4.95 (dd, J = 1.0, 6.2 Hz, 2H), 2.77 (s, 3H), 2.24 – 2.15 (m, 1H), 1.22 – 1.13 (m, 2H), 1.11 – 1.02 (m, 2H).
255		[M+H]+ 249.2 NMR2: 8.05 (s, 1H), 3.97 (s, 3H), 2.81 (s, 3H), 2.28 – 2.18 (m, 1H), 1.29 – 1.22 (m, 2H), 1.18 – 1.10 (m, 2H).

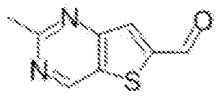
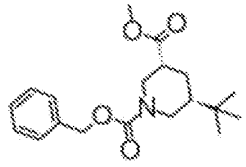
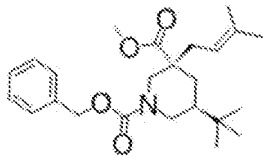
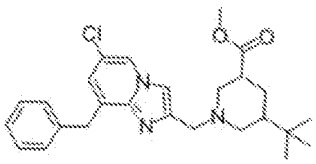
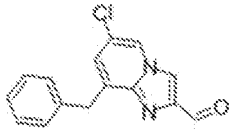
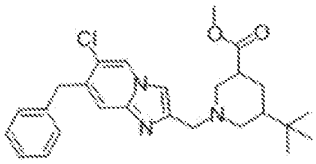
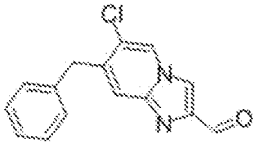
256		[M+H]+ 269.2, 271.1 NMR2; 8.03 (s, 1H), 3.98 (s, 3H), 2.72 – 2.60 (m, 1H), 1.29 – 1.20 (m, 4H).
257		[M+H]+ 251.1 NMR1; 7.48 (s, 1H), 3.86 (s, 3H), 2.70 – 2.60 (m, 1H), 1.17 – 1.00 (m, 4H).
258		[M+H]+ 253.2
259		[M+H]+ 315.2 NMR2; 8.77 (d, *J* = 7.7 Hz, 1H), 8.01 (s, 1H), 3.86 (s, 3H), 3.84 (s, 3H), 3.62 (t, *J* = 7.7 Hz, 1H), 1.42 – 1.31 (m, 1H), 0.79 – 0.70 (m, 2H), 0.63 – 0.48 (m, 2H).
260		[M+H]+ 232.1 NMR2; 10.64 (brs, 1H), 6.57 (s, 1H), 4.90 (s, 2H), 4.71 (bra, 1H), 2.77 (q, *J* = 1.8 Hz, 3H).
261		[M+H]+ 362.3 NMR2; 6.76 (s, 1H), 5.79 (s, 2H), 4.91 (d, *J* = 6.3 Hz, 2H), 3.60 – 3.51 (m, 2H), 3.02 (t, *J* = 6.4 Hz, 1H), 2.79 (q, *J* = 1.8 Hz, 3H), 0.98 – 0.87 (m, 2H), -0.06 (s, 9H).
262		[M+H]+ 446.8 NMR2; 6.76 (s, 1H), 5.79 (d, *J* = 10.9 Hz, 1H), 5.77 (d, *J* = 10.9 Hz, 1H), 5.05 (dd, *J* = 13.2, 0.8 Hz, 1H), 4.81 (dd, *J* = 13.1, 0.7 Hz, 1H), 4.76 (dd, *J* = 4.0, 2.9 Hz, 1H), 3.96 – 3.85 (m, 1H), 3.62 – 3.47 (m, 3H), 2.79 (q, *J* = 1.8 Hz, 3H), 1.91 – 1.47 (m, 6H), 0.95 – 0.84 (m, 2H), -0.07 (s, 9H).

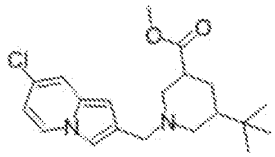
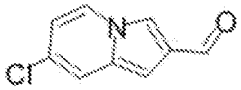
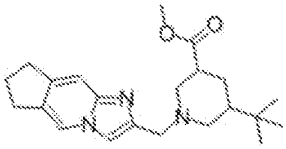
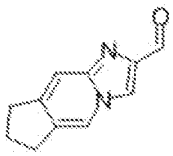
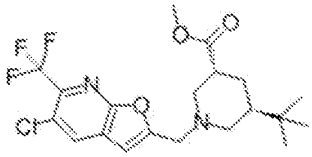
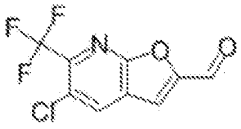
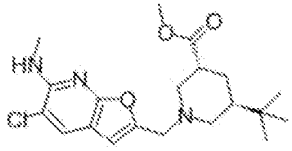
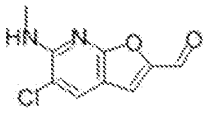
263		[M+H]+ 504.9 NMR2; 6.62 (s, 1H), 5.74 (d, J = 10.8 Hz, 1H), 5.70 (d, J = 10.8 Hz, 1H), 5.09 (dd, J = 13.0, 0.8 Hz, 1H), 4.81 – 4.70 (m, 2H), 3.95 – 3.84 (m, 1H), 3.61 – 3.45 (m, 3H), 2.78 (s, 3H), 1.89 – 1.48 (m, 6H), 0.95 – 0.85 (m, 2H), -0.07 (s, 9H).
264		[M+H]+ 456.4, 458.2 NMR2; 6.61 (s, 1H), 5.74 (d, J = 10.9 Hz, 1H), 5.71 (d, J = 10.9 Hz, 1H), 5.01 (dd, J = 13.0, 0.7 Hz, 1H), 4.76 (d, J = 13.0 Hz, 1H), 4.76 – 4.71 (m, 1H), 3.95 – 3.84 (m, 1H), 3.61 – 3.46 (m, 3H), 2.73 (s, 3H), 1.89 – 1.67 (m, 2H), 1.67 – 1.49 (m, 4H), 0.95 – 0.83 (m, 2H), -0.07 (s, 9H).
265		[M+H]+ 326.2, 328.1 NMR2; 9.22 (brs, 1H), 6.50 – 6.44 (m, 1H), 4.87 (s, 2H), 4.72 – 4.66 (m, 1H), 4.04 – 3.94 (m, 1H), 3.64 – 3.54 (m, 1H), 2.73 (s, 3H), 1.92 – 1.76 (m, 2H), 1.66 – 1.48 (m, 4H).
266		[M+H]+ 326.2, 328.2 NMR2; 5.14 (brs, 2H), 4.87 (dd, J = 3.9, 2.9 Hz, 1H), 4.54 (s, 2H), 3.94 – 3.81 (m, 1H), 3.61 – 3.52 (m, 1H), 2.36 (s, 3H), 1.91 – 1.49 (m, 6H).
267		[M+H]+ 268 NMR2; 7.14 – 7.08 (m, 1H), 4.92 (s, 2H), 4.48 – 4.39 (m, 2H), 2.79 (t, J = 5.8 Hz, 2H), 2.56 – 2.51 (m, 3H), 2.36 (s, 6H).
268		[M+H]+ 310.3 NMR2; 7.97 (s, 1H), 4.53 (t, J = 5.8 Hz, 2H), 4.42 (q, J = 7.1 Hz, 2H), 2.80 (t, J = 5.8 Hz, 2H), 2.60 (s, 3H), 2.37 (s, 6H), 1.42 (t, J = 7.1 Hz, 3H).
269		NMR2; 7.27 (t, J = 1.0 Hz, 1H), 5.01 (dd, J = 1.0, 6.2 Hz, 2H), 2.76 (s, 3H), 2.10 (t, J = 6.2 Hz, 1H).
270		[M+H]+ 269.1 NMR2; 7.41 (s, 1H), 5.10 (s, 2H).

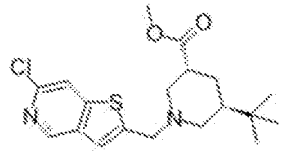
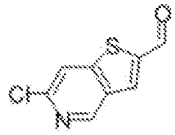
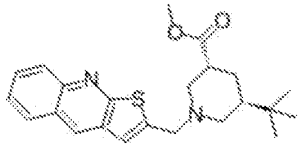
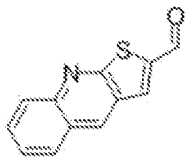
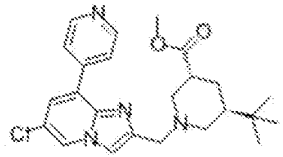
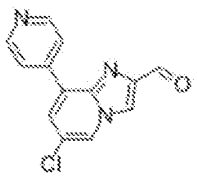
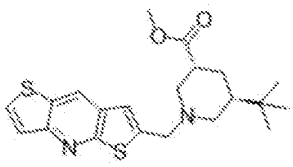
271		[M+H]+ 311.1 NMR2; 8.16 (s, 1H), 4.50 (q, J = 7.1 Hz, 2H), 1.47 (t, J = 7.1 Hz, 3H).
272		[M+H]+ 293.1 NMR2; 7.85 (s, 1H), 4.46 (q, J = 7.1 Hz, 2H), 1.45 (t, J = 7.1 Hz, 3H).
273		[M+H]+ 179.2 NMR2; 6.82 (s, 1H), 4.83 (d, J = 6.1 Hz, 2H), 2.63 (s, 3H), 2.61 (s, 3H), 2.32 (d, J = 6.1 Hz, 1H).
274		[M+H]+ 293.3 NMR2; 6.76 (s, 1H), 4.83 (s, 2H), 2.62 (s, 3H), 2.60 (s, 3H), 0.94 (s, 9H), 0.14 (s, 6H).
275		NMR2; 8.05 (s, 1H), 4.45 (q, J = 7.1 Hz, 2H), 2.80 (s, 3H), 1.44 (t, J = 7.1 Hz, 3H).
276		NMR2; 7.69 (s, 1H), 4.42 (q, J = 7.1 Hz, 2H), 2.61 (s, 3H), 1.42 (t, J = 7.1 Hz, 3H).
277		NMR2; 7.20 (s, 1H), 4.29 (q, J = 7.1 Hz, 2H), 4.21 (brs, 1H), 4.08 (dq, J = 2.8, 6.8 Hz, 1H), 1.49 (d, J = 6.8 Hz, 3H), 1.34 (t, J = 7.1 Hz, 3H).
278		NMR2; 8.02 (s, 1H), 4.32 (q, J = 7.2 Hz, 2H), 4.20 - 4.12 (m, 1H), 1.67 (d, J = 7.1 Hz, 3H), 1.36 (t, J = 7.2 Hz, 3H).
279		[M+H]+ 195.2 NMR2; 7.28 - 7.26 (m, 1H), 4.98 (d, J = 5.5 Hz, 2H), 2.65 (s, 3H), 2.64 (s, 3H), 2.21 (t, J = 5.5 Hz, 1H).

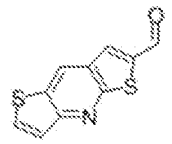
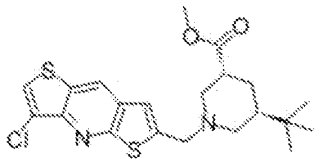
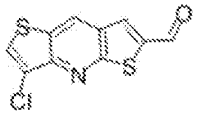
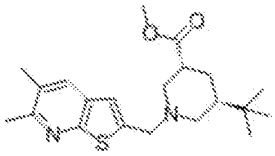
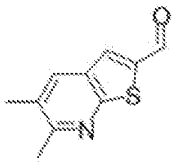
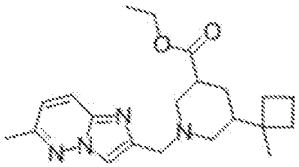
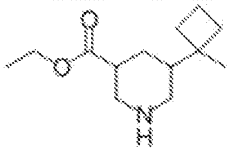
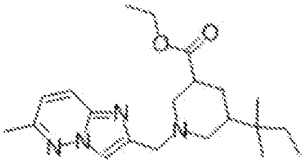
280		[M+H]+ 187.2 NMR2; 8.22 (brs, 4H), 7.31 (s, 1H), 4.28 (q, J = 7.1 Hz, 2H), 1.33 (t, J = 7.1 Hz, 3H).
281		[M+H]+ 217.2 NMR2; 7.94 (s, 1H), 6.92 (brs, 2H), 4.32 (q, J = 7.1 Hz, 2H), 1.36 (t, J = 7.1 Hz, 3H).
282		[M+H]+ 237.2 NMR2; 8.07 (s, 1H), 4.44 (q, J = 7.1 Hz, 2H), 2.69 (s, 3H), 2.68 (s, 3H), 1.43 (t, J = 7.1 Hz, 3H).
283		NMR2; 7.90 (d, J = 8.6 Hz, 1H), 7.84 – 7.80 (m, 1H), 7.63 (dd, J = 8.7, 1.8 Hz, 1H), 3.83 (d, J = 13.6 Hz, 1H), 3.72 (s, 3H), 3.58 (d, J = 13.7 Hz, 1H), 3.45 – 3.30 (m, 2H), 3.17 – 3.07 (m, 1H), 2.97 – 2.91 (m, 1H), 2.73 (s, 6H), 2.60 – 2.53 (m, 1H), 1.93 – 1.82 (m, 2H), 1.73 – 1.61 (m, 1H), 1.47 (q, J = 7.0 Hz, 2H), 1.04 (t, J = 12.5 Hz, 1H), 0.90 (s, 9H), 0.83 (t, J = 7.4 Hz, 3H).
284		[M+H]+ 218 NMR2; 8.35 (s, 1H), 8.26 (s, 1H), 7.78 (dq, J = 9.0, 0.9 Hz, 1H), 7.69 (d, J = 8.7 Hz, 1H), 7.51 (ddd, J = 9.1, 6.5, 1.3 Hz, 1H), 7.27 (ddd, J = 8.8, 6.4, 1.1 Hz, 1H), 4.86 (s, 2H).
285		[M+H]+ 381 NMR2; 8.29 (s, 1H), 8.26 (s, 1H), 7.78 (dq, J = 9.0, 1.0 Hz, 1H), 7.69 (d, J = 8.6 Hz, 1H), 7.48 (ddd, J = 9.1, 6.5, 1.3 Hz, 1H), 7.23 (ddd, J = 8.6, 6.5, 1.1 Hz, 1H), 3.97 (d, J = 15.0 Hz, 1H), 3.76 (d, J = 15.0 Hz, 1H), 3.70 (s, 3H), 3.47 – 3.38 (m, 1H), 3.06 – 2.98 (m, 1H), 2.66 – 2.60 (m, 1H), 2.24 (dd, J = 13.2, 3.6 Hz, 1H), 2.06 (dd, J = 11.3, 3.5 Hz, 1H), 1.89 (t, J = 11.0 Hz, 1H), 1.63 (tt, J = 11.4, 3.5 Hz, 1H), 1.11 (td, J = 12.8, 5.0 Hz, 1H), 0.83 (s, 9H).

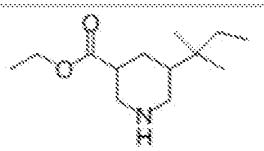
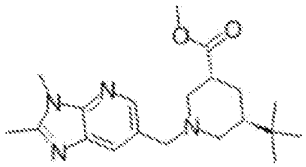
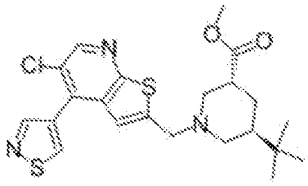
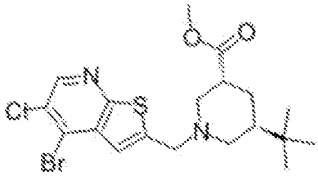
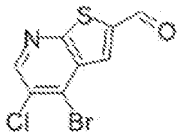
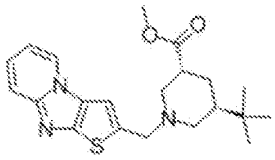
286		[M+H]+ 461.2 NMR2: 7.89 (d, J = 2.6 Hz, 1H), 7.34 (d, J = 2.7 Hz, 1H), 6.53 (s, 1H), 6.50 (s, 1H), 5.79 (s, 1H), 3.81 (dd, J = 15.3, 1.0 Hz, 1H), 3.63 (d, J = 15.6 Hz, 1H), 3.47 – 3.39 (m, 1H), 3.03 – 2.95 (m, 1H), 2.67 (h, J = 2.6 Hz, 1H), 2.30 – 2.22 (m, 1H), 2.15 (dd, J = 11.3, 3.6 Hz, 1H), 1.93 (t, J = 11.0 Hz, 1H), 1.66 (s, 2H), 1.64 – 1.58 (m, 1H), 1.48 – 1.43 (m, 9H), 1.41 (t, J = 4.3 Hz, 1H), 1.12 (td, J = 12.9, 5.0 Hz, 1H), 0.88 (s, 9H).
287		[M+H]+ 397 NMR2: 8.63 (d, J = 2.6 Hz, 1H), 8.32 (d, J = 2.5 Hz, 1H), 8.22 (dd, J = 2.6, 0.6 Hz, 1H), 7.81 – 7.75 (m, 1H), 6.86 (d, J = 0.8 Hz, 1H), 6.57 (dd, J = 2.5, 1.9 Hz, 1H), 3.85 (dd, J = 15.2, 1.0 Hz, 1H), 3.70 (s, 3H), 3.70 (dd, J = 15.1, 0.7 Hz, 1H), 3.46 (dq, J = 11.2, 1.9 Hz, 1H), 3.05 (ddt, J = 10.8, 3.7, 1.8 Hz, 1H), 2.79 – 2.72 (m, 1H), 2.29 (dt, J = 13.3, 3.2 Hz, 1H), 2.21 (dd, J = 11.4, 3.6 Hz, 1H), 1.99 (t, J = 11.0 Hz, 1H), 1.62 (ddt, J = 12.3, 11.1, 3.5 Hz, 1H), 1.20 (td, J = 12.9, 5.0 Hz, 1H), 0.91 (s, 9H).
288		[M+H]+ 225 NMR:1 7.96 (s, 1 H), 3.96 (s, 3 H), 2.48 (s, 3 H)
289		[M+H]+ 243 NMR2: 8.11 (s, 1H), 4.01 (s, 3H), 2.85 (s, 3H)
290		[M+H]+ 209 NMR2: 9.25 (s, 1H), 8.10 (s, 1H), 4.01 (s, 3H), 2.88 (s, 3H)
291		[M+H]+ 181 NMR2: 9.10 (s, 1H), 7.33 (s, 1H), 5.05 (s, 2H), 2.83 (s, 3H)

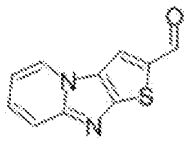
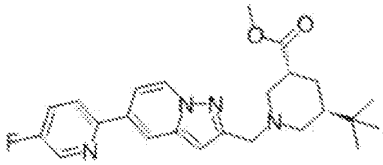
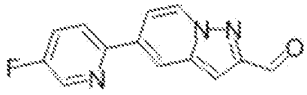
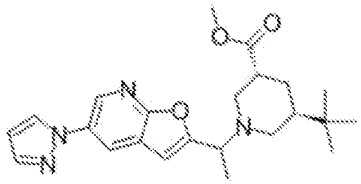
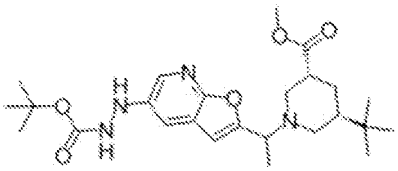
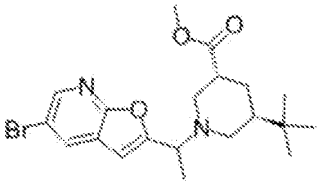
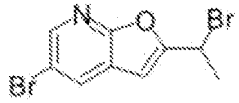
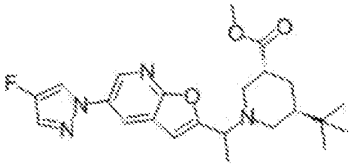
292		NMR2: 10.27 (s, 1H), 9.33 (s, 1H), 8.12 (s, 1H), 2.90 (s, 3H)
293		$[M+H]^+$ 334.5 NMR2: 7.40 - 7.28 (m, 5H), 5.13 (q, J=11.3 Hz, 2H), 4.60 (qd, J=1.8, 13.5 Hz, 1H), 4.34 - 4.24 (m, 1H), 3.69 - 3.53 (m, 1H), 2.90 (dd, J=4.0, 13.2 Hz, 1H), 2.68 (s, 1H), 2.49 - 2.42 (m, 1H), 2.28 (d, J=12.9 Hz, 1H), 1.35 (dt, J=5.2, 12.6 Hz, 1H), 0.91 (s, 9H).
294		NMR2: 7.42 - 7.28 (m, 5H), 5.17 - 5.10 (m, 2H), 5.04 (t, J=7.6 Hz, 1H), 4.63 (d, J=11.9 Hz, 1H), 4.29 - 4.24 (m, 1H), 3.61 - 3.50 (m, 3H), 2.52 - 2.44 (m, 1H), 2.40 - 2.29 (m, 2H), 2.23 - 2.15 (m, 2H), 1.70 (s, 3H), 1.58 (s, 3H), 1.37 - 1.28 (m, 1H), 0.99 (t, J=12.8 Hz, 1H), 0.90 (s, 9H).
295		$[M+H]^+$ 454
296		$[M+H]^+$ 271.1
297		$[M+H]^+$ 454
298		$[M+H]^+$ 271.2

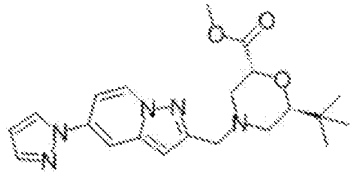
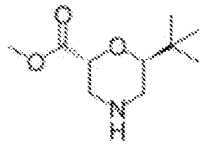
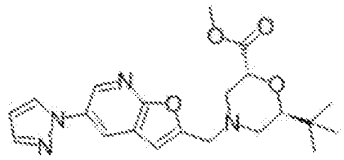
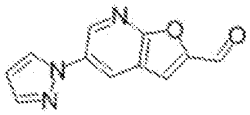
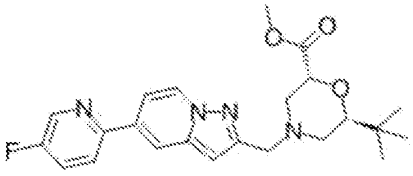
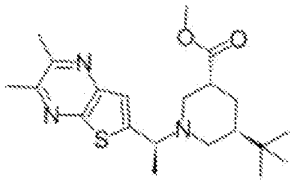
299		NMR2: 7.93-7.87 (m, 1H), 7.27-7.11 (m, 2H), 6.59 (dd, J = 9.5, 1.8 Hz, 1H), 6.38 (s, 1H), 3.76 (d, J = 13.8 Hz, 1H), 3.73 (s, 3H), 3.50 (d, J = 13.9 Hz, 1H), 3.39 (dd, J = 11.3, 2.6 Hz, 1H), 3.01 (d, J = 10.4 Hz, 1H), 2.71-2.63 (m, 1H), 2.27 (d, J = 13.0 Hz, 1H), 2.05-1.88 (m, 1H), 1.81 (t, J = 10.9 Hz, 1H), 1.76-1.60 (m, 2H), 0.91 (s, 9H).
300		[M+H]+ 180
301		[M+H]+ 370
302		[M+H]+ 187.1
303		[M+H]+ 433
304		NMR2: 10.03 (s, 1H), 8.34 (s, 1H), 7.58 (s, 1H).
305		[M+H]+ 394
306		[M+H]+ 211

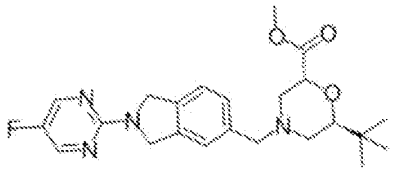
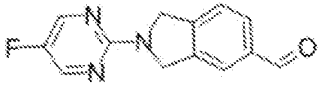
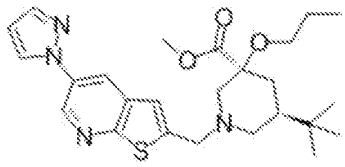
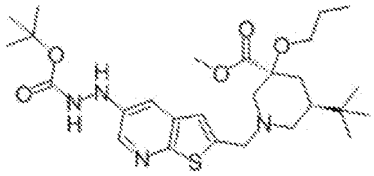
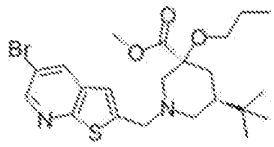
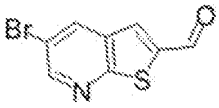
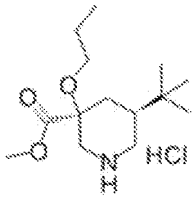
307		[M+H]+ 381, 383
308		[M+H]+ 198
309		[M+H]+ 397
310		[M+H]+ 214.0
311		[M+H]+ 441, 443
312		[M+H]+ 258.0, 260.0
313		NMR2; 8.42 (s, 1H), 7.78 (d, J = 5.6 Hz, 1H), 7.58 (dd, J = 5.6, 0.8 Hz, 1H), 7.15 (s, 1H), 3.91 (dd, J = 14.4, 1.3 Hz, 1H), 3.81-3.67 (m, 4H), 3.43 (dd, J = 11.2, 2.6 Hz, 1H), 3.10-3.00 (m, 1H), 2.71 (dd, J = 5.6, 3.0 Hz, 1H), 2.29 (d, J = 13.0 Hz, 1H), 2.14 (dd, J = 11.2, 3.5 Hz, 1H), 1.92 (t, 1H), 1.82-1.72 (m, 1H), 0.93-0.90 (m, 10H).

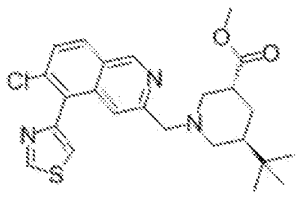
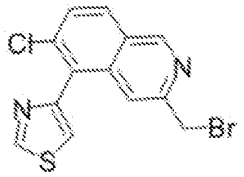
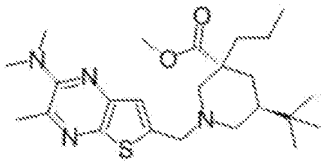
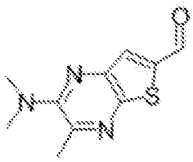
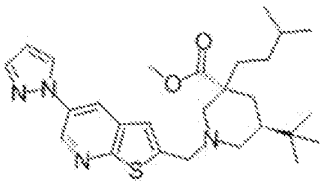
314		NMR2: 10.16 (s, 1H), 8.76 (s, 1H), 8.08 (s, 1H), 8.00 (d, J = 5.6 Hz, 1H), 7.64 (dd, J = 5.7, 0.8 Hz, 1H).
315		[M+H]+ 438
316		NMR2: 10.18 (1H, s), 8.75 (1H, s), 8.09 (1H, s), 7.89 (1H, s).
317		[M+H]+ 375
318		[M+H]+ 192
319		[M+H]+ 372
320		NMR2: 4.37-4.10 (m, 3H), 3.44 (d, J = 13.2 Hz, 1H), 2.95 (d, J = 12.5 Hz, 1H), 2.72-2.58 (m, 2H), 2.33-2.18 (m, 1H), 2.18-2.08 (m, 1H), 1.98-1.84 (m, 3H), 1.81-1.72 (m, 2H), 1.54-1.43 (m, 2H), 1.35-1.27 (m, 4H), 1.05 (d, J = 12.1 Hz, 3H).
321		[M+H]+ 373

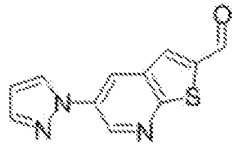
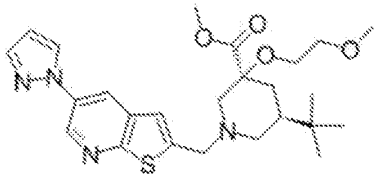
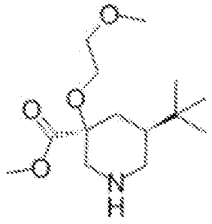
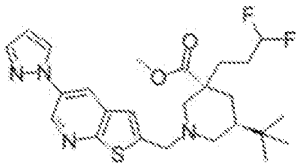
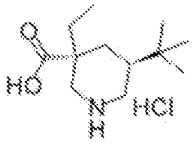
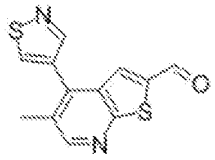
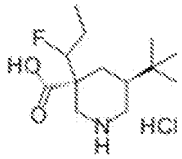
322		[M+H]+ 228
323		[M+H]+ 359
324		[M+H]+ 166
325		[M+H]+ 464
326		[M+H]+ 461
327		NMR2; 10.15 (1H, s), 8.68 (1H, s), 8.09 (1H, s).
328		NMR2; 8.11 (dd, J = 5.8, 5.8 Hz, 1 H), 7.55-7.52 (m, 1 H), 7.15-7.08 (m, 1 H), 7.04 (s, 1 H), 6.72 (dd, J = 6.8, 6.8 Hz, 1 H), 3.86-3.78 (m, 1 H), 3.62 (s, 3 H), 3.61-3.56 (m, 1 H), 3.32 (d, J = 11.1 Hz, 1 H), 2.94 (d, J = 10.4 Hz, 1 H), 2.61-2.55 (m, 1 H), 2.17 (d, J = 13.1 Hz, 1 H), 1.98 (dd, J = 3.5, 11.1 Hz, 1 H), 1.83-1.73 (m, 1 H), 1.70-1.60 (m, 1 H), 1.11-1.00 (m, 1 H), 0.80 (s, 9 H)

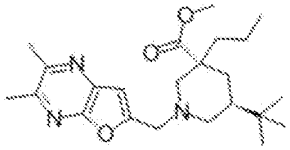
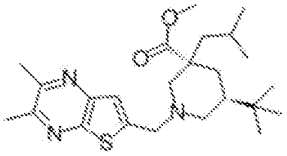
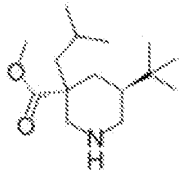
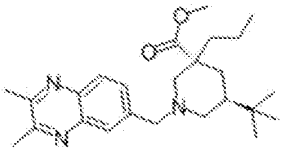
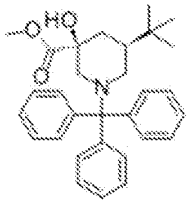
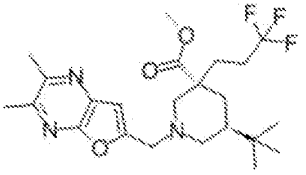
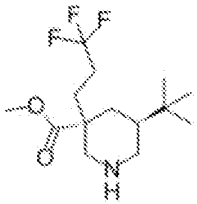
329		NMR1; 9.97 (s, 1 H), 9.11-9.08 (m, 1 H), 8.63 (s, 1 H), 7.80 (d, J = 9.3 Hz, 1 H), 7.67-7.62 (m, 1 H), 7.20 (dd, J = 6.4, 6.4 Hz, 1 H)
330		[M+H]+ 425
331		[M+H]+ 242
332		[M+H]+ 411 Single isomer
333		[M+H]+ 475 Epimer mixture
334		[M+H]+ 423, 425 Epimer mixture
335		[M+H]+ 304, 306, 308 Racemic mixture
336		NMR3; 8.65 – 8.50 (m, 1H), 8.35 – 8.23 (m, 2H), 7.73 – 7.64 (m, 1H), 6.87 – 6.75 (m, 1H), 4.56 – 4.35 (m, 1H), 4.12 – 3.86 (m, 1H), 3.72 – 3.51 (m, 3H), 3.09 – 2.93 (m, 1H), 2.79 – 2.62 (m, 1H), 2.41 – 2.15 (m, 1H), 2.11 – 1.93 (m, 1H), 1.70 – 1.41 (m,

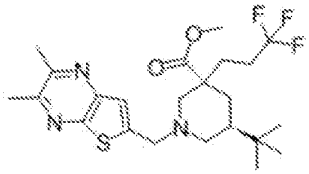
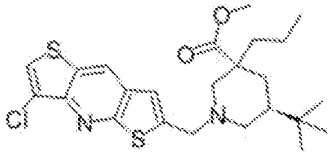
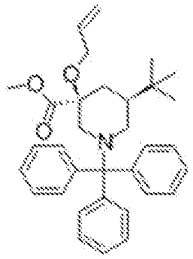
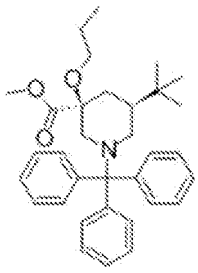
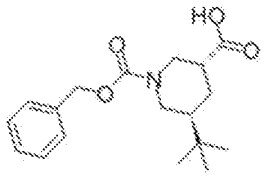
		4H), 1.36 – 1.00 (m, 2H), 0.98 – 0.77 (m, 9H). Epimer mixture
337		[M+H]+ 398
338		NMR2; 4.34 (d, J = 4.3 Hz, 1 H), 3.79 (s, 3 H), 3.50-3.44 (m, 1 H), 3.35 (d, J = 12.6 Hz, 1 H), 3.00-2.87 (m, 2 H), 2.61 (dd, J = 11.7, 11.7 Hz, 1 H), 0.92 (s, 9 H)
339		[M+H]+ 212.9
340		NMR2;: δ 8.39 (d, J = 2.3 Hz, 1 H), 8.20 (d, J = 2.5 Hz, 1 H), 7.94 (d, J = 2.5 Hz, 1 H), 7.77 (d, J = 1.8 Hz, 1 H), 6.69 (s, 1 H), 6.52 (dd, J = 2.0, 2.0 Hz, 1 H), 4.43-4.40 (m, 1 H), 3.84-3.76 (m, 4 H), 3.73-3.67 (m, 2 H), 3.38 (d, J = 11.4 Hz, 1 H), 2.85 (d, J = 10.9 Hz, 1 H), 2.43 (dd, J = 4.3, 11.4 Hz, 1 H), 2.17 (dd, J = 10.9, 10.9 Hz, 1 H), 0.94 (s, 9 H).
341		[M+H]+ 214
342		[M+H]+ 427
343		[M+H]+ 390 Single isomer

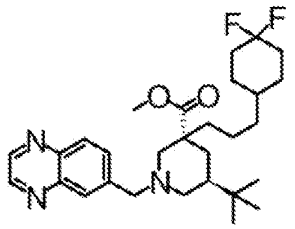
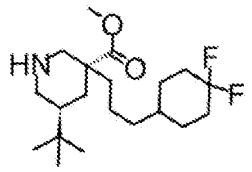
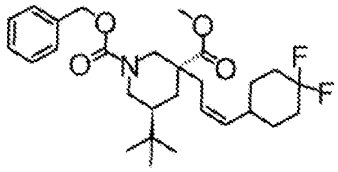
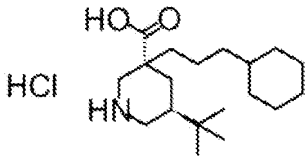
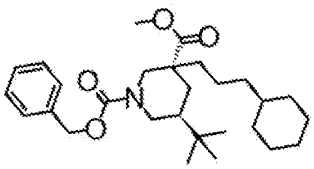
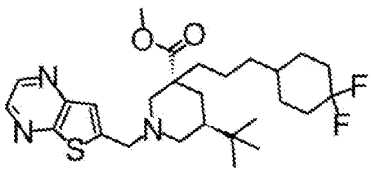
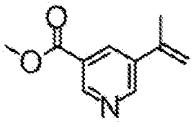
344		[M+H]+ 429
345		[M+H]+ 244
346		[M+H]+ 471
347		[M+H]+ 535
348		NMR3 8.51 (d, J = 2.2 Hz, 1H), 8.30 (d, J = 2.2 Hz, 1H), 7.18 (d, J = 1.2 Hz, 1H), 3.92 (dd, J = 14.4, 1.2 Hz, 1H), 3.82 – 3.73 (m, 1H), 3.74 (s, 3H), 3.50 – 3.38 (m, 2H), 3.15 (dt, J = 8.6, 6.5 Hz, 1H), 3.03 – 2.95 (m, 1H), 2.58 (d, J = 12.2 Hz, 1H), 1.99 (d, J = 10.5 Hz, 1H), 1.91 (t, J = 11.1 Hz, 1H), 1.70 – 1.57 (m, 1H), 1.47 (h, J = 7.1 Hz, 2H), 1.04 (t, J = 12.5 Hz, 1H), 0.91 (s, 9H), 0.86 (t, J = 7.4 Hz, 3H)
349		[M+H]+ 242, 244
350		NMR3: 3.90 (dt, J = 12.5, 1.5 Hz, 1H), 3.86 (s, 3H), 3.45 (dt, J = 8.4, 6.3 Hz, 1H), 3.38 – 3.32 (m, 2H), 2.89 (d, J = 12.3 Hz, 1H), 2.78 (t, J = 12.3Hz, 1H), 2.47 (dq, J = 12.7, 2.4 Hz, 1H), 1.62 – 1.32 (m, 4H), 0.95 (s, 9H), 0.92 (t, J = 7.4 Hz, 3H).

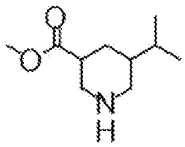
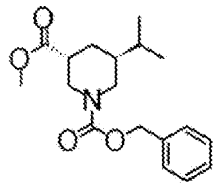
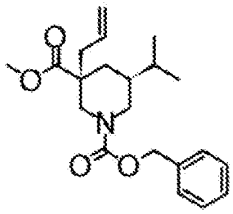
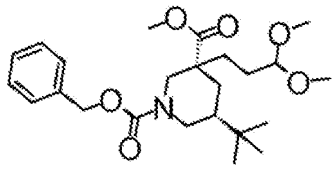
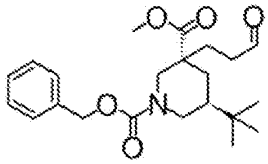
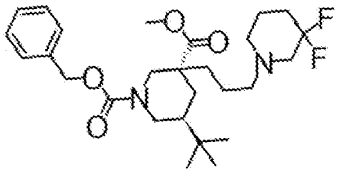
351		NMR1; 9.20 (s, 1 H), 9.08 (d, J = 2.0 Hz, 1 H), 7.94 (d, J = 8.1 Hz, 1 H), 7.63 (d, J = 8.8 Hz, 1 H), 7.57 (d, J = 1.8 Hz, 1 H), 7.45 (s, 1 H), 3.75 (dd, J = 13.8, 35.0 Hz, 2 H), 3.59 (s, 3 H), 3.25 (dd, J = 1.8, 11.1 Hz, 1 H), 2.96-2.85 (m, 1 H), 2.69-2.58 (m, 1 H), 2.26-2.15 (m, 2 H), 1.79 (dd, J = 11.1, 11.1 Hz, 1 H), 1.50 (tt, J = 3.3, 11.7 Hz, 1 H), 1.18-1.06 (m, 1 H), 0.83 (s, 9 H).
352		NMR1; 9.27 (s, 1 H), 9.09 (d, J = 2.0 Hz, 1 H), 7.99 (d, J = 8.8 Hz, 1 H), 7.72 (d, J = 8.8 Hz, 1 H), 7.60 (d, J = 2.0 Hz, 1 H), 7.45 (s, 1 H), 4.63 (s, 2 H)
353		$[M+H]^+$ 447
354		NMR2; 10.09 (s, 1H), 7.95 (s, 1H), 2.99 (s, 6H), 2.69 (s, 3H)
355		NMR2; 8.85 (d, J = 2.5 Hz, 1 H), 8.26 (d, J = 2.5 Hz, 1 H), 7.99 (d, J = 2.3 Hz, 1 H), 7.79 (d, J = 1.8 Hz, 1 H), 7.13 (s, 1 H), 6.53 (dd, J = 2.0, 2.0 Hz, 1 H), 3.87 (d, J = 14.4 Hz, 1 H), 3.72 (s, 3 H), 3.68 (d, J = 6.8 Hz, 1 H), 3.33 (d, J = 10.9 Hz, 1 H), 3.01 (d, J = 8.6 Hz, 1 H), 2.34 (d, J = 12.9 Hz, 1 H), 1.87-1.74 (m, 2 H), 1.72-1.61 (m, 1 H), 1.53-1.36 (m, 2 H), 1.36-1.28 (m, 1 H), 1.24-1.13 (m, 1 H), 0.99-0.93 (m, 1 H), 0.89 (s, 9 H), 0.83 (dd, J = 4.8, 6.6 Hz, 6 H), 0.79-0.70 (m, 1 H).

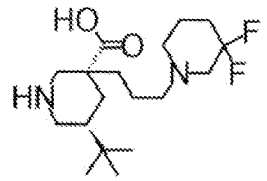
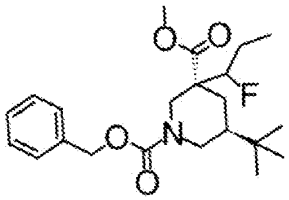
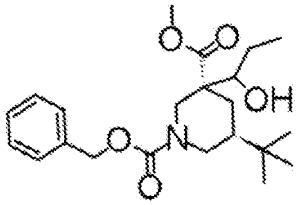
356		[M+H]+ 230
357		[M+H]+ 487.4
358		NMR2: 3.79 (s, 3H), 3.63 - 3.52 (m, 2H), 3.52 - 3.48 (m, 3H), 3.37 (s, 3H), 3.07 - 3.04 (m, 1H), 2.50 - 2.42 (m, 2H), 2.27 (dd, J=11.8, 11.8 Hz, 1H), 1.33 (dd, J=12.6, 12.6 Hz, 1H), 1.20 - 1.11 (m, 1H), 0.86 (s, 9H).
359		[M+H]+ 491.5
360		[M+H]+ 214.4
361		[M+H]+ 261
362		[M+H]+ 246.2 Single isomer

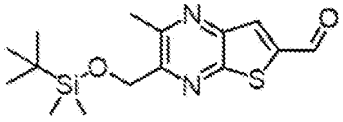
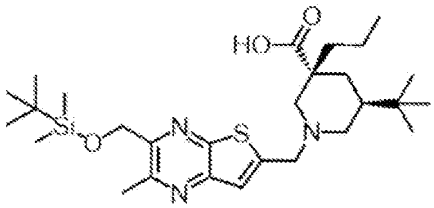
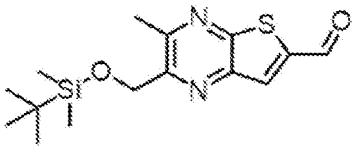
363		[M+H]+ 402
364		[M+H]+ 432
365		NMR2; 3.70 (s, 3H), 3.52 (dd, J = 13.0, 2.5 Hz, 1H), 3.10 (dt, J = 12.9, 3.1 Hz, 1H), 2.74 (br s, 1H), 2.31 – 2.19 (m, 3H), 1.74 – 1.57 (m, 1H), 1.49 (dd, J = 14.0, 6.9 Hz, 1H), 1.32 (dd, J = 14.0, 5.7 Hz, 1H), 1.08 (tdd, J = 10.8, 3.5, 2.2 Hz, 1H), 1.00 (t, J = 12.5 Hz, 1H), 0.87 – 0.79 (m, 15H)
366		[M+H]+ 412.8
367		NMR2; 7.46- 7.32 (m, 6H), 7.29 – 7.20 (m, 6H), 7.18 – 7.10 (m, 3H), 3.98 (s, 3H), 3.37 (d, J=10.9 Hz, 1H), 3.21 - 3.16 (m, 1H), 2.62 (s, 1H), 2.29 - 2.20 (m, 2H), 1.53 (d, J=10.9 Hz, 1H), 1.04 - 0.88 (m, 2H), 0.78 (s, 9H).
368		NMR2; 6.77 (s, 1H), 3.90 (d, J = 18.0 Hz, 1H), 3.75 (s, 3H), 3.39 (d, J = 12.5 Hz, 1H), 3.02 (s, 1H), 2.65 (s, 3H), 2.63 (s, 3H), 2.31 (d, J = 13.0 Hz, 1H), 2.21-2.04 (m, 1H), 2.04-1.82 (m, 3H), 1.82-1.68 (m, 1H), 1.68-1.53 (m, 4H), 0.91 (s, 9H).
369		NMR2; 3.85 (s, 3H), 3.73-3.63 (m, 1H), 3.42 (d, J = 14.1 Hz, 1H), 2.55-2.43 (m, 2H), 2.36 (d, J = 14.2 Hz, 1H), 2.13-1.95 (m, 2H), 1.95-1.80 (m, 1H), 1.80-1.67 (m, 1H), 1.50-1.37 (m, 1H), 1.18-1.05 (m, 1H), 0.95-0.89 (m, 9H).

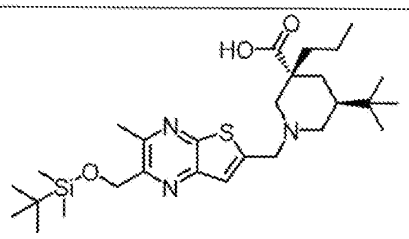
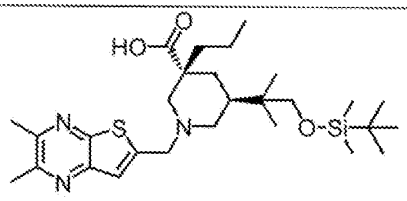
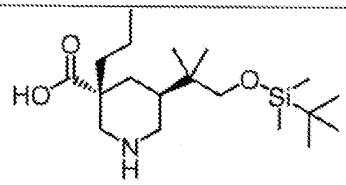
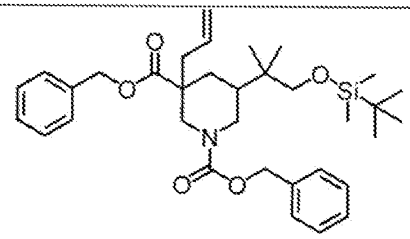
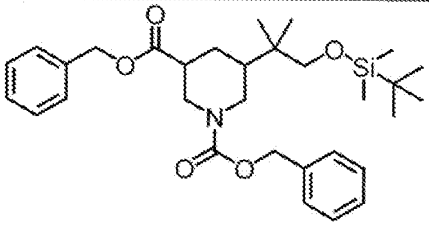
370		NMR2: 7.20 (s, 1H), 3.91 (s, 1H), 3.77 (s, 4H), 3.35 (d, J = 13.6 Hz, 1H), 3.02 (s, 1H), 2.66 (s, 6H), 2.39-2.23 (m, 1H), 2.23-2.07 (m, 1H), 2.02-1.81 (m, 3H), 1.77-1.53 (m, 4H), 0.98-0.86 (m, 9H).
371		NMR2: 8.40 (s, 1H), 7.67 (s, 1H), 7.17 (s, 1H), 3.90 (d, J = 14.6 Hz, 1H), 3.80-3.69 (m, 4H), 3.38 (d, J = 10.8 Hz, 1H), 3.02 (d, J = 10.1 Hz, 1H), 2.37 (d, J = 12.7 Hz, 1H), 1.87-1.76 (m, 2H), 1.75-1.61 (m, 1H), 1.40-1.22 (m, 5H), 1.22-1.02 (m, 2H), 1.02-0.91 (m, 1H), 0.90 (s, 9H).
372		NMR2: δ 7.43 – 7.32 (m, 6H), 7.28 – 7.08 (m, 9H), 5.86 - 5.75 (m, 1H), 5.20 (d, J=16.9 Hz, 1H), 5.11 (d, J=10.4 Hz, 1H), 3.99 (dd, J=5.6, 11.4 Hz, 1H), 3.93 (s, 3H), 3.68 (dd, J=9.7, 11.2 Hz, 1H), 3.58 (d, J=10.9 Hz, 1H), 3.17 (d, J=10.9 Hz, 1H), 2.57 (d, J=11.4 Hz, 1H), 2.11 - 2.03 (m, 1H), 1.61 (d, J=10.9 Hz, 1H), 0.96 - 0.83 (m, 2H), 0.79 (s, 9H).
373		NMR2: δ 7.44 - 7.32 (m, 6H), 7.30 - 7.16 (m, 6H), 7.13 – 7.11 (m, 3H), 3.92 (s, 3H), 3.79 - 3.71 (m, 1H), 3.59 - 3.35 (m, 3H), 3.30 - 3.13 (m, 2H), 3.08 - 3.01 (m, 1H), 2.58 - 2.49 (m, 1H), 2.11 - 1.99 (m, 1H), 1.54 - 1.40 (m, 2H), 0.93 - 0.81 (m, 3H), 0.79 (s, 9H).
374		NMR2: 7.39 (s, 5H), 5.16 - 5.06 (m, 2H), 4.63 (d, J=13.1 Hz, 1H), 4.27 - 4.26 (m, 1H), 2.93 - 2.84 (m, 1H), 2.83 (s, 1H), 2.76 - 2.70 (m, 1H), 2.47 (dd, J=12.0, 12.0 Hz, 1H), 2.32 (d, J=13.1 Hz, 1H), 1.58 - 1.30 (m, 1H), 0.90 (s, 9H).

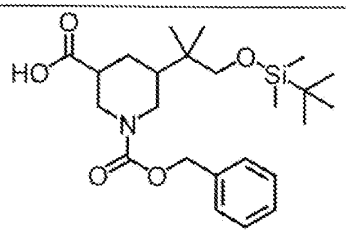
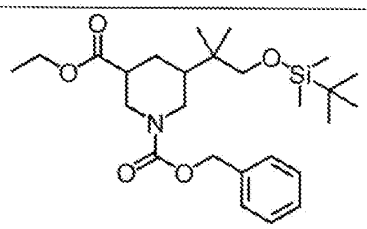
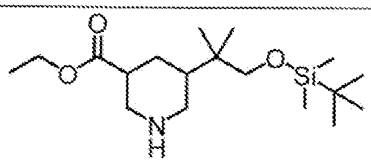
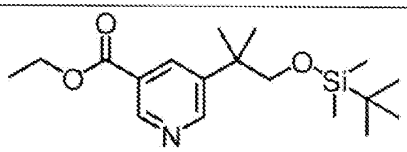
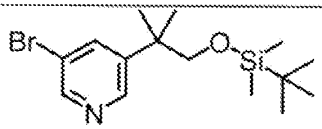
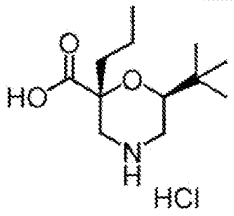
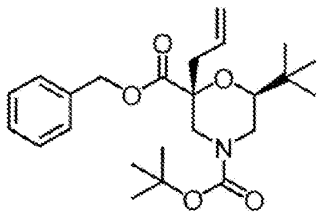
375		[M+H]+ 502
376		NMR1: 4.34 (t, J = 5.1 Hz, 1H), 3.60 (s, 3H), 3.50-3.39 (m, 1H), 3.39-3.22 (m, 2H), 2.90 (d, J = 12.1 Hz, 1H), 2.24-2.05 (m, 3H), 2.05-1.91 (m, 3H), 1.70 (d, J = 13.3 Hz, 3H), 1.41-1.26 (m, 3H), 1.19-1.09 (m, 4H), 0.85-0.43 (m, 9H).
377		[M+H]+ 492
378		NMR3: 3.77 (d, J = 0.6 Hz, 2H), 3.67 (dd, J = 21.6, 12.7 Hz, 1H), 2.78-2.64 (m, 2H), 2.27 (t, J = 10.6 Hz, 1H), 2.00 (dd, J = 4.0, 0.6 Hz, 3H), 1.77-1.54 (m, 7H), 1.55-1.07 (m, 7H), 0.91-0.85 (m, 11H).
379		[M+H]+ 458.5
380		[M+H]+ 508
381		NMR2: 9.12 (d, J = 2.0 Hz, 1H), 8.89 (d, J = 2.3 Hz, 1H), 8.34 (t, J = 2.2 Hz, 1H), 5.52 (s, 1H), 5.31-5.24 (m, 1H), 3.98 (s, 3H), 2.22 (s, 3H).

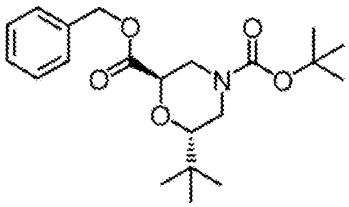
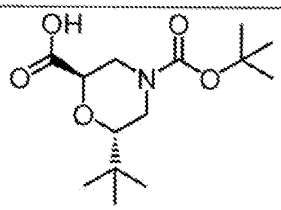
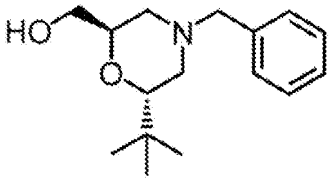
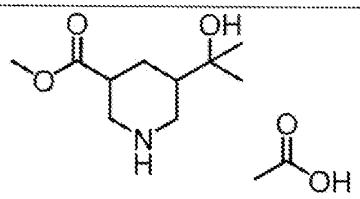
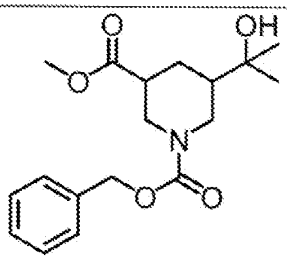
382		NMR2; 3.76, 3.71 (2s, 3H), 3.55 - 3.45 (m, 1H), 3.33 - 3.20 (m, 1H), 2.97 - 2.70 (m, 2H), 2.61 - 2.40 (m, 1H), 2.25 - 2.16 (m, 1H), 1.88 - 1.62 (m, 1H), 1.58 - 1.47 (m, 2H), 0.94 - 0.89 (m, 6H).
383		NMR2; 7.46-7.30 (m, 5H), 5.28-5.03 (m, 2H), 4.25 (s, 1H), 4.05-3.76 (m, 1H), 3.63 (s, 3H), 3.28 (d, 1H), 2.89 (s, 1H), 2.67 (s, 1H), 2.26-1.86 (m, 1H), 1.60-1.38 (m, 2H), 1.38-1.06 (m, 1H), 0.95 (d, J = 8.0 Hz, 6H).
384		NMR2; 7.42 - 7.29 (m, 5H), 5.75 - 5.62 (m, 1H), 5.17 - 5.02 (m, 4H), 4.70 - 4.60 (m, 1H), 4.25 - 4.25 (m, 1H), 3.51 (br s, 3H), 2.48 -2.46 (m, 1H), 2.37 - 2.15 (m, 4H), 1.46 - 1.40 (m, 3H), 0.94 - 0.88 (m, 6H).
385		[M-MeO]$^+$ 404.2
386		NMR2; 9.73 (s, 1H), 7.42-7.27 (m, 5H), 5.16 (dd, J = 12.5, 7.5 Hz, 1 H), 5.14-5.06 (m, 1H), 4.28 (s, 2H), 3.55 (d, J = 11.8 Hz, 3H), 2.48-2.42 (m, 3H), 1.32-1.19 (m, 2H), 0.99-0.79 (m, 13H).
387		[M+H]$^+$ 495.2

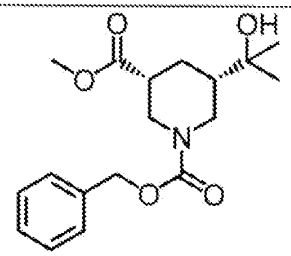
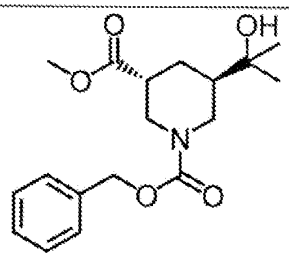
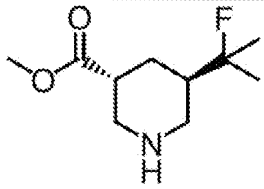
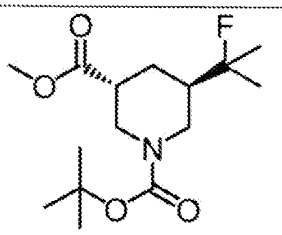
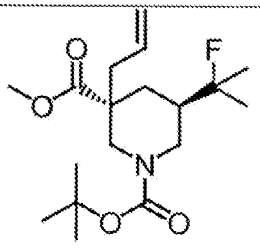
388		[M+H]+ 347.1
389		[M+H]+ 394.4
390		[M+H]+ 392.3

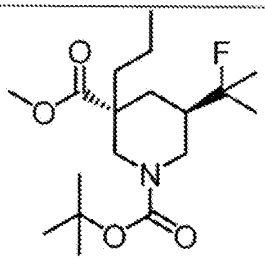
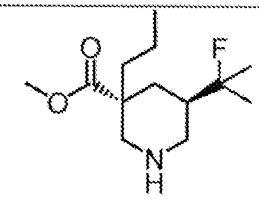
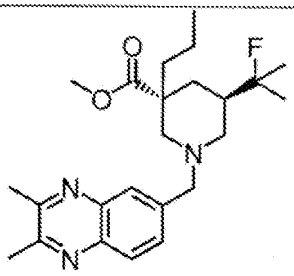
391		[M+H]+ 323.1
392		[M+H]+ 535.2
393		[M+H]+ 323.3

394		[M+H]+ 535.1
395	 and its enantionmer	[M+H]+ 534.9 Racemate
396	 and its enantionmer	[M+H]+ 359.0 Racemate
397		[M+H]+ 581.3 Racemate
398	 and its enantiomer	[M+H]+ 540.8

399		$[M+H]^+$ 450.5
400		$[M+H]^+$ 478.5
401		$[M+H]^+$ 344.9
402		$[M+H]^+$ 338.9
403		$[M+H]^+$ 345.6
404		$[M+H]^+$ 230.1 NMR3; 3.75 (dd, *J* = 12.8, 1.2 Hz, 1H), 3.52 (dd, *J* = 11.5, 2.1 Hz, 1H), 3.22 (dt, *J* = 12.3, 1.6 Hz, 1H), 2.96 – 2.83 (m, 2H), 1.81 – 1.68 (m, 2H), 1.60 – 1.30 (m, 2H), 1.02 – 0.91 (m, 12H).
405		$[M+Na]^+$ 440.3 NMR2; 7.38 – 7.28 (m, 5H), 5.88 – 5.73 (m, 1H), 5.24 – 4.87 (m, 4H), 4.51 – 4.47 (m, 1H), 3.98 – 3.94 (m, 1H), 3.38 (d, J = 11.2 Hz, 1H), 2.66 (d, J = 13.1 Hz, 1H), 2.55 – 2.51 (m, 1H), 2.49 – 2.33 (m, 2H), 1.41 (s, 9H), 0.91 (s, 9H).

406		[M+Na]+ 400.3 NMR2; 7.42 – 7.30 (m, 5H), 5.26 – 5.08 (m, 2H), 4.49 – 4.38 (m, 2H), 4.00 – 3.95 (m, 1H), 3.57 – 3.50 (m, 1H), 3.09 (dd, J = 13.4, 4.8 Hz, 1H), 2.65 – 2.61 (m, 1H), 1.42 (s, 9H), 0.92 (s, 9H).
407		[M+Na]+ 310.3 NMR2; 4.48 – 4.41 (m, 2H), 4.00 (s, 1H), 3.52 (d, J = 11.2 Hz, 1H), 3.17 – 3.09 (m, 1H), 2.67 (t, J = 12.0 Hz, 1H), 1.45 (s, 9H), 0.96 (s, 9H).
408		[M+Na]+ 264.3 NMR2; 7.42 – 7.22 (m, 5H), 4.18 – 4.07 (m, 1H), 3.88 – 3.81 (m, 1H), 3.73 – 3.63 (m, 2H), 3.53 (d, J = 13.1 Hz, 1H), 3.38 (d, J = 13.1 Hz, 1H), 2.77 (ddt, J = 26.1, 11.6, 1.8 Hz, 2H), 2.32 (dd, J = 11.5, 4.4 Hz, 1H), 1.98 (t, J = 10.9 Hz, 1H), 0.90 (s, 9H).
409		[M+H]+ 202.2
410		[M+H]+ 336.1

411	 and its enantiomer	$[M+H]^+$ 338.2 Racemate
412	 and its enantiomer	$[M+H]^+$ 338.2 Racemate
413	 and its enantiomer	$[M+H]^+$ 204.4 Racemate
414	 and its enantiomer	$[M+Na]^+$ 326.6 Racemate
415	 and its enantiomer	$[M+Na]^+$ 366.7 Racemate

416	 and its enantiomer	[M+Na]+ 368.7 Racemate
417	 and its enantiomer	[M+H]+ 246.5 Racemate
418	 and its enantiomer	[M+H]+ 416.8 Racemate

[0370] Examples

Example 2: Synthesis of (3R,5S)-5-tert-butyl-1-[(5-phenylfuro[2,3-b]pyridin-2-yl)methyl]piperidine-3-carboxylic acid; hydrochloride

A mixture of methyl (3R,5S)-5-(tert-butyl)-1-((5-phenylfuro[2,3-b]pyridin-2-yl)methyl)piperidine-3-carboxylate (59 mg) and 6M HCl (1 mL) in 1,4-dioxane (0.2 mL) was stirred at 90°C for 2 h. The mixture was concentrated, co-evaporated with toluene to give the desired product (44 mg).

[0371] Example 5: Synthesis of (3R,5S)-5-tert-butyl-1-{[5-chloro-6-(trifluoromethyl)furo[2,3-b]pyridin-2-yl]methyl}piperidine-3-carboxylic acid, hydrochloride salt

Methyl 1-({8-benzyl-6-chloroimidazo[1,2-a]pyridin-2-yl}methyl)-5-tert-butylpiperidine-3-carboxylate (91 mg) was suspended in conc. HCl (2 mL) and stirred at 100°C for 2 h. The solvent was removed in vacuo and the residue was lyophilised from MeCN:water. The

mixture of isomers was separated by chiral SFC (AD 100 x 4.6 mm; 5 um; Prep 250 x 20 mm, 5 um 50% isocratic EtOH+0.1% DEA). The fractions containing product were concentrated in vacuo and the residue was concentrated from HCl/Et_2O to give the desired product (33 mg).

[0372] Example 14: Synthesis of (3R,5S)-5-tert-butyl-1-[(5-phenylfuro[2,3-c]pyridin-2-yl)methyl]piperidine-3-carboxylic acid; dihydrochloride

A mixture of methyl (3R,5S)-5-(tert-butyl)-1-((5-phenylfuro[2,3-c]pyridin-2-yl)methyl)piperidine-3-H11carboxylate (79 mg) and 6M HCl (1 ml) was stirred at 90°C for 4 h. The mixture was concentrated, triturated with AcOEt to give the desired product (74 mg).

[0373] Example 17: Synthesis of (3R,5S)-5-tert-butyl-1-[(2-methyl-4-phenylthieno[2,3-d]pyrimidin-6-yl)methyl]piperidine-3-carboxylic acid; hydrochloride

A solution of methyl (3R,5S)-5-tert-butyl-1-[(2-methyl-4-phenylthieno[2,3-d]pyrimidin-6-yl)methyl]piperidine-3-carboxylate (152.5 mg) in 6M HCl (3 mL) was stirred at 90°C for 3 h. The reaction mixture was concentrated in vacuo to give the desired product (164 mg).

[0374] Example 22: Synthesis of (3R,5S)-5-tert-butyl-1-[[5-(1,2-thiazol-3-yl)furo[2,3-b]pyridin-2-yl]methyl]piperidine-3-carboxylic acid

A mixture of methyl (3R,5S)-5-tert-butyl-1-[[5-(1,2-thiazol-3-yl)furo[2,3-b]pyridin-2-yl]methyl]piperidine-3-carboxylate (40 mg) and 6M HCl (1 mL) was stirred at 90°C for 3 h. The mixture was diluted with water. A formed solid was collected, washed with water to give the desired product (15 mg).

[0375] Example 31: Synthesis of (3R,5S)-5-tert-butyl-1-[(5-chloro-6-pyrrolidin-1-ylfuro[2,3-b]pyridin-2-yl)methyl]piperidine-3-carboxylic acid; dihydrochloride

A mixture of methyl (3R,5S)-5-tert-butyl-1-[(5-chloro-6-pyrrolidin-1-ylfuro[2,3-b]pyridin-2-yl)methyl]piperidine-3-carboxylate (102.5 mg) and 6M HCl was stirred at 80°C for 3 h. The mixture was concentrated and triturated with AcOEt to give the desired product (55.6 mg).

[0376] Example 37: Synthesis of (3R,5S)-5-tert-butyl-1-[(5-pyrimidin-2-yl-6,7-dihydro-4H-thieno[3,2-c]pyridin-2-yl)methyl]piperidine-3-carboxylic acid; dihydrochloride

To the methyl (3R,5S)-5-(tert-butyl)-1-((5-(pyrimidin-2-yl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-

yl)methyl)piperidine-3-carboxylate (209 mg) was added 5M HCl (3 mL). After stirring at 70°C for 1h, the reaction mixture was concentrated. To the residue was added 5M HCl (3 mL) again. After stirring at 70°C for 2 h, the reaction mixture was cooled to r.t. and concentrated. To the residue was added 1,4-dioxane, evaporated 3 times and the resultant solid was dried at 60°C overnight to afford the desired product (199 mg).

[0377] Example 68: Synthesis of (3R,5S)-5-tert-butyl-1-[[(1S,8R)-11-(4-methoxy-2-pyridinyl)-5-thia-11-azatricyclo[6.2.1.$0^{2,6}$]undeca-2(6),3-dien-4-yl]methyl]piperidine-3-carboxylic acid;dihydrochloride

A mixture of methyl (3R,5S)-5-tert-butyl-1-[[(1S,8R)-12-(4-methoxy-2-pyridinyl)-5-thia-12-azatricyclo[6.3.1.$0^{2,6}$]dodeca-2(6),3-dien-4-yl]methyl]piperidine-3-carboxylate (124 mg) and 6M HCl aq. was stirred at 80°C for 3 h. The mixture was concentrated, triturated with AcOEt to give the desired product (126.2 mg).

[0378] Example 81: Synthesis of (3R,5S)-5-tert-butyl-1-[[5-[4-(dimethylamino)-2-pyridinyl]-6,7-dihydro-4H-thieno[3,2-c]pyridin-2-yl]methyl]piperidine-3-carboxylic acid; dihydrochloride

Methyl (3R,5S)-5-tert-butyl-1-[[5-[4-(dimethylamino)-2-pyridinyl]-6,7-dihydro-4H-thieno[3,2-c]pyridin-2-yl]methyl]piperidine-3-carboxylate (220 mg) in 5M HCl (7 mL) was degassed using ultrasonic device with suction, and the vessel was filled with N_2. The reaction mixture was stirred at 80°C for 2 h. The mixture was concentrated with azeotropic evaporation by toluene. The residue was triturated with AcOEt and precipitated solid was collected by filtration washing with AcOEt. After drying in vacuo at 60°C for 2 h, the desired product (249 mg) was obtained.

[0379] Example 88: Synthesis of (3R,5S)-1-[[5-(2,1-benzothiazol-4-yl)-7-methylfuro[2,3-c]pyridin-2-yl]methyl]-5-tert-butylpiperidine-3-carboxylic acid; dihydrochloride

A mixture of methyl (3R,5S)-1-[[5-(2,1-benzothiazol-4-yl)-7-methylfuro[2,3-c]pyridin-2-yl]methyl]-5-tert-butylpiperidine-3-carboxylate (106 mg) and 6M HCl (3 mL) was heated at 70°C for 2 h. The reaction mixture was concentrated and the residue was triturated with AcOEt to give the desired product (117 mg) .

[0380] Example 111: Synthesis of (3S,5S)-5-tert-butyl-1-[(2,3-dimethylquinoxalin-6-yl)methyl]-3-propoxypiperidine-3-carboxylic acid; dihydrochloride

To a solution of methyl (3S,5S)-5-tert-butyl-1-[(2,3-dimethylquinoxalin-6-yl)methyl]-3-propoxypiperidine-3-carboxylate (46 mg) in THF:MeOH:water (3:3:1) (1.05 mL) was added LiOH (23 mg).

The reaction mixture was stirred at r.t. for 18 h and raised to 60°C and stirred for 3 h. The reaction mixture was neutralized by 1M HCl and extracted with DCM. The organic layer was concentrated and purified by silica gel column chromatography (AcOEt/Hexane). The collected fractions were concentrated and dried in vacuo. The residue was dissolved in AcOEt and 4M HCl in AcOEt (0.2 mL) was added. The solution was triturated and stirred for a while. The resulting suspension was filtered to give the desired product (21 mg).

[0381] Example 113: Synthesis of (3S,5S)-5-tert-butyl-1-[(5,6-dimethyl-1H-pyrrolo[3,2-b]pyridin-2-yl)methyl]-3-propoxypiperidine-3-carboxylic acid; hydrochloride

Methyl (3S,5S)-5-(tert-butyl)-1-((5,6-dimethyl-1H-pyrrolo[3,2-b]pyridin-2-yl)methyl)-3-propoxypiperidine-3-carboxylate (178 mg) in 5M HCl (10 mL) was stirred at 80°C for 10 h. The reaction was concentrated with azeotropic evaporation by toluene and AcOEt. The residue was triturated with AcOEt and the resulting solid was collected by filtration. After drying in vacuo at 60°C overnight, the desired product (183 mg) was obtained.

[0382] Example 114: Synthesis of (3S,5S)-5-tert-butyl-1-[(5,6-dimethyl-7-oxo-4H-pyrazolo[1,5-a]pyrimidin-2-yl)methyl]-3-propoxypiperidine-3-carboxylic acid; hydrochloride

Methyl (3S,5S)-5-(tert-butyl)-1-((7-chloro-5,6-dimethylpyrazolo[1,5-a]pyrimidin-2-yl)methyl)-3-propoxypiperidine-3-carboxylate (243 mg) in 5M HCl (10 mL) was stirred at 80°C for 10 h. The reaction was concentrated with azeotropic evaporation by toluene and AcOEt. The residue was triturated in AcOEt and the solid precipitated was collected by filtration. After drying in vacuo at 60°C for 2 h, the desired product (244 mg) was obtained.

[0383] Example 119: Synthesis of (3R,5S)-5-tert-butyl-1-[(2,3-dimethylthieno[2,3-b]pyrazin-6-yl)methyl]-3-propylpiperidine-3-carboxylic acid

To a solution of 2,3-dimethylthieno[2,3-b]pyrazine-6-carbaldehyde (800 mg) and (3R,5S)-5-(tert-butyl)-3-propylpiperidine-3-carboxylic acid hydrochloride (998 mg) in DCM (20 mL) were added TEA (2.1 mL) and $NaBH(OAc)_3$ (1.6 g), and the reaction mixture was stirred at r.t. for 15 h. The reaction mixture was diluted with water and 5M HCl (7.5 mL) was added. The mixture was stirred at r.t. for 30 min, then neutralized by adding 5M NaOH (7.5 mL) and extracted with AcOEt. The organic phase was washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by recrystallization (AcOEt/Hexane) to afford the desired product (947 mg).

[0384] Example 122: Synthesis of

(3R,5S)-5-tert-butyl-1-[(3-cyclopropyl-2-methylthieno[2,3-b]pyrazin-6-yl)methyl]-3-propylpiperidine-3-carboxylic acid

To a solution of (3R,5S)-5-tert-butyl-3-propylpiperidine-3-carboxylic acid;hydrochloride (100 mg), 3-cyclopropyl-2-methylthieno[2,3-b]pyrazine-6-carbaldehyde (75 mg) and TEA (53 μL) in DCM (2.5 mL) pre-stirred for 10 min was added $NaBH(OAc)_3$ (102 mg) and stirred at r.t. for 4 h. Water was added and extracted with DCM, concentrated and the residue was purified by silica gel column chromatography (EtOAc/Hexane) to give the desired product (66.3 mg).

[0385] Example 128: Synthesis of (3R,5S)-5-tert-butyl-1-[(2-chloro-3-methylthieno[2,3-b]pyrazin-6-yl)methyl]-3-propylpiperidine-3-carboxylic acid

A mixture of 2-chloro-3-methylthieno[2,3-b]pyrazine-6-carbaldehyde (2 g) and (3R,5S)-5-(tert-butyl)-3-propylpiperidine-3-carboxylic acid (2.57 g) in DCE (100 mL) was stirred at r.t. for 10 min. $NaBH(OAc)_3$ (2.99 g) was added and the mixture was stirred at r.t. for 24 h. It was quenched with water and extracted with DCM. The organic layer was concentrated in vacuo. The residue was purified by silica gel column chromatography (DCM/AcOEt followed by AcOEt/MeOH) to give the desired product (2.1 g).

[0386] Example 132: Synthesis of (3R,5S)-5-tert-butyl-1-[(2-ethoxy-3-methylthieno[2,3-b]pyrazin-6-yl)methyl]-3-propylpiperidine-3-carboxylic acid

To a solution of (3R,5S)-5-tert-butyl-1-[(2-chloro-3-methylthieno[2,3-b]pyrazin-6-yl)methyl]-3-propylpiperidine-3-carboxylic acid (80 mg) in EtOH (2 mL) was added 60 wt% NaH (11.3 mg) and the reaction was stirred at reflux for 5 h. The reaction was neutralized with 1M HCl aq. and extracted with DCM. The organic phase was concentrated and the residue was purified by silica gel column chromatography (EtOAc/Hexane) to give the desired product (43 mg).

[0387] Example 136: Synthesis of (3R,5S)-5-tert-butyl-1-[[3-methyl-2-(trifluoromethyl)-5H-pyrrolo[2,3-b]pyrazin-6-yl]methyl]-3-propylpiperidine-3-carboxylic acid; hydrochloride

To a solution of 3-methyl-2-(trifluoromethyl)-5H-pyrrolo[2,3-b]pyrazine-6-carbaldehyde (180 mg), 3-methyl-2-(trifluoromethyl)-5H-pyrrolo[2,3-b]pyrazine-6-carbaldehyde (130 mg), and TEA (95 μL) in DCM (3 mL) pre-stirred for 10 min and cooled to 0°C was added $NaBH(OAc)_3$ (301 mg) and the reaction mixture was stirred at r.t. overnight. The solvent was removed by evaporation, and the residue was purified by silica gel column

chromatography (AcOEt/MeOH). The obtained product was dissolved in AcOEt and treated with 4M HCl in AcOEt (709 μL). The solvent was removed and the residue was dried in vacuo at 60°C for 3 h to afford the desired product (111 mg).

[0388] Example 137: Synthesis of (3R,5S)-5-tert-butyl-1-[(2,3-dimethylthieno[2,3-b]pyrazin-6-yl)methyl]-3-(4,4,4-trifluorobutyl)piperidine-3-carboxylic acid; hydrochloride

To a solution of (3R,5S)-5-tert-butyl-3-(4,4,4-trifluorobutyl)piperidine-3-carboxylic acid (158 mg), 2,3-dimethylthieno[2,3-b]pyrazine-6-carbaldehyde (98 mg) in DCM (5 mL) pre-stirred for 10 min was added $NaBH(OAc)_3$ (151 mg) and the reaction mixture was stirred at r.t. for 5 h. Water was added and extracted with DCM. The organic phase was concentrated and the residue was purified by silica gel column chromatography (EtOAc/Hexane) followed by GPC ($CHCl_3$). The obtained product was dissolved in AcOEt and treated with 4M HCl in AcOEt. The solvent was removed, and the residue was dried in vacuo to afford the desired product (19.6 mg).

[0389] Example 139: Synthesis of (3R,5S)-3-butyl-5-tert-butyl-1-[[3-methyl-2-(trifluoromethyl)-5H-pyrrolo[2,3-b]pyrazin-6-yl]methyl]piperidine-3-carboxylic acid; hydrochloride

To a solution of (3R,5S)-5-(tert-butyl)-3-butylpiperidine-3-carboxylic acid hydrochloride (72.7 mg), 3-methyl-2-(trifluoromethyl)-5H-pyrrolo[2,3-b]pyrazine-6-carbaldehyde (50 mg), and TEA (37 μL) in DCM (1.5 mL) pre-stirred for 10 min and cooled to 0°C was added $NaBH(OAc)_3$ (116 mg), and the reaction mixture was stirred at r.t. overnight. The solvent was removed by evaporation and the residue was purified by silica gel column chromatography (AcOEt/MeOH) followed by GPC ($CHCl_3$). The obtained product was dissolved in AcOEt and treated with 4M HCl (273 μL). The solvent was removed and the residue was dried in vacuo at 60°C for 3 h to afford the desired product (44 mg).

[0390] Example 145: Synthesis of (3R,5S)-3-butyl-5-tert-butyl-1-[(2,3-dimethylthieno[2,3-b]pyrazin-6-yl)methyl]piperidine-3-carboxylic acid

To a solution of (3R,5S)-3-butyl-5-tert-butylpiperidine-3-carboxylic acid; hydrochloride (156 mg), 2,3-dimethylthieno[2,3-b]pyrazine-6-carbaldehyde (90 mg), and TEA (78 μL) in DCM (5 mL) pre-stirred for 10 min was added $NaBH(OAc)_3$ (139 mg), and the reaction mixture was stirred at r.t. overnight. Water was added to the reaction solution and extracted with DCM. The organic phase was concentrated and the residue was purified by silica gel column chromatography (EtOAc/Hexane) followed by GPC ($CHCl_3$) to afford the desired product (89.3 mg).

[0391] Example 149: Synthesis of (3R,5S)-5-tert-butyl-1-[[2-[2-(dimethylamino)ethoxy]-3-methylthieno[2,3-b]pyrazin-6-

yl]methyl]-3-propylpiperidine-3-carboxylic acid; dihydrochloride

A mixture of 2-[2-(dimethylamino)ethoxy]-3-methylthieno[2,3-b]pyrazine-6-carbaldehyde (54.2 mg) and (3R,5S)-5-tert-butyl-3-propylpiperidine-3-carboxylic acid (46.4 mg) in DCM (3 mL) was stirred at r.t. $NaBH(OAc)_3$ (64.9 mg) was added and the mixture was stirred at r.t. for 20 h. The reaction was quenched with water and separated by phase separator. The organic layer was concentrated and the residue was purified by silica gel column chromatography (Diol, AcOEt / Hexane). The resulting product was dissolved in MeCN (5 mL) and 6M HCl was added. The mixture was concentrated and the residue was triturated with AcOEt to give the desired product (43 mg).

[0392] Example 152: Synthesis of (3R,5S)-5-tert-butyl-1-[(5,6-dimethyl-3-phenyl-1H-pyrrolo[3,2-b]pyridin-2-yl)methyl]-3-propylpiperidine-3-carboxylic acid; trihydrochloride

To a solution of (3R,5S)-5-(tert-butyl)-3-propylpiperidine-3-carboxylic acid (72.7 mg), 5,6-dimethyl-3-phenyl-1H-pyrrolo[3,2-b]pyridine-2-carbaldehyde (80 mg), and chloro(pentamethylcyclopentadienyl)(8-quinolinolato)iridium (III) (3.24 mg) in THF (1 mL) was added formic acid (36.8 μl) and the reaction mixture was stirred at 60°C for 2 h. After cooling to r.t., the reaction was directly purified by reverse phase column chromatography (water/MeCN, 0.1%TFA) to afford a mixture including the desired product (TFA salt). The mixture was treated with a small amount of TEA and evaporated, then purified by GPC ($CHCl_3$) to isolate the desired product. It was dissolved in AcOEt and treated with 4M HCl in AcOEt (400 μl). The solvent was removed in vacuo and the residue was triturated in AcOEt. Solids precipitated were collected by filtration and dried in vacuo to afford the desired product (96 mg).

[0393] Example 156: Synthesis of (3R,5S)-5-tert-butyl-1-[[3-methyl-2-(4-methylpiperazin-1-yl)thieno[2,3-b]pyrazin-6-yl]methyl]-3-propylpiperidine-3-carboxylic acid; trihydrochloride

A mixture of (3R,5S)-5-tert-butyl-1-[(2-chloro-3-methylthieno[2,3-b]pyrazin-6-yl)methyl]-3-(3-methylbutyl)piperidine-3-carboxylic acid; hydrochloride (1.00 g), 1-Methylpiperazine (0.52 mL), Pd-PEPPSI IPent (93 mg) and Cs_2CO_3 (3.84 g) in DME (5 mL) was stirred at 80°C under N_2 overnight. The reaction mixture was cooled to r.t., then filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (AcOEt/MeOH) to give the desired product. To a solution of the product in AcOEt was added 4M HCl in AcOEt. After stirring at r.t. for 10 min, the mixture was concentrated under reduced pressure. The residue was triturated in AcOEt, filtered and dried to give the desired product (1.14 g).

[0394] Example 160: Synthesis of

(3R,5S)-5-tert-butyl-1-[(2-chloro-3-methylthieno[2,3-b]pyrazin-6-yl)methyl]-3-(3-methylbutyl)piperidine-3-carboxylic acid; hydrochloride

A mixture of 2-chloro-3-methylthieno[2,3-b]pyrazine-6-carbaldehyde (100 mg), (3R,5S)-5-(tert-butyl)-3-isopentylpiperidine-3-carboxylic acid hydrochloride (137 mg), TEA (0.2 mL) and $NaBH(OAc)_3$ (299 mg) in DMSO (5 mL) was stirred at 0°C to r.t. overnight. The mixture was diluted with water, extracted with EtOAc, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (AcOEt/MeOH) to give the desired product. To a solution of the product in AcOEt was added 4M HCl/AcOEt. After stirring at r.t. for 10 min, the mixture was concentrated under reduced pressure. The residue was triturated with AcOEt, filtered and dried to give the desired product (27 mg).

[0395] Example 166: Synthesis of (3R,5S)-5-tert-butyl-1-[(2-cyclopropyl-3-methylthieno[2,3-b]pyrazin-6-yl)methyl]-3-propylpiperidine-3-carboxylic acid

A mixture of (3R,5S)-5-tert-butyl-1-[(2-chloro-3-methylthieno[2,3-b]pyrazin-6-yl)methyl]-3-propylpiperidine-3-carboxylic acid (200 mg), cyclopropaneboronic acid (81 mg), $Pd(dppf)Cl_2$ _CH_2Cl_2 (38.5 mg), PCy_3 HBF_4 (34.7 mg) and K_3PO_4 (300 mg) in 1,4-dioxane/water (5 mL/2 mL) was stirred at reflux overnight. The reaction solution was filtered through Celite and the filtrate was concentrated. The residue was purified by silica gel column chromatography (Hexane/AcOEt) to afford the desired product (83 mg).

[0396] Example 174: Synthesis of (3R,5S)-5-tert-butyl-1-[[2-chloro-3-(trifluoromethyl)thieno[2,3-b]pyrazin-6-yl]methyl]-3-propylpiperidine-3-carboxylic acid; hydrochloride

To a stirred solution of (3R,5S)-5-tert-butyl-3-propylpiperidine-3-carboxylic acid (28.0 mg), 2-chloro-3-(trifluoromethyl)thieno[2,3-b]pyrazine-6-carbaldehyd (29.9 mg) and TEA (46.9 μL, 0.336 mmol) in DCE (1 mL) was added $NaBH(OAc)_3$ (71.3 mg) at r.t. and the mixture was stirred for 14 h. The reaction mixture was diluted with EtOAc. The organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (Hexane/EtOAc) to give the desired product. To a stirred solution of the product in EtOAc (1 mL) was added 4M HCl/EtOAc (100 μL). After the mixture was stirred at rt for 10 min, it was concentrated under reduced pressure. The residue was triturated with Et_2O to give the desired product (19.2 mg).

[0397] Example 184: Synthesis of (3R,5S)-5-tert-butyl-1-[[2-[(dimethylamino)methyl]-3-methylthieno[2,3-b]pyrazin-6-yl]methyl]-3-propylpiperidine-3-carboxylic acid; dihydrochloride

To a solution of

(3R,5S)-5-tert-butyl-1-[[3-methyl-2-[[(2-methylpropan-2-yl)oxycarbonylamino]methyl]thieno[2,3-b]pyrazin-6-yl]methyl]-3-propylpiperidine-3-carboxylic acid (45.9 mg) in EtOAc (2 mL) was added 4M HCl in EtOAc (221 μL) at rt. The mixture was stirred at 60°C for 3 h. The mixture was concentrated under reduce pressure. To a stirred solution of the residue and TEA (61.7 μL) in DCM (2 mL) was added formaldehyde aq. (43 μL) at r.t., and the mixture was stirred at r.t. for 10 min. Then $NaBH(OAc)_3$ (112 mg) was added to the mixture. After the mixture was stirred at r.t. for 16 h, the reaction was quenched with water. The whole was extracted with DCM. The aqueous layer was basified with Na_2CO_3 and extracted with DCM. The combined organic phase was washed with brine, dried over Na_2SO_4, filtered and concentrated to give an oily residue, which was purified by flash chromatography over ODS gel (0.1%TFA-water/0.1%TFA-MeCN). To a stirred solution of the product in EtOAc (2 mL) was added 4M HCl/EtOAc (200 μL) and stirred at r.t. for 10 min. The reaction solution was concentrated under reduced pressure and the residue was triturated with Et_2O to give the desired product (7.6 mg).

[0398] Example 188: Synthesis of (3R,5S)-5-tert-butyl-1-[[3-methyl-2-[4-methyl-3-(trifluoromethyl)piperazin-1-yl]thieno[2,3-b]pyrazin-6-yl]methyl]-3-propylpiperidine-3-carboxylic acid

To a solution of (3R,5S)-5-tert-butyl-1-[[3-methyl-2-[3-(trifluoromethyl)piperazin-1-yl]thieno[2,3-b]pyrazin-6-yl]methyl]-3-propylpiperidine-3-carboxylic acid (200 mg) in DCM (5 mL) were added AcOH (0.021 mL), paraformaldehyde (33.3 mg) and $NaBH(OAc)_3$ and stirred at r.t. for 30 min. sat. $NaHCO_3$ aq. was added and extracted with AcOEt, washed with water and brine, dried over Na_2SO_4, filtered and concentrated. The residue was triturated in IPE, filtered and the obtained solid was dried in vacuo at 80°C to afford the desired product (172 mg).

[0399] Example 190: Synthesis of (3R,5S)-5-tert-butyl-1-[(2,3-dimethylfuro[2,3-b]pyrazin-6-yl)methyl]-3-(4,4,4-trifluorobutyl)piperidine-3-carboxylic acid

A mixture of 2,3-dimethylfuro[2,3-b]pyrazine-6-carbaldehyde (86 mg), (3R,5S)-5-(tert-butyl)-3-(4,4,4-trifluorobutyl)piperidine-3-carboxylic acid (144 mg), TEA (0.14 mL) and $NaBH(OAc)_3$ (207 mg) in DCM (3 mL) was stirred at 0°C to r.t. overnight. The mixture was diluted with water, extracted with DCM, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/AcOEt) to give the desired product (172 mg).

[0400] Example 200: Synthesis of (3R,5S)-5-tert-butyl-1-({imidazo[1,2-b]cinnolin-2-yl}methyl)piperidine-3-carboxylic acid, di-hydrochloride salt

Step 1

A mixture of methyl (3R,5S)-5-tert-butyl-1-({imidazo[1,2-b]cinnolin-2-yl}methyl)piperidine-3-carboxylate (1.2 g) in conc. HCl (20 mL) was stirred at 100°C for 1 h. The reaction was cooled to rt and the crude mixture was washed with TBME and MeCN. The solid was collected by filtration and dried in vacuo to give the desired product (1.2 g).

Step 2

Methyl (3R,5S)-5-tert-butylpiperidine-3-carboxylate (150.0 mg) was added to a suspension of 2-(chloromethyl)imidazo[1,2-b]cinnoline (70.0 mg) in MeCN (10 mL) followed by K_2CO_3 (140 mg). The reaction was stirred at 80°C for 24 h. The reaction mixture was partitioned between EtOAc and $NaHCO_3$ aq.. The organic phase was concentrated in vacuo and the residue was purified by silica gel column chromatography (EtOAc/petrol) to give the desired product (150 mg).

Step 3

A mixture of methyl (3R,5S)-5-tert-butyl-1-({imidazo[1,2-b]cinnolin-2-yl}methyl)piperidine-3-carboxylate (1.2 g) in conc. HCl (20 mL) was stirred at 100°C for 1 h. The reaction was cooled to r.t. and the crude mixture was washed with TBME and MeCN. The solid was collected by filtration and dried in vacuo to give the desired product (1.2 g).

[0401] Example 206: Synthesis of (3R,5S)-5-tert-butyl-1-{[5-(1H-pyrazol-1-yl)furo[2,3-b]pyridin-2-yl]methyl}piperidine-3-carboxylic acid, hydrochloride salt

A solution of methyl (3R,5S)-5-tert-butyl-1-{[5-(1H-pyrazol-1-yl)furo[2,3-b]pyridin-2-yl]methyl}piperidine-3-carboxylate (88.0 mg) in conc. HCl (2.2 mL) was stirred at 100°C for 1 h. The reaction mixture was concentrated in vacuo to give the desired product (57.0 mg).

[0402] Example 209: Synthesis of (3R,5S)-5-tert-butyl-1-[(1S)-1-[5-(1H-pyrazol-1-yl)furo[2,3-b]pyridin-2-yl]ethyl]piperidine-3-carboxylic acid, hydrochloride salt

A solution of methyl (3R,5S)-5-tert-butyl-1-[(1S)-1-[5-(1H-pyrazol-1-yl)furo[2,3-b]pyridin-2-yl]ethyl]piperidine-3-carboxylate (67.0 mg) in conc. HCl (1.6 mL) was stirred at 100°C for 1 h. The resulting mixture was concentrated to dryness to give the desired product (71.0 mg).

[0403] Example 222: Synthesis of (3R,5S)-5-tert-butyl-3-(3-methylbutyl)-1-({2-methylthieno[3,2-d]pyrimidin-6-yl}methyl)piperidine-3-carboxylic acid, hydrochloride salt

2-Methylthieno[3,2-d]pyrimidine-6-carbaldehyde (59 mg) was added to a solution of (3R,5S)-5-tert-butyl-3-(3-methylbutyl)piperidine-3-carboxylic acid hydrochloride salt

(126 mg) and triethylamine (0.16 mL) in 2-methyltetrahydrofuran (10 mL). After stirring at r.t. for 30 min, phenylsilane (0.25 mL) was added followed by chlorido(8-quinolinolato-κ2N,O)(η5-pentamethylcyclopentadienyl)iridium (III) (1.7 mg). The reaction mixture was degassed with N_2 and stirred at 65°C for 4 h. The mixture was purified by silica gel column chromatography (NH_2 column, EtOAc/EtOH followed by SiO_2, THF/cyclohexane) to give the desired product as a free base. The material was dissolved in MeCN (3 mL), treated with 1M HCl (1 mL) and immediately freeze dried. The solid was triturated in Et_2O, filtered and dried in vacuo to afford the desired product as a hydrochloride salt.

[0404] Example 234: Synthesis of (3R,5S)-5-tert-butyl-3-[3-(4,4-difluorocyclohexyl)propyl]-1-[(quinoxalin-6-yl)methyl] piperidine-3-carboxylic acid

A suspension of methyl (3R,5S)-5-tert-butyl-3-[3-(4,4-difluorocyclohexyl)propyl]-1-[(quinoxalin-6-yl)methyl] piperidine-3-carboxylate (653 mg) and LiOH (1.25 g) in 1,4-dioxane (15 mL) and water (10 mL) was stirred at 100°C for 48 h. The solvent was removed in vacuo and the residue was purified by reverse phase column chromatography (water/MeCN, 0.1%TFA) to give the desired product (174 mg).

[0405] Example 242: Synthesis of rac-(3R,5S)-1-[(2,3-dimethylthieno[2,3-b]pyrazin-6-yl)methyl]-5-(1-hydroxy-2-methylpropan-2-yl)-3-propylpiperidine-3-carboxylic acid; 2,2,2-trifluoroacetic acid

To the rac-(3R,5S)-5-[1-[tert-butyl(dimethyl)silyl]oxy-2-methylpropan-2-yl]-1-[(2,3-dimethylthieno[2,3-b]pyrazin-6-yl)methyl]-3-propylpiperidine-3-carboxylic acid (139 mg) was added 1N TBAF in THF (0.391 ml) at 0°C. After stirring at rt for 2h, 1N TBAF in THF (0.391 ml) was added again. After stirring at 50°C for over night, 1N TBAF in THF (0.391 ml) was added again. After stirring at 50°C for 2h, 1N TBAF in THF (0.391 ml) was added again. After stirring at 50°C for 2h, the reaction mixture was cooled to r.t. The mixture was diluted with H_2O, extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc) to give the desired product and TBAF mixture. Therefore, to the mixture was added H_2O and extracted EtOAc 10 times. But desired product was not extraced by EtOAc sufficiently. Then All water phase recovered and evaporated. The residue was throughed by silica gel column chromatography (EtOAc/MeOH) to give the desired product and TBAF mixture again. Then, the mixture was purified by reverse phase column chromatography (H_2O/MeCN, including TFA) twice and freeze drying to give the desired product as TFA salt (79 mg).

[0406] Example 245: Synthesis of (3R,5R)-1-[(2,3-dimethylquinoxalin-6-yl)methyl]-5-(2-fluoropropan-2-yl)-3-propylpiperidine-3-carboxylic acid

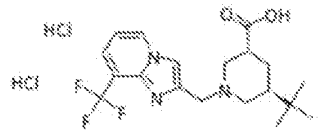
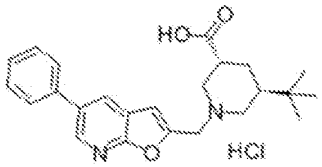
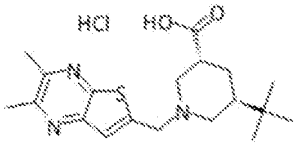
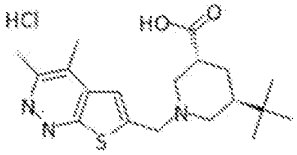
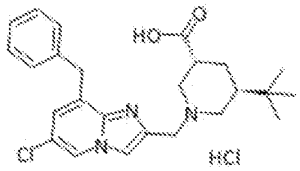
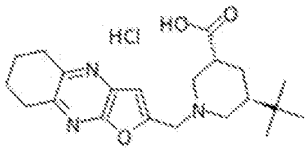
A mixture of methyl 1-[(2,3-dimethylquinoxalin-6-yl)methyl]-5-(1-fluoro-1-methyl-ethyl)-3-propyl-piperidine-3-carboxylate (230 mg) and NaOH (2.25 mL, 42.6 mmol) in EtOH (4.48 mL) was stirred at r.t. for 2 days. Then was added other sodium hydroxide in water (5.86 mL) and the mixture was stirred at room temperature overnight. Then the mixture was heated at 55°C overnight. 6N-HCl was added at 0°C to adjust pH less than 4. Water was added and extracted with EtOAc, dried over Na_2SO_4, filtered and concentrated. The residue was purified by chromatography (Sfar D Si, 25g; Cyclohexane/ EtOAc+EtOH (3:1)) to afford 1-[(2,3-dimethylquinoxalin-6-yl)methyl]-5-(1-fluoro-1-methyl-ethyl)-3-propyl-piperidine-3-carboxylic acid. Sent to SFC chiral separation to obtain two products. (3R,5R)-1-[(2,3-dimethylquinoxalin-6-yl)methyl]-5-(2-fluoropropan-2-yl)-3-propylpiperidine-3-carboxylic acid (70.4 mg).

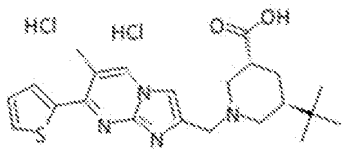
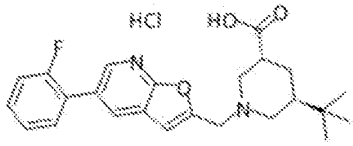
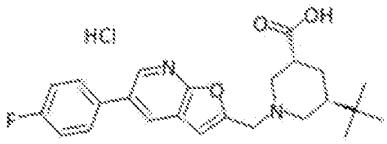
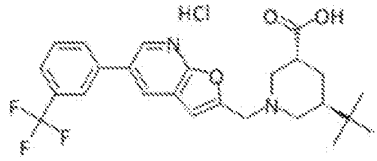
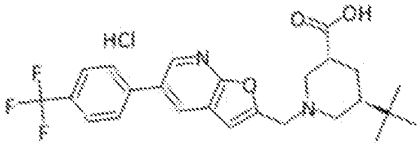
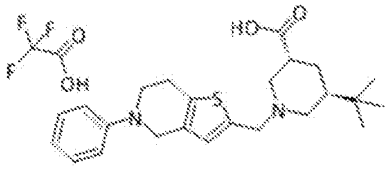
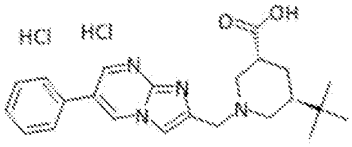
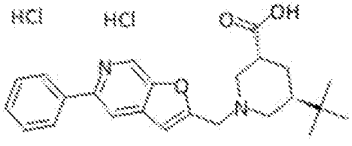
[0407] The compounds of Examples were manufactured in the same manner as in any of the above Examples. Structural formulae and physicochemical data of the compounds of Examples are shown in the following table.

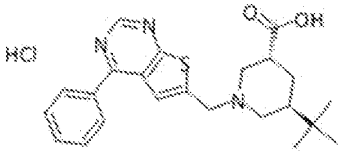
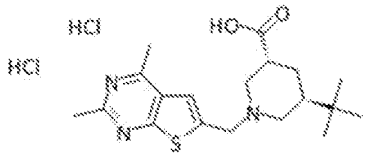
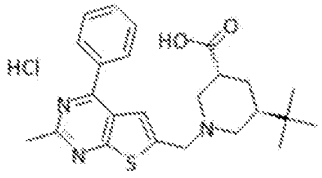
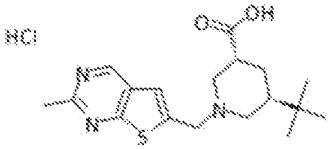
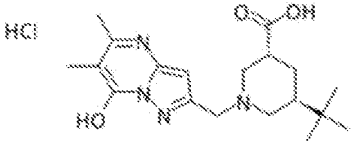
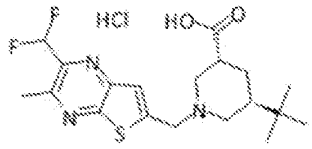
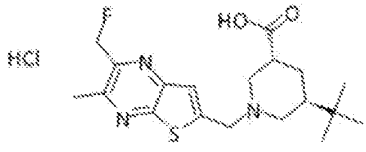
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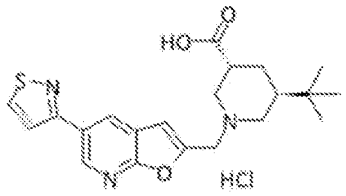
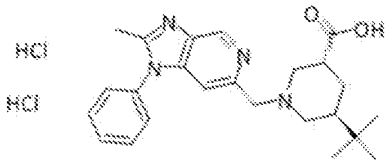
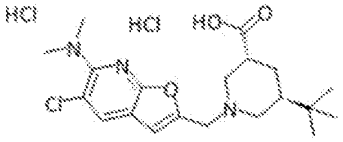
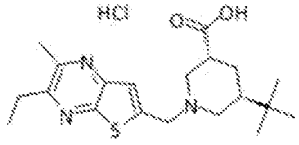
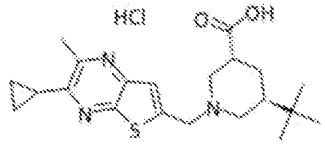
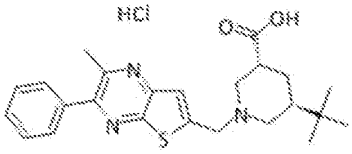
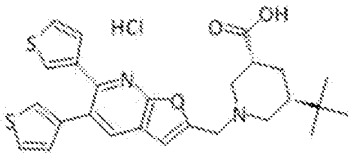
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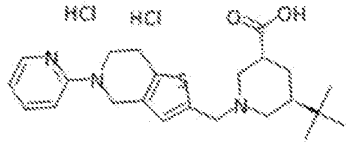
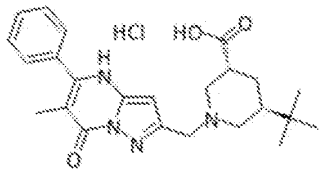
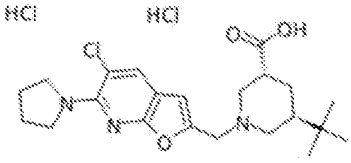
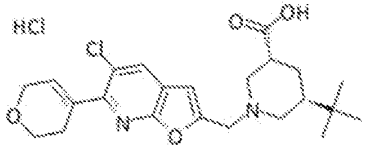
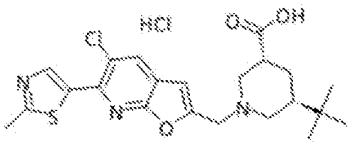
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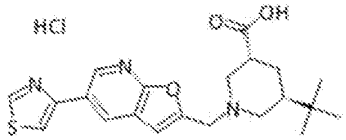
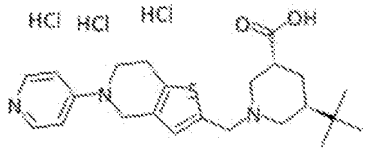
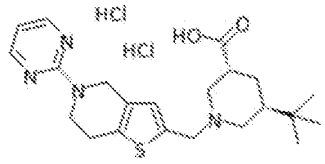
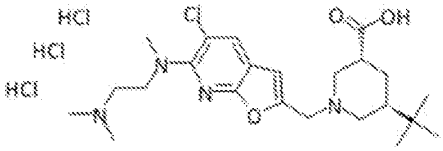
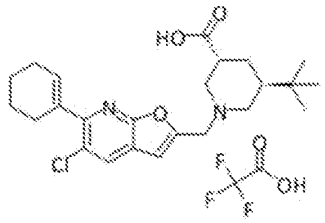
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3		113	[M+H]+ 362.3
4		113	[M+H]+ 362.4
5		5	[M+H]+ 440 NMR1; 8.91 (1H, s), 8.18 (1H, s), 7.42 (2H, d), 7.33-7.13 (4H, m), 4.57 (1H, d), 4.42 (1H, d), 4.28 (2H, s), 3.68 (1H, d), 3.58 (1H, d), 3.08 (2H, d), 2.94-2.81 (2H, m), 2.13 (1H, d), 1.60-1.35 (2H, m), 1.28-1.15 (1H, m), 0.88 (9H, s).
6		113	[M+H]+ 372.2

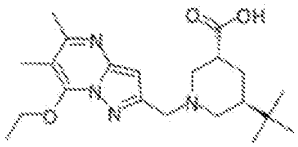
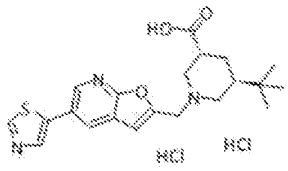
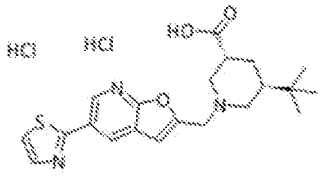
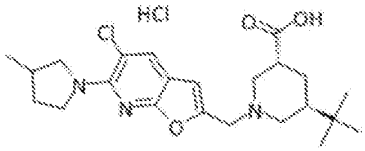
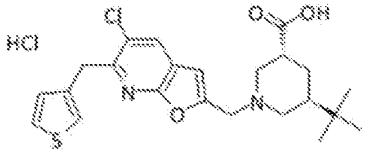
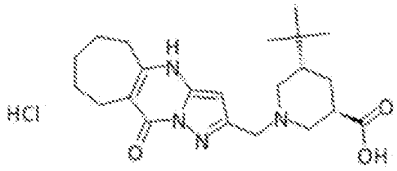
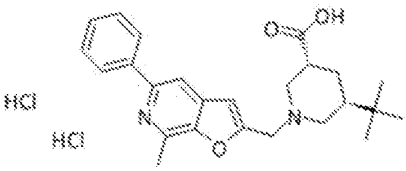
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8		113	$[M+H]^+$ 411.1
9		113	$[M+H]^+$ 411.0
10		113	$[M+H]^+$ 461.0
11		113	$[M+H]^+$ 461.2
12		113	$[M+H]^+$ 413.2
13		200	$[M+H]^+$ 393.5
14		14	$[M+H]^+$ 393.3 NMR1; 0.53 (s, 1H), 9.12 (s, 1H), 8.37 (s, 1H), 8.14 – 8.07 (m, 2H), 7.56 – 7.40 (m, 4H), 4.75 (d, J = 14.4 Hz, 1H), 4.61 (d, J = 14.6 Hz, 1H), 3.89-3.50

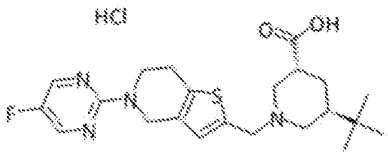
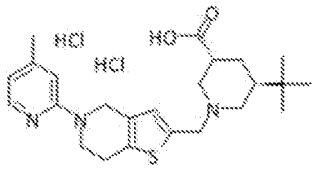
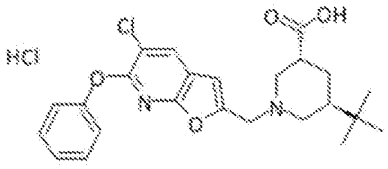
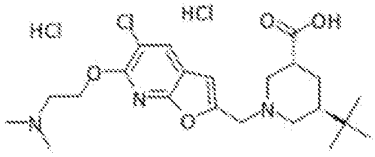
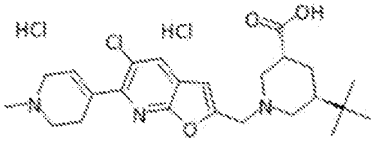
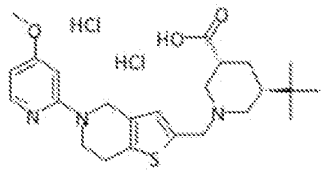
			(m, 3H), 2.91 (s, 2H), 2.14 (d, J = 11.8 Hz, 1H), 1.57 – 1.45 (m, 2H), 0.89 (s, 9H)
15		113	$[M+H]^+$ 410.3
16		113	$[M+H]^+$ 362.3
17		17	$[M+H]^+$ 424.3 NMR1; 9.39 (s, 1H), 8.78 (s, 1H), 8.05 – 7.93 (m, 3H), 7.69 – 7.58 (m, 3H), 4.83 – 4.62 (m, 2H), 3.59 (d, J = 11.0 Hz, 1H), 3.51 (d, J = 11.0 Hz, 1H), 3.15 – 2.97 (m, 2H), 2.91 – 2.75 (m, 1H), 2.80 (s, 3H), 2.14 (d, J = 12.4 Hz, 1H), 1.60 – 1.40 (m, 2H), 0.90 (s, 9H).
18		113	$[M+H]^+$ 348.3
19		113	$[M+H]^+$ 361.4
20		113	$[M+H]^+$ 398.4
21		113	$[M+H]^+$ 380.4

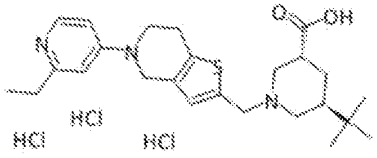
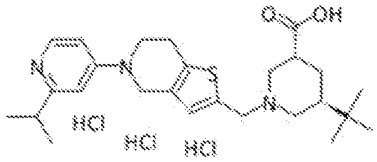
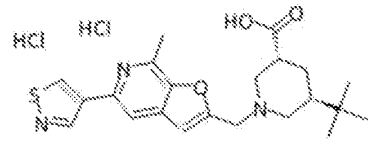
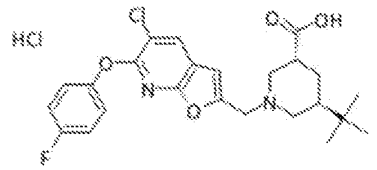
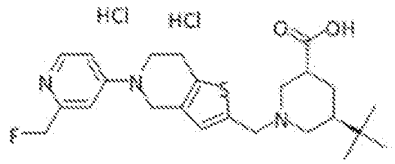
22		22	$[M+H]^+$ 400.2 NMR1; 9.26 (d, J = 4.7 Hz, 1H), 9.08 (d, J = 2.2 Hz, 1H), 8.85 (d, J = 2.2 Hz, 1H), 8.10 (d, J = 4.7 Hz, 1H), 7.39 (s, 1H), 4.67 (s, 1H), 4.58 (s, 1H), 3.64 (d, J = 12.2 Hz, 1H), 3.54 (d, J = 11.6 Hz, 1H), 3.11 (s, 2H), 2.88 (s, 1H), 2.14 (d, J = 11.8 Hz, 1H), 1.52 (q, J = 14.4 Hz, 2H), 0.88 (s, 9H)
23		113	$[M+H]^+$ 407.5
24		113	$[M+H]^+$ 394.4
25		113	$[M+H]^+$ 376.5
26		113	$[M+H]^+$ 388.4
27		113	$[M+H]^+$ 424.4
28		113	$[M+H]^+$ 481.2

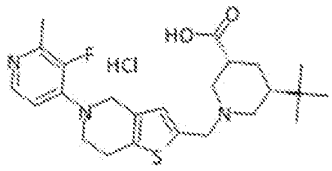
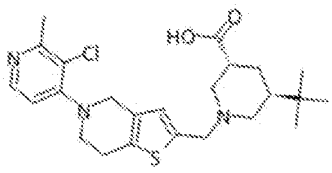
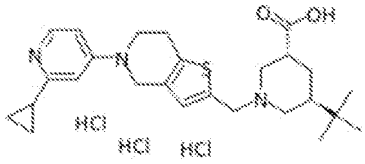
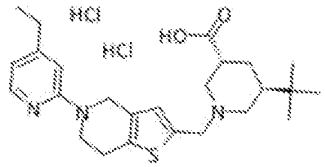
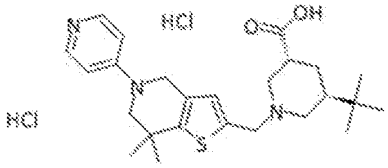
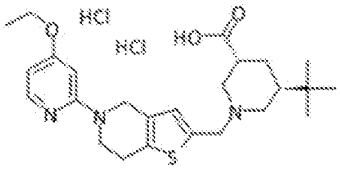
29		113	NMR1; 9.02 (s, 1H), 8.09 (dd, J = 5.9, 1.8 Hz, 1H), 7.97 – 7.89 (m, 1H), 7.35 (d, J = 9.1 Hz, 1H), 7.17 (s, 1H), 6.91 (t, J = 6.4 Hz, 1H), 4.82 – 4.68 (m, 2H), 4.56 (d, J = 13.8 Hz, 1H), 4.42 (d, J = 12.5 Hz, 1H), 4.05 (q, J = 5.8 Hz, 2H), 3.59 – 3.33 (m, 4H), 3.10 (s, 1H), 3.01 (t, J = 5.9 Hz, 3H), 2.77 (d, J = 9.5 Hz, 1H), 2.14 (d, J = 9.7 Hz, 1H), 1.55 – 1.40 (m, 2H), 0.89 (s, 9H).
30		113	$[M+H]^+$ 423.5
31		31	$[M+H]^+$ 420.4 NMR1; 10.01 (1H, br), 8.05 (1H, s), 7.04 (1H, s), 4.57 – 4.49 (1H, m), 4.41 – 4.33 (1H, m), 3.70 – 3.26 (6H, m), 3.11 – 3.06 (2H, m), 2.80 – 2.75 (1H, m), 2.13 (1H, d, J=11.8 Hz), 1.93 – 1.84 (4H, m), 1.56 – 1.41 (2H, m), 0.87 (9H, s)
32		113	$[M+H]^+$ 433.2
33		113	$[M+H]^+$ 448.2
34		113	$[M+H]^+$ 439.4

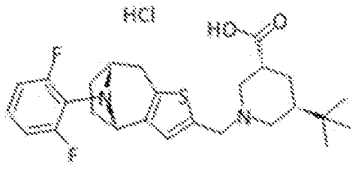
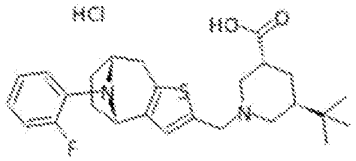
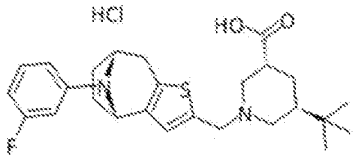
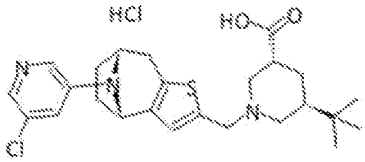
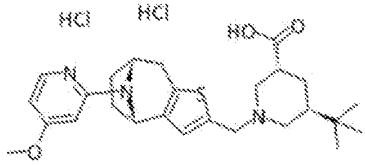
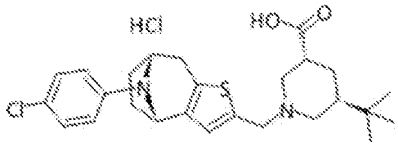
35		113	[M+H]+ 400
36		113	NMR1; 13.93 (s, 1H), 13.06 (s, 1H), 9.14 (s, 1H), 8.32 (d, J = 7.2 Hz, 2H), 7.33 (s, 2H), 7.16 (s, 1H), 4.77 (d, J = 16.4 Hz, 1H), 4.72 (d, J = 16.4 Hz, 1H), 4.56 (d, J = 13.7 Hz, 1H), 4.43 (dd, J = 13.9, 6.7 Hz, 1H), 4.02 (tq, J = 13.3, 6.7, 5.4 Hz, 2H), 3.60 – 3.48 (m, 2H), 3.47 – 3.36 (m, 1H), 3.13 – 2.93 (m, 4H), 2.77 (q, J = 10.7 Hz, 1H), 2.15 (d, J = 11.8 Hz, 1H), 1.57 – 1.38 (m, 2H), 0.89 (s, 9H).
37		37	NMR1; 9.17 (s, 1H), 8.45 (d, J = 4.8 Hz, 2H), 7.34 (s, 2H), 7.20 (s, 1H), 6.73 (t, J = 4.8 Hz, 1H), 4.89 – 4.75 (m, 2H), 4.55 (d, J = 14.3 Hz, 1H), 4.40 (dd, J = 13.9, 7.1 Hz, 1H), 4.13 (td, J = 5.6, 2.6 Hz, 2H), 3.54 – 3.41 (m, 2H), 3.08 (s, 1H), 3.04 – 2.93 (m, 1H), 2.92 (q, J = 8.4, 6.1 Hz, 2H), 2.79 (q, J = 11.0 Hz, 1H), 2.14 (d, J = 12.3 Hz, 1H), 1.58 – 1.38 (m, 2H), 0.88 (s, 9H).
38		113	[M+H]+ 451.4
39		113	[M+H]+ 431.4

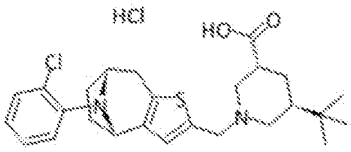
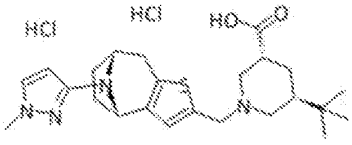
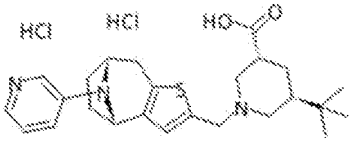
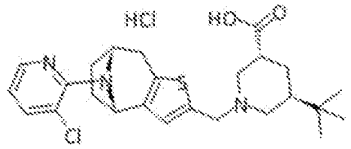
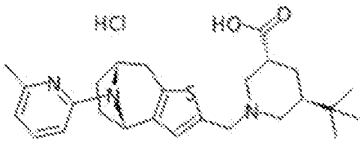
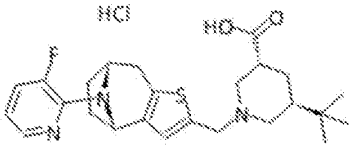
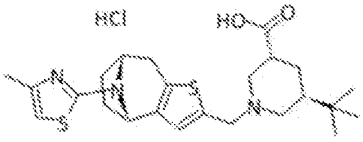
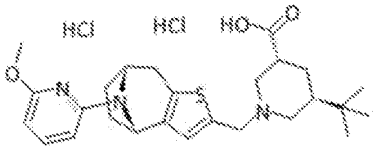
40		122	[M+H]+ 389.4
41		113	[M+H]+ 400.2
42		113	[M+H]+ 400.1
43		113	[M+H]+ 434.4
44		113	[M+H]+ 447.4
45		113	[M+H]+ 401.4
46		113	[M+H]+ 407

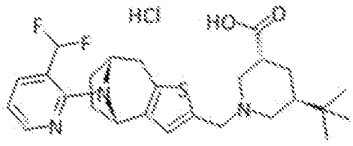
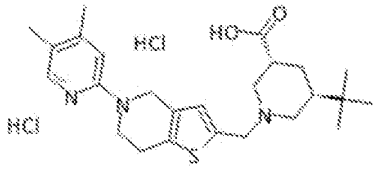
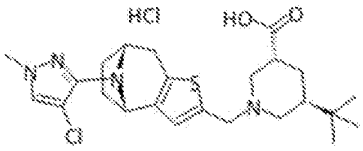
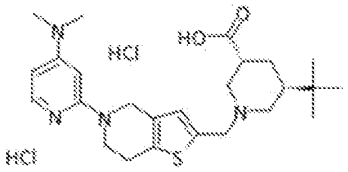
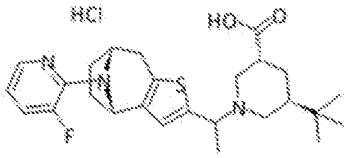
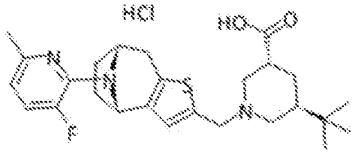
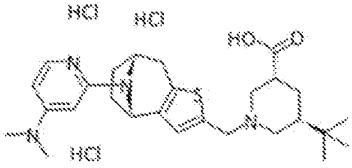
47		113	$[M+H]^+$ 433.4
48		113	$[M+H]^+$ 428.4
49		113	$[M+H]^+$ 443.4
50		113	$[M+H]^+$ 438.4
51		113	$[M+H]^+$ 446.3
52		113	$[M+H]^+$ 444.4

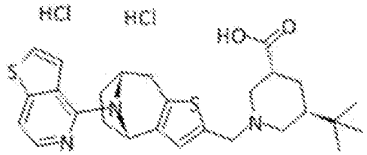
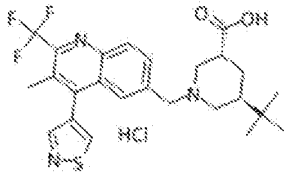
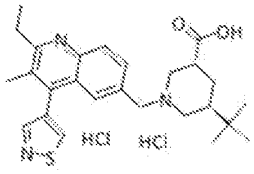
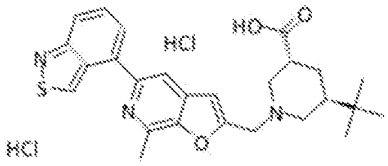
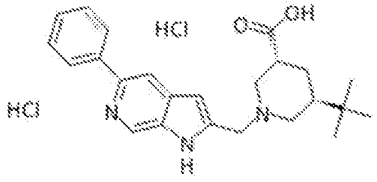
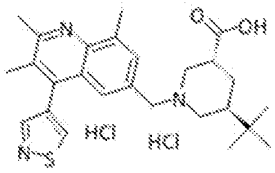
S3		113	NMR1; 14.18 (s, 1H), 13.04 (s, 1H), 9.27 (s, 1H), 8.19 (dd, J = 7.7, 4.0 Hz, 1H), 7.34 – 7.19 (m, 2H), 7.18 (s, 1H), 4.79 (d, J = 16.5 Hz, 1H), 4.72 (d, J = 16.5 Hz, 1H), 4.56 (d, J = 13.9 Hz, 1H), 4.44 (d, J = 13.9 Hz, 1H), 4.03 (ddq, J = 19.7, 13.8, 7.8, 6.6 Hz, 2H), 3.57 – 3.39 (m, 3H), 3.09 (s, 1H), 3.01 (t, J = 5.6 Hz, 3H), 2.86 – 2.71 (m, 3H), 2.15 (d, J = 12.4 Hz, 1H), 1.54 (t, J = 12.5 Hz, 1H), 1.44 (td, J = 12.9, 5.0 Hz, 1H), 1.29 (t, J = 7.6 Hz, 3H), 0.89 (s, 9H).
S4		113	NMR1; 14.33 (d, J = 5.7 Hz, 1H), 9.38 (s, 1H), 8.16 (t, J = 6.5 Hz, 1H), 7.20 (s, 3H), 5.32 (s, 2H), 4.81 (d, J = 16.5 Hz, 1H), 4.73 (d, J = 16.4 Hz, 1H), 4.57 (d, J = 13.6 Hz, 1H), 4.47 (dd, J = 13.9, 6.8 Hz, 1H), 4.04 (dq, J = 13.4, 7.2, 6.2 Hz, 2H), 3.52 (d, J = 11.2 Hz, 1H), 3.43 (d, J = 12.0 Hz, 1H), 3.20 (p, J = 6.9 Hz, 1H), 3.01 (t, J = 6.0 Hz, 4H), 2.80 (q, J = 11.1 Hz, 1H), 2.16 (d, J = 12.8 Hz, 1H), 1.56 (t, J = 12.4 Hz, 1H), 1.44 (td, J = 13.0, 5.0 Hz, 1H), 1.34 (d, J = 6.9 Hz, 6H), 0.89 (s, 9H).
S5		113	$[M+H]^+$ 414
S6		113	$[M+H]^+$ 461.3
S7		113	$[M+H]^+$ 446.4

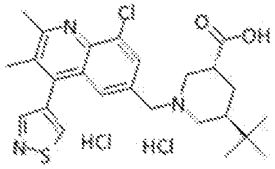
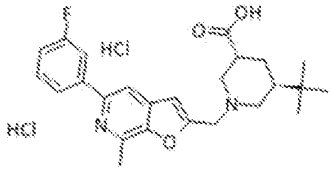
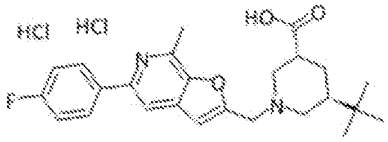
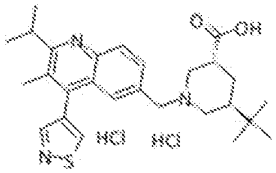
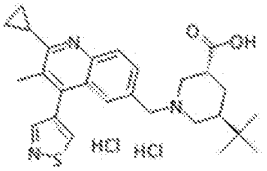
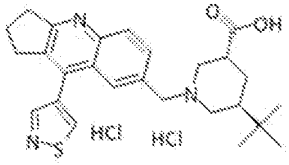
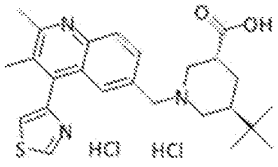
58		113	NMR1; 8.22 (d, J = 6.9 Hz, 1H), 7.31 (m, 1H), 7.12 (s, 1H), 4.74 (s, 2H), 4.66 – 4.29 (m, 2H), 4.21 – 3.82 (m,2H), 3.70 – 2.62 (m, 11H), 1.46 (m, 2H), 0.88 (s, 9H)
59		113	$[M+H]^+$ 462.3
60		113	NMR1; 14.00 (s, 1H), 13.05 (s, 2H), 9.23 (s, 1H), 8.10 (d, J = 7.3 Hz, 1H), 7.15 (s, 2H), 6.86 (s, 1H), 4.77 (d, J = 16.4 Hz, 1H), 4.69 (d, J = 16.4 Hz, 1H), 4.55 (d, J = 13.8 Hz, 1H), 4.43 (d, J = 13.9 Hz, 1H), 4.08 – 3.91 (m, 2H), 3.51 (d, J = 11.5 Hz, 1H), 3.46 – 3.38 (m, 1H), 3.09 (s, 1H), 2.99 (s, 3H), 2.76 (s, 1H), 2.23 (tt, J = 7.5, 5.8 Hz, 1H), 2.15 (d, J = 12.3 Hz, 1H), 1.58 – 1.38 (m, 2H), 1.19 (dq, J = 9.1, 2.6 Hz, 4H), 0.89 (s, 9H)
61		113	$[M+H]^+$ 442.3
62		113	$[M+H]^+$ 442.3
63		113	$[M+H]^+$ 458.3

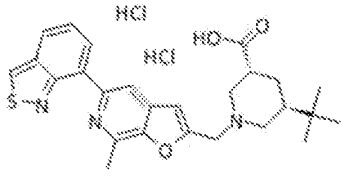
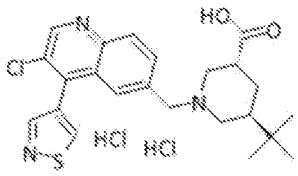
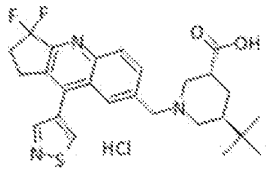
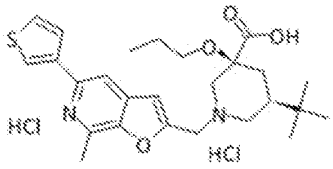
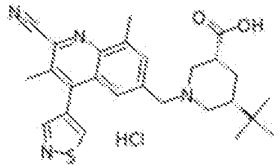
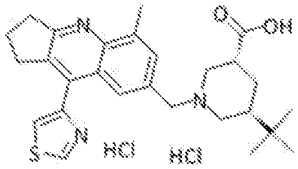
64		113	[M+H]+ 475.3
65		113	[M+H]+ 457.3
66		113	[M+H]+ 457.3
67		113	[M+H]+ 474.3
68		68	[M+H]+ 470.3 NMR1; 8.96 (1H, s), 7.88 (1H, d, J=7.1 Hz), 7.25 (1H, s), 6.84 – 6.58 (2H, m), 5.84 – 5.80 (1H, m), 5.21 – 5.17 (1H, m), 4.52 (1H, d, J=14.0 Hz), 4.40 – 4.32 (1H, m), 3.94 (3H, s), 3.47 (1H, d, J=11.5 Hz), 3.10 – 3.06 (1H, m), 2.96 – 2.91 (1H, m), 2.87 – 2.78 (1H, m), 2.77 – 2.70 (1H, m), 2.41 – 2.34 (1H, m), 2.25 – 2.16 (1H, m), 2.16 – 2.10 (1H, m), 2.01 – 1.80 (3H, m), 1.50 – 1.40 (2H, m), 0.88 (9H, s)
69		113	[M+H]+ 473.2

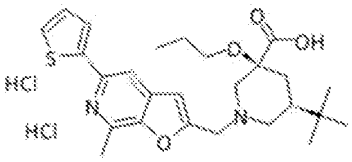
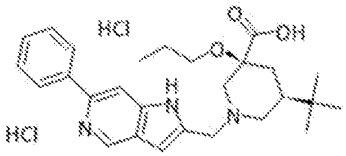
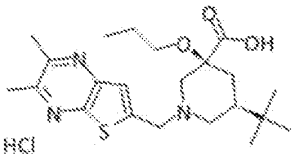
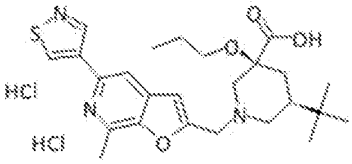
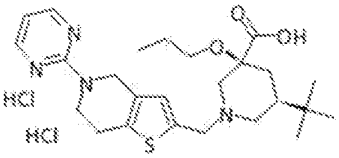
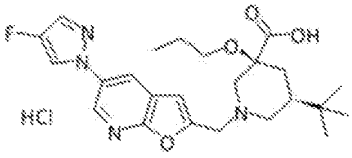
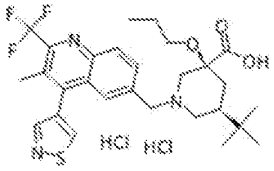
70		113	[M+H]+ 473.2
71		113	[M+H]+ 443.4
72		113	[M+H]+ 440.4
73		113	[M+H]+ 474.3
74		113	[M+H]+ 454.4
75		113	[M+H]+ 458.3
76		113	[M+H]+ 460.3
77		113	[M+H]+ 470.4

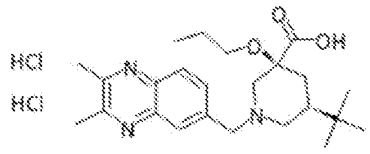
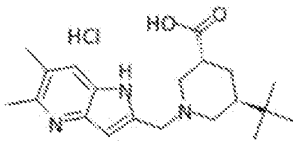
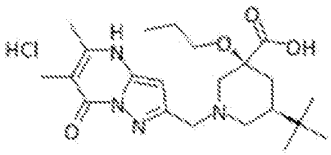
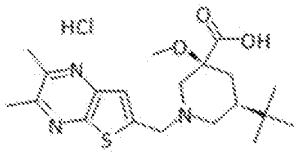
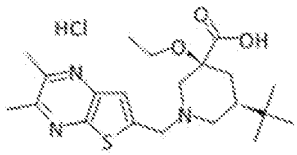
78		113	[M+H]+ 490.3
79		113	[M+H]+ 442.4
80		113	[M+H]+ 477.3
81		81	[M+H]+ 457.4 NMR1: 13.09 (brs, 1H), 9.11 (brs, 1H), 9.20 (s, 1H), 7.70 (d, J = 6.8 Hz, 1H), 7.15 (s, 1H), 6.53 (dd, J = 1.7, 6.8 Hz, 1H), 6.02 (d, J = 1.7 Hz, 1H), 4.70 - 4.41 (m, 4H), 3.99 - 3.87 (m, 2H), 3.53 - 3.45 (m, 2H), 3.15 (s, 6H), 3.09 - 2.70(m, 5H), 2.16 - 2.13 (m, 1H), 1.54 - 1.41 (m, 2H), 0.88(s, 9H).
82		113	[M+H]+ 472.4 Epimer mixture
83		113	[M+H]+ 472.3
84		113	[M+H]+ 483.3

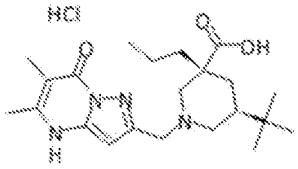
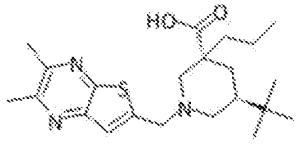
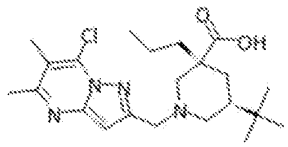
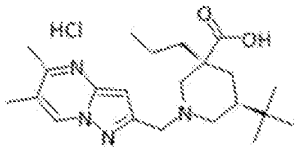
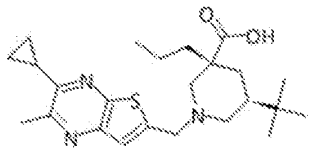
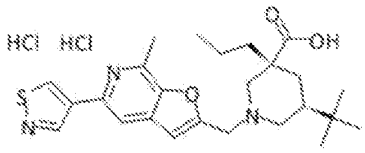
85		113	[M+H]+ 496.3
86		113	[M+H]+ 482.3
87		113	[M+H]+ 452.3
88		88	[M+H]+ 465 NMR1; 10.27 (s, 1H), 9.59 (s, 1H), 8.22 (s, 1H), 7.90 (d, J = 8.8 Hz, 1H), 7.73 (dd, J = 6.9, 0.9 Hz, 1H), 7.64 (dd, J = 8.8, 6.9 Hz, 1H), 7.44 (s, 1H), 4.79 (d, J = 14.4 Hz, 1H), 4.66 (d, J = 14.4 Hz, 1H), 3.62 (t, J = 10.1 Hz, 2H), 3.19 (s, 1H), 3.12 (s, 1H), 2.95 (s, 1H), 2.86 (s, 3H), 2.15 (d, J = 12.4 Hz, 1H), 1.64 – 1.43 (m, 2H), 0.90 (s, 9H).
89		113	NMR1; 13.12 (brs, 1H), 9.57 (brs, 1H), 9.20 (s, 1H), 8.48 (s, 1H), 8.00 - 7.98 (m, 2H), 7.64 - 7.57 (m, 3H), 7.17 (s, 1H), 4.82 - 4.67 (m, 1H), 4.64 - 4.52 (m, 1H), 3.60 - 2.96 (m, 4H), 2.90 - 2.72 (m, 1H), 2.18 - 2.10 (m, 1H), 1.61 - 1.40 (m, 2H), 0.90 (s, 9H).
90		113	[M+H]+ 452.2

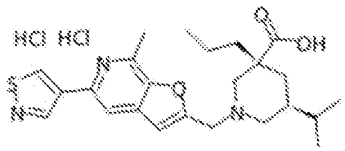
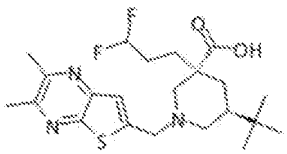
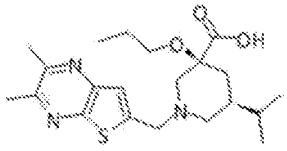
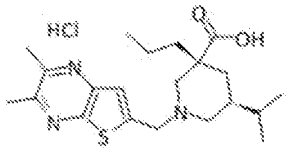
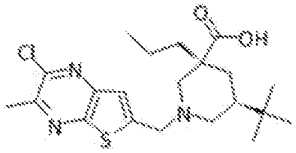
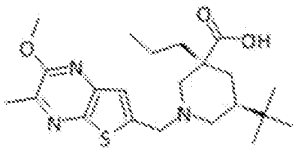
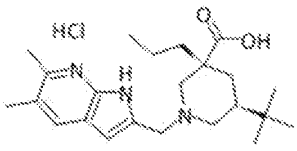
91		113	[M+H]+ 472.2
92		113	[M+H]+ 425
93		113	[M+H]+ 425
94		113	[M+H]+ 466.4
95		113	[M+H]+ 464.3
96		113	[M+H]+ 450.4
97		113	[M+H]+ 438.4

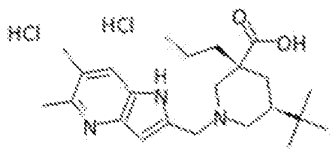
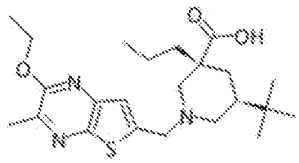
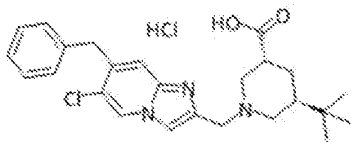
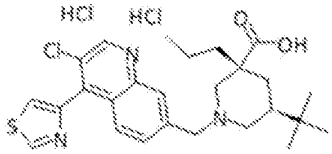
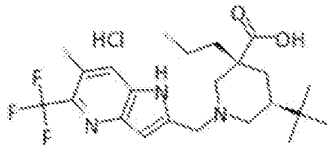
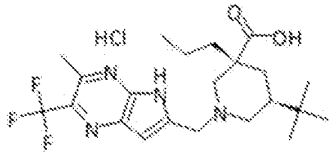
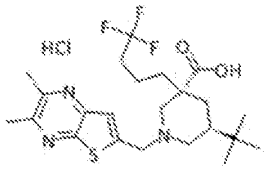
98		113	NMR1; 10.00 (s, 1H), 9.75 (s, 1H), 9.01 (s, 1H), 8.26 (d, J = 6.8 Hz, 1H), 8.09 (d, J = 8.5 Hz, 1H), 7.59 (s, 1H), 7.50 (dd, J = 8.5, 6.9 Hz, 1H), 5.12 (s, 2H), 4.81 (d, J = 14.4 Hz, 1H), 4.69 (d, J = 14.4 Hz, 1H), 3.63 (t, J = 13.9 Hz, 2H), 3.21 (s, 1H), 3.12 (s, 1H), 3.01 – 2.85 (m, 1H), 2.90 (s, 3H), 2.15 (d, J = 12.8 Hz, 1H), 1.61 (t, J = 12.5 Hz, 1H), 1.48 (td, J = 12.9, 5.0 Hz, 1H), 0.90 (s, 9H).
99		113	$[M+H]^+$ 444.3, 446.2
100		113	$[M+H]^+$ 486.4
101		113	$[M+H]^+$ 471.4
102		113	$[M+H]^+$ 463.3
103		113	$[M+H]^+$ 464.4

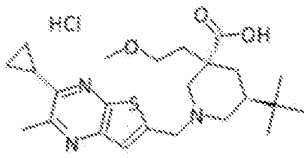
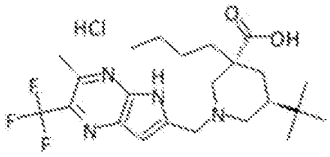
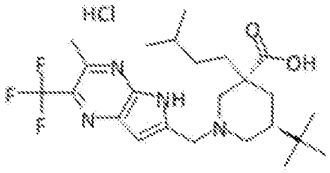
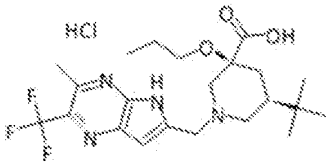
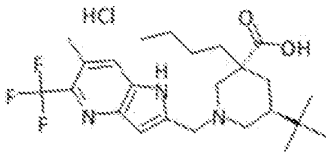
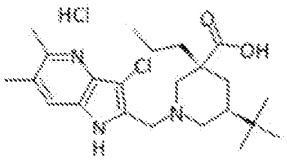
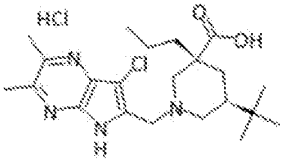
104		113	[M+H]+ 471.4
105		113	[M+H]+ 450.5
106		113	[M+H]+ 420.3
107		113	[M+H]+ 473
108		113	[M+H]+; 473.4
109		113	[M+H]+ 459.4
110		113	[M+H]+ 550.5

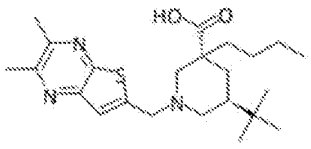
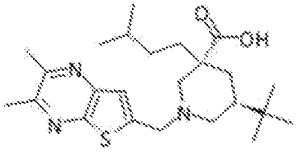
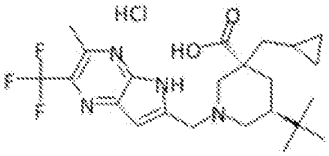
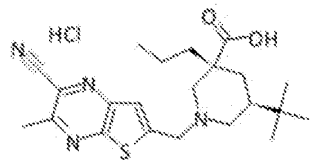
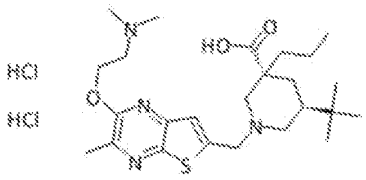
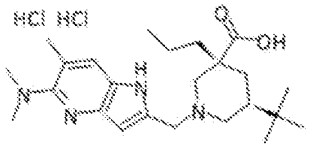
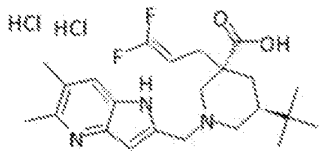
111		111	[M+H]+ 414.4 NMR1; 9.26 (s, 1H), 8.21 (s, 1H), 8.06 (d, J = 8.5 Hz, 1H), 7.89 (d, J = 8.5 Hz, 1H), 4.71 (d, J = 12.9 Hz, 1H), 4.40 (d, J = 13.4 Hz, 1H), 3.27 – 3.17 (m, 3H), 2.93 – 2.89 (m, 2H), 2.71 (s, 6H), 2.36 (s, 1H), 1.51 (t, J = 12.6 Hz, 1H), 1.46 – 1.31 (m, 3H), 1.18 (t, J = 7.1 Hz, 1H), 0.91 (s, 9H), 0.78 (t, J = 7.4 Hz, 3H).
112		113	[M+H]+ 344.4
113		113	[M+H]+ 402.5 NMR1; 12.92 (bss, 1H), 8.40 (s, 1H), 6.99 (s, 1H), 4.75 – 4.10 (m, 2H), 3.78 – 2.65 (m, 6H), 2.73 (s, 3H), 2.48 (s, 3H), 2.37 – 2.30 (m, 1H), 1.58 – 1.36 (m, 4H), 0.87 (s, 9H), 0.81 (t, J = 7.4 Hz, 3H)
114		114	[M+H]+ 419.4 NMR1; 12.50 (bss, 1H), 9.35 (s, 1H), 6.34 (s, 1H), 4.54 (d, J = 13.5 Hz, 1H), 4.30 (d, J = 13.5 Hz, 1H), 3.67 – 3.15 (m, 4H), 2.98 – 2.87 (m, 2H), 2.34 (s, 3H), 2.38 – 2.30 (m, 1H), 1.99 (s, 3H), 1.54 – 1.31 (m, 4H), 0.90 (s, 9H), 0.81 (t, J = 7.4 Hz, 3H).
115		111	[M+H]+ 392.8
116		111	[M+H]+ 406.8

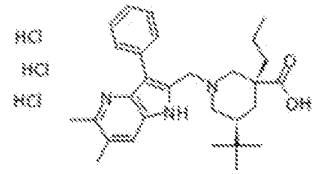
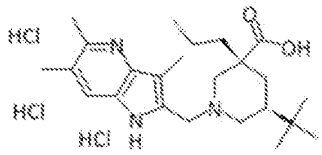
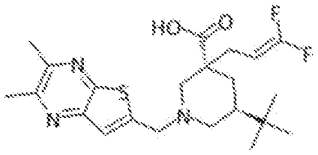
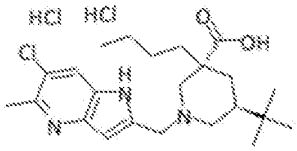
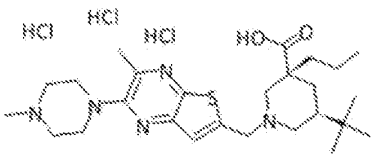
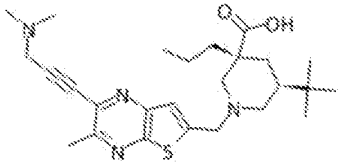
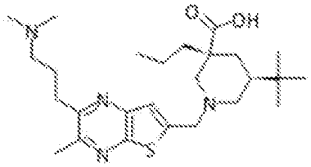
117		113	[M+H]+ 403.4
118		111	[M+H]+ 387.4
119		119	[M+H]+ 404.6 NMR2; 13.49 (brs, 1H), 7.27 (s, 1H), 4.01 (s, 2H), 3.26 – 3.19 (m, 1H), 3.19 – 3.12 (m, 1H), 2.65 (s, 3H), 2.64 (s, 3H), 2.08 – 1.87 (m, 4H), 1.71 – 1.58 (m, 1H), 1.32 – 1.12 (m, 3H), 1.06 – 0.95 (m, 1H), 0.88 (t, J = 7.0 Hz, 3H), 0.83 (s, 9H).
120		122	[M+H]+ 421.4
121		122	[M+H]+ 387.4
122		122	[M+H]+ 430.8 NMR2; 7.23 (1H, d, J=0.8 Hz), 4.06 – 3.93 (2H, m), 3.23 – 3.10 (2H, m), 2.78 (3H, s), 2.25 – 2.14 (1H, m), 2.03 (1H, d, J=11.5 Hz), 2.03 – 1.88 (3H, m), 1.70 – 1.58 (1H, m), 1.30 – 1.12 (5H, m), 1.16 – 1.05 (2H, m), 1.01 (1H, t, J=13.2 Hz), 0.88 (3H, t, J=7.0 Hz), 0.83 (9H, s)
123		122	[M+H]+ 456

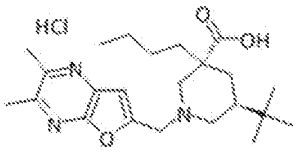
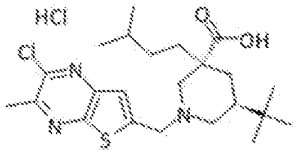
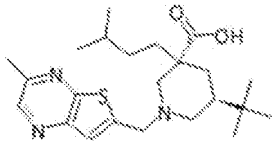
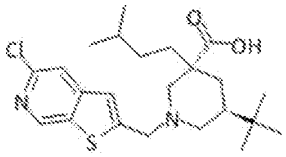
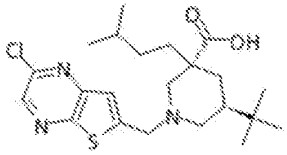
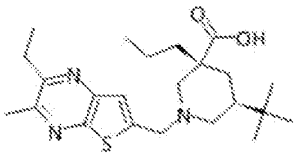
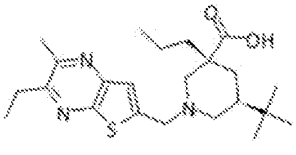
124		122	[M+H]+ 421
125		122	[M+H]+ 440.4
126		111	[M+H]+ 406.4
127		122	[M+H]+ 390.8
128		128	NMR2; 7.28 (s, 1H), 4.01 (s, 2H), 3.22 (d, J = 11.4 Hz, 1H), 3.15 (d, J = 8.5 Hz, 1H), 2.77 (s, 3H), 2.08 – 1.86 (m, 4H), 1.71 – 1.58 (m, 1H), 1.32 – 1.15 (m, 3H), 1.02 (s, J = 13.0 Hz, 1H), 0.89 (t, J = 7.0 Hz, 3H), 0.84 (s, 9H). [M+H]+ 424.4, 426.3
129		122	[M+H]+ 420.4
130		122	[M+H]+ 386.4

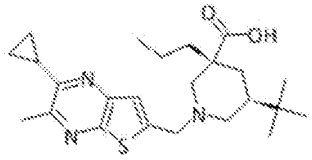
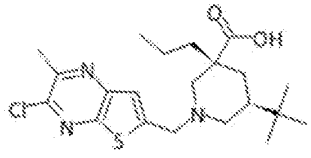
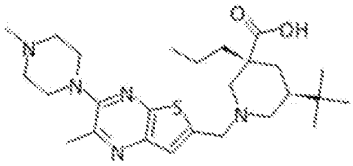
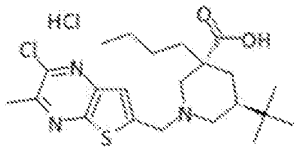
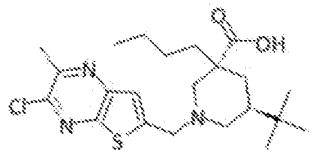
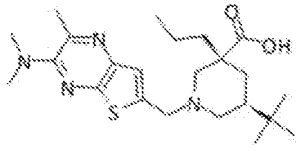
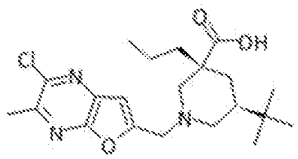
131		122	[M+H]+ 386.4
132		132	[M+H]+ 434.8
133		5	[M+H]+ 440
134		113	[M+H]+ 486.4, 488.3
135		122	[M+H]+ 440.5
136		136	[M+H]+ 441.4 NMR2; 12.73 (bss, 1H), 9.25 (bss, 1H), 7.07 (s, 1H), 4.75 – 4.56 (m, 1H), 4.54 – 4.25 (m, 1H), 3.72-2.60 (m, 3H), 2.74 (d, J = 2.1 Hz, 3H), 2.09 (d, J = 12.8 Hz, 1H), 1.57 – 1.43 (m, 2H), 1.44 – 1.32 (m, 1H), 1.29 – 1.00 (m, 4H), 0.87 (s, 9H), 0.82 (t, J = 7.2 Hz, 3H).
137		137	[M+H]+ 472.8 NMR1; 7.79 (1H, s), 4.66 (2H, d, J=61.0 Hz), 3.53 (4H, s), 2.62 (6H, s), 2.29 – 2.11 (3H, m), 1.62 – 1.46 (3H, m), 1.40 – 1.32 (2H, m), 1.27 – 1.14 (1H, m), 0.89 (9H, s)

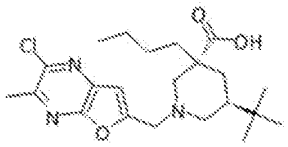
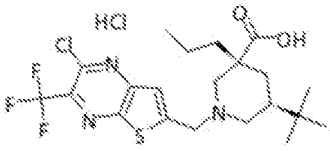
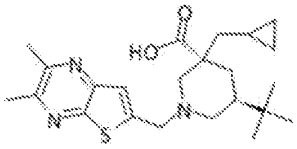
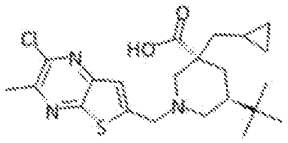
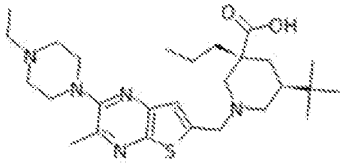
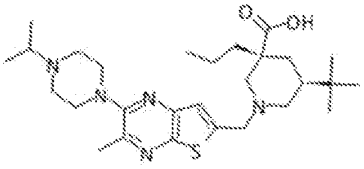
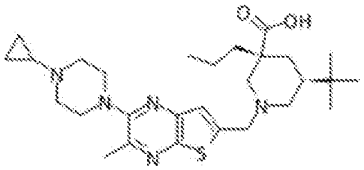
138		122	[M+H]+ 446.9
139		139	[M+H]+ 455.5 NMR1; 13.28 (brs, 1H), 12.75 (brs, 1H), 9.26 (brs, 1H), 7.08 (s, 1H), 4.86 – 4.55 (m, 1H), 4.57 – 4.25 (m, 1H), 3.86 – 3.60 (m, 2H), 2.95 - 2.69 (m, 2H), 2.74 (d, J = 1.9 Hz, 3H), 2.13 – 2.05 (m, 1H), 1.58 – 1.33 (m, 3H), 1.27 – 0.95 (m, 5H), 0.87 (s, 9H), 0.83 (t, J = 7.0 Hz, 3H).
140		122	[M+H]+ 469.4
141		122	[M+H]+ 457.4
142		122	[M+H]+ 454.4
143		182	[M+H]+ 420.4
144		166	[M+H]+ 421.3

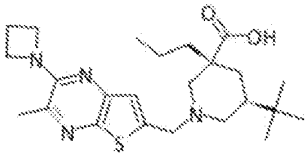
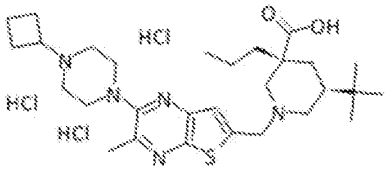
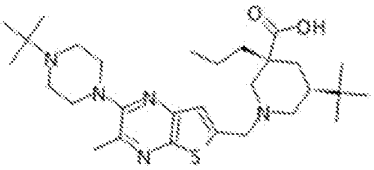
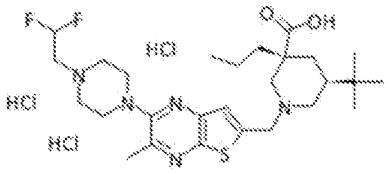
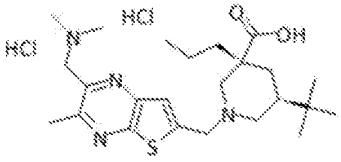
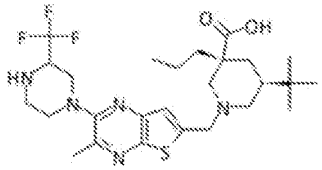
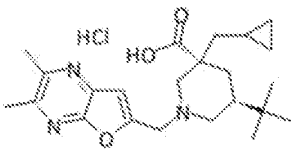
145		145	[M+H]+ 418.7 NMR2: 7.27 (1H, s), 4.04 – 3.99 (2H, m), 3.26 – 3.03 (2H, m), 2.66 (6H, d, J=1.0 Hz), 2.08 – 1.85 (4H, m), 1.64 (1H, s), 1.42 – 1.08 (5H, m), 1.01 (1H, t, J=13.1 Hz), 0.87 (3H, t, J=6.9 Hz), 0.83 (9H, s)
146		122	[M+H]+ 423.4
147		122	[M+H]+ 453.6
148		122	[M+H]+ 415
149		149	[M+H]+ 478 NMR1: 13.29 (s, 1H), 10.86 (s, 1H), 9.35 (s, 1H), 7.77 (s, 1H), 4.77 (d, J = 17.0 Hz, 3H), 4.60 – 4.56 (m, 1H), 3.48 – 3.44 (m, 4H), 2.89 – 2.83 (m, 7H), 2.58 (s, 3H), 2.15 (d, J = 13.5 Hz, 1H), 1.53 – 1.49 (m, 2H), 1.45 – 1.36 (m, 1H), 1.22 – 1.01 (m, 3H), 0.89 (s, 10H), 0.80 (t, J = 7.2 Hz, 3H).
150		122	[M+H]+ 415.5
151		122	[M+H]+ 420.4

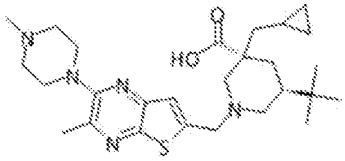
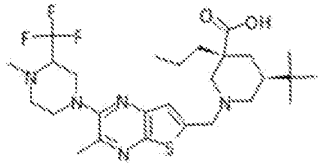
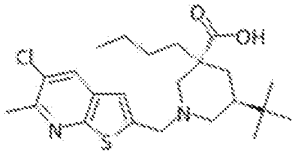
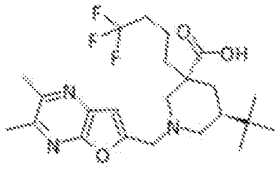
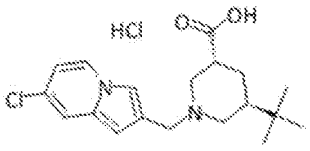
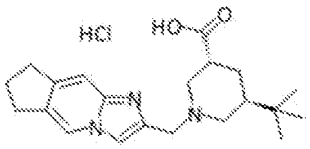
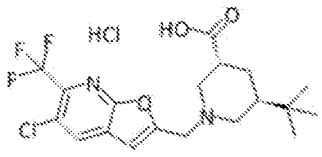
152		152	$[M+H]^+$ 462.6
153		152	$[M+H]^+$ 409.5
154		122	$[M+H]^+$ 420.5
155		122	$[M+H]^+$ 438.5
156		156	$[M+H]^+$ 488.4 NMR1; 7.78 (s, 1H), 4.78 (d, J = 13.8 Hz, 1H), 4.60 (d, J = 13.8 Hz, 1H), 3.70 (d, J = 13.1 Hz, 2H), 3.44-3.18 (m, 8H), 2.98 – 2.76 (m, 2H), 2.82 (d, J = 4.5 Hz, 3H), 2.63 (s, 3H), 2.15 (d, J = 12.5 Hz, 1H), 1.70 – 1.32 (m, 3H), 1.28 – 1.00 (m, 3H), 0.89 (s, 9H), 0.80 (t, J = 7.1 Hz, 3H).
157		122	$[M+H]^+$ 471.4
158		122	$[M+H]^+$ 475.3

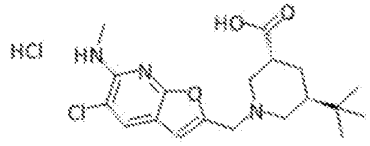
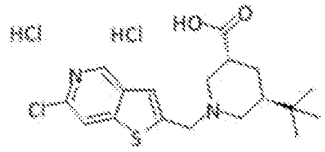
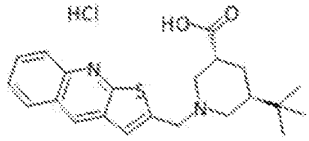
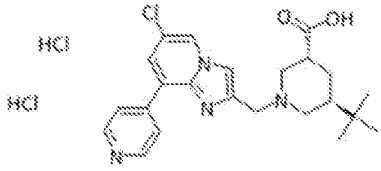
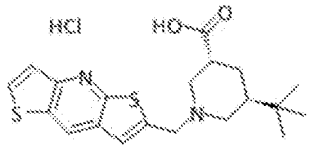
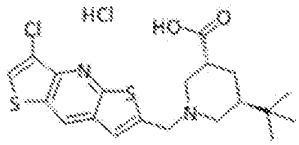
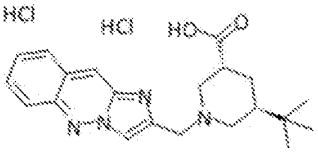
159		122	[M+H]+ 402.3
160		160	[M+H]+ 452.3 NMR1; 7.86 (s, 1H), 4.80 (s,1H), 4.64 (s, 1H), 3.65 – 3.46 (m, 2H), 3.04 – 2.68 (m, 2H), 2.72 (s, 3H), 2.14 (d, J = 12.4 Hz, 1H), 1.61 – 1.32 (m, 4H), 1.32 – 1.10 (m, 1H), 1.07 – 0.94 (m, 2H), 0.89 (s, 9H), 0.80 (dd, J = 1.5, 6.6 Hz, 6H).
161		122	[M+H]+ 418.3
162		122	[M+H]+ 437.3
163		122	[M+H]+ 438.3
164		122	[M+H]+ 418.3
165		122	[M+H]+ 418.4

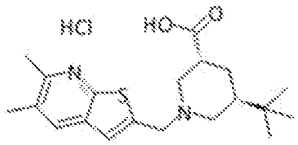
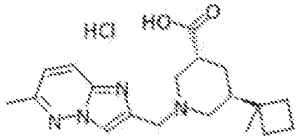
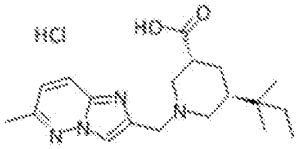
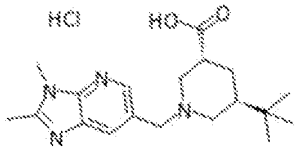
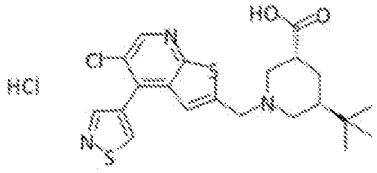
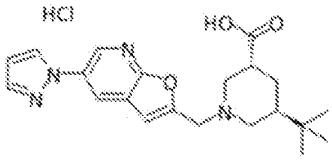
166		166	[M+H]+ 430.4
167		122	[M+H]+ 424.3
168		156	[M+H]+ 488.4
169		122	[M+H]+ 438.3
170		122	[M+H]+ 438.3
171		156	[M+H]+ 433.4
172		122	[M+H]+ 408.3

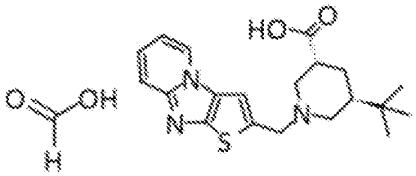
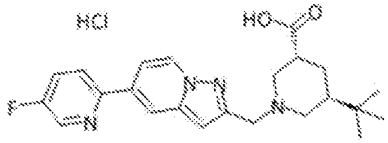
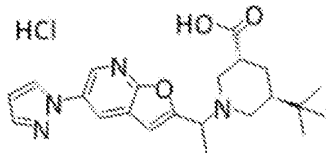
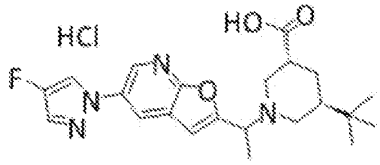
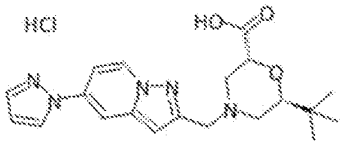
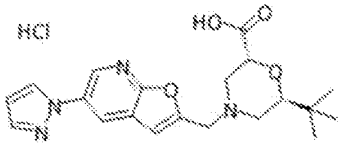
173		122	[M+H]+ 422.4
174		174	[M+H]+ 478.3 NMR3; 7.76 (s, 1H), 4.60-4.52 (m, 1H), 4.48 - 4.38 (m, 1H), 3.60 - 3.53 (m, 1H), 3.50 - 3.42 (m, 1H), 2.64 - 2.45 (m, 2H), 2.34 - 2.26 (m, 1H), 1.70 - 1.55 (m, 2H), 1.52 - 1.41 (m, 1H), 1.30 - 1.13 (m, 3H), 0.95 (s, 9H), 0.87 (t, J = 7.2 Hz, 3H).
175		122	[M+H]+ 416.4
176		122	[M+H]+ 436.3
177		156	[M+H]+ 501.7
178		156	[M+H]+ 516.6
179		184	[M+H]+ 514.4

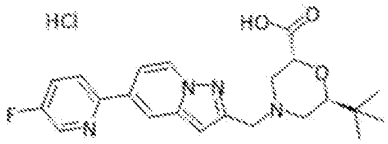
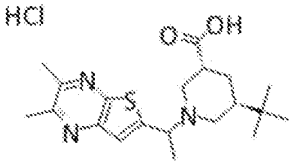
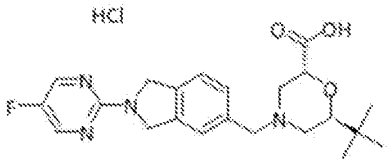
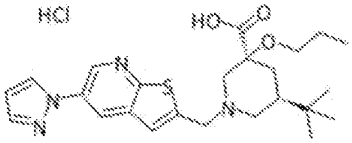
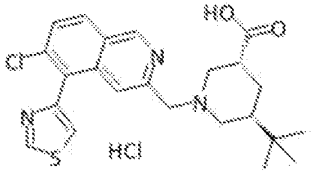
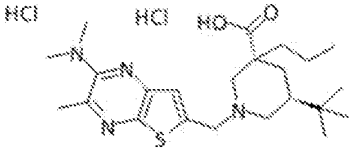
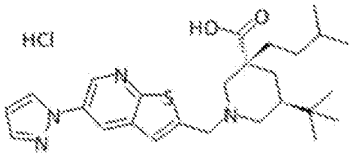
180		156	$[M+H]^+$ 445.3
181		184	$[M+H]^+$ 528.5
182		156	$[M+H]^+$ 530.3
183		184	$[M+H]^+$ 538.4
184		184	$[M+H]^+$ 447.4
185		156	$[M+H]^+$ 542.4 Epimer mixture
186		122	$[M+H]^+$ 400.3

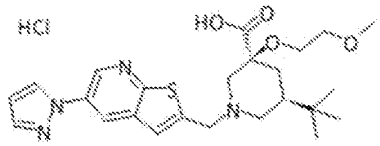
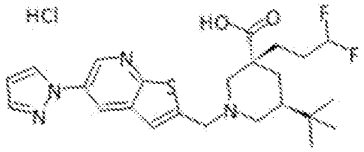
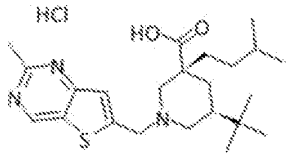
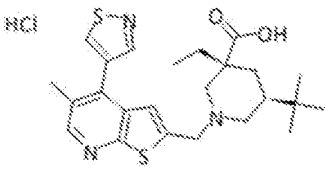
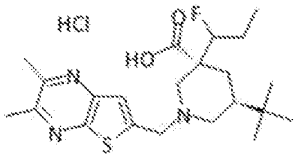
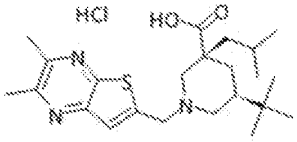
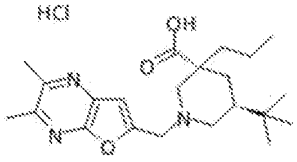
187		156	$[M+H]^+$ 500.6
188		188	$[M+H]^+$ 556.4 Epimer mixture
189		122	$[M+H]^+$ 437.5
190		190	$[M+H]^+$ 456.3 NMR2; 6.84 (s, 1H), 4.00 (d, J = 14.9 Hz, 1H), 3.95 (d, J = 14.9 Hz, 1H), 3.22 (d, J = 11.4 Hz, 1H), 3.19 – 3.10 (m, 1H), 2.65 (s, 3H), 2.63 (s, 3H), 2.21 – 1.86 (m, 6H), 1.77 – 1.62 (m, 1H), 1.62 – 1.42 (m, 2H), 1.36 – 1.20 (m, 1H), 0.98 (t, J = 13.2 Hz, 1H), 0.84 (s, 9H).
191		5	$[M+H]^+$ 439
192		5	$[M+H]^+$ 356
193		5	$[M-H]^-$ 417

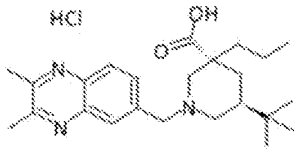
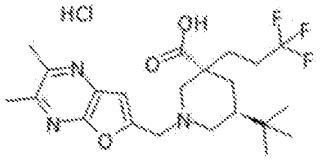
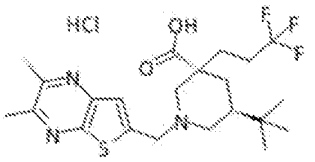
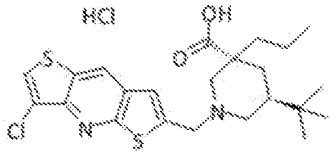
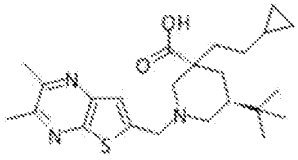
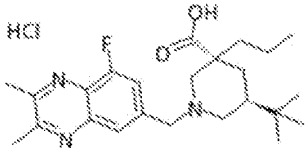
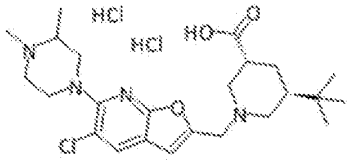
194		5	$[M-H]^-$ 378
195		113	$[M+H]^+$ 367
196		5	$[M+H]^+$ 383
197		5	$[M+H]^+$ 427
198		5	$[M+H]^+$ 389
199		113	$[M+H]^+$ 423
200		200	NMR1; 9.52 (s, 1H), 9.00 (s, 1H), 8.87 (s, 1H), 8.04 (d, J = 8.7 Hz, 1H), 7.91 (d, J = 9.1 Hz, 1H), 7.74 (ddd, J = 9.1, 6.5, 1.3 Hz, 1H), 7.48 (dd, J = 8.7, 6.4 Hz, 1H), 4.75 (d, J = 13.7 Hz, 1H), 4.56 (d, J = 13.7 Hz, 1H), 3.71 (d, J = 12.4 Hz, 1H), 3.63 (d, J = 11.6 Hz, 1H), 3.15 (d, J = 11.7 Hz, 1H), 3.09 (s, 1H), 2.95 (t, J = 11.8 Hz, 1H), 2.14 (d, J = 13.0 Hz, 1H), 1.60 (t, J = 12.4 Hz, 1H), 1.45 (td, J = 13.0, 5.1 Hz, 1H), 0.89 (s, 9H).

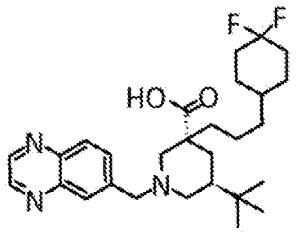
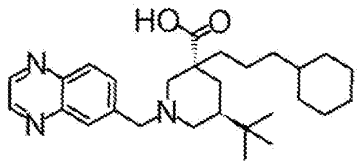
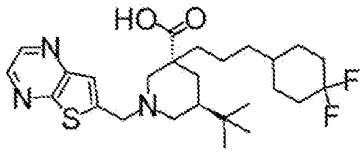
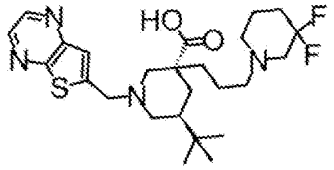
201		113	$[M+H]^+$ 361
202		113	$[M+H]^+$ 343
203		113	$[M+H]^+$ 345
204		113	$[M+H]^+$ 345
205		113	$[M+H]^+$ 451
206		206	NMR1: 9.53 (s, 1H), 8.90 (d, *J* = 2.5 Hz, 1H), 8.65 (d, *J* = 2.6 Hz, 1H), 8.59 (d, *J* = 2.5 Hz, 1H), 7.83 (d, *J* = 1.8 Hz, 1H), 7.40 (s, 1H), 6.65 ~ 6.59 (m, 1H), 4.71 (d, *J* = 14.3 Hz, 1H), 4.59 (d, *J* = 14.3 Hz, 1H), 3.56 (d, *J* = 11.5 Hz, 2H), 3.18 (s, 1H), 3.12 (s, 1H), 2.91 (s, 1H), 2.14 (d, *J* = 12.3 Hz, 1H), 1.61 ~ 1.42 (m, 2H), 0.88 (s, 9H).

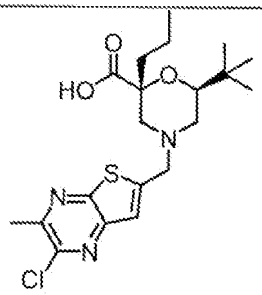
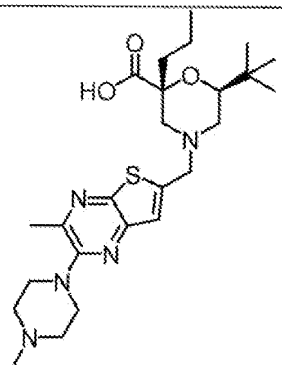
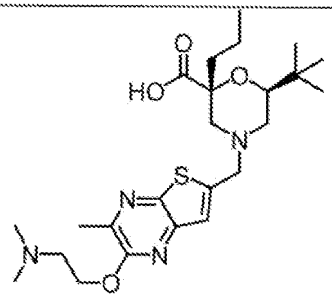
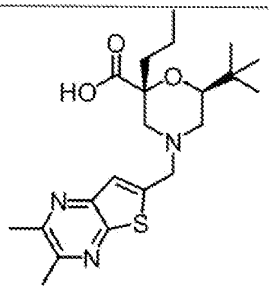
207		113	[M+H]+ 372 NMR1: 12.27 (s, 1 H), 8.83 (d, J = 6.8 Hz, 1 H), 7.68 (d, J = 9.1 Hz, 1 H), 7.57 (s, 1 H), 7.41-7.36 (m, 1 H), 7.00-7.01 (m, 1 H), 3.84 (dd, J = 15.0, 36.9 Hz, 2 H), 3.04 (d, J = 10.1 Hz, 1 H), 2.69-2.66 (m, 1 H), 2.17-2.08 (m, 2 H), 1.84 (dd, J = 10.9, 10.9 Hz, 1 H), 1.68-1.58 (m, 1 H), 1.19-1.09 (m, 1 H), 0.88 (s, 9 H).
208		113	[M+H]+ 411
209		5	[M+H]+ 397.3 Single isomer
210		5	[M+H]+ 415.3 Single isomer Column: Lux iA3 (21.2 mm x 250 mm, 5 μm) Solvent: isocratic 25% EtOH (0.2% MH3), Isomer 2
211		113	[M+H]+ 384
212		113	[M+H]+ 385

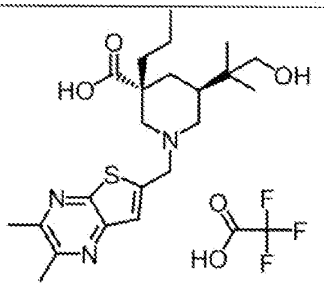
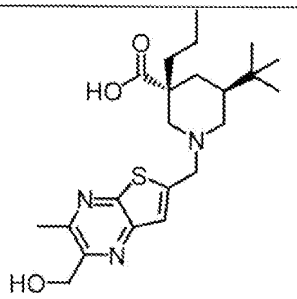
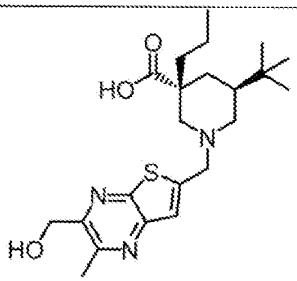
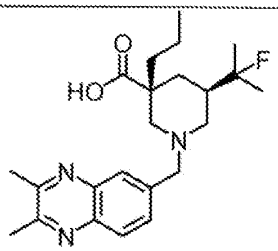
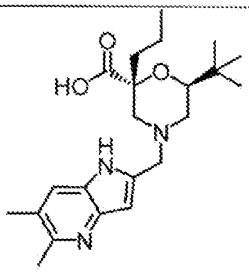
213		113	$[M+H]^+$ 413
214		113	$[M+H]^+$ 376 Single isomer
215		113	$[M+H]^+$ 415
216		111	$[M+H]^+$ 457.1
217		200	$[M+H]^+$ 444
218		111	$[M+H]^+$ 433
219		113	$[M+H]^+$ 469.4

220		113	$[M+H]^+$ 473.4
221		113	$[M+H]^+$ 477.2
222		222	NMR1; 12.11 (s, 1H), 9.24 (s, 1H), 7.38 (s, 1H), 3.87 (q, J = 15.3 Hz, 2H), 3.25 (d, J = 11.0 Hz, 1H), 2.92 (d, J = 10.4 Hz, 1H), 2.68 (s, 3H), 2.17 (d, J = 12.5 Hz, 1H), 1.84 – 1.71 (m, 2H), 1.57 (d, J = 12.1 Hz, 1H), 1.43 – 1.35 (m, 2H), 1.36 – 1.12 (m, 2H), 0.98 (s, 1H), 0.81 (d, J = 5.3 Hz, 15H), 0.70 (t, J = 12.7 Hz, 1H).
223		152	$[M+H]^+$ 458.2
224		152	$[M+H]^+$ 422.3 Single isomer
225		113	$[M+H]^+$ 418
226		113	$[M+H]^+$ 388

227		113	[M+H]+ 398.3
228		113	[M+H]+ 442.8
229		113	[M+H]+ 459.0
230		113	[M+H]+ 466.0
231		111	[M+H]+ 430
232		113	[M+H]+ 416.6
233		113	[M+H]+ 463.5 Epimer mixture

234		234	[M+H]+ 488
235		152	[M+H]+ 452.4 NMR3: 8.96 (d, J = 1.1 Hz, 2H), 8.33 (s, 1H), 8.23 (d, J = 8.7 Hz, 1H), 8.00 (dd, J = 8.7, 1.9 Hz, 1H), 4.79-4.67 (m, 1H), 4.43 (d, J = 14.1 Hz, 1H), 3.68 (d, J = 11.6 Hz, 1H), 3.53-3.38 (m, 1H), 2.95 (t, J= 12.5 Hz, 1H), 2.76 (d, J= 11.7 Hz, 1H), 2.26 (d, J = 13.2 Hz, 1H), 1.75-1.48 (m, 8H), 1.44-1.28 (m, 2H), 1.24-1.00 (m, 7H), 0.97 (d, J= 1.4 Hz, 9H), 0.70 (d, J = 12.0 Hz, 2H).
236		234	[M+H]+ 494 NMR1: 8.66 (d, J = 3.0 Hz, 1H), 8.50 (d, J = 3.1 Hz, 1H), 7.54 (s, 1H), 3.80 (s, 2H), 3.40 (d, J = 10.4 Hz, 1H), 2.88 (d, J = 9.6 Hz, 1H), 2.27 (d, J = 12.0 Hz, 1H), 1.95 (s, 2H), 1.79 (s, 1H), 1.75-1.62 (m, 5H), 1.59 (d, J = 11.8 Hz, 1H), 1.29 (s, 3H), 1.23-1.15 (m, 1H), 1.08 (s, 5H), 0.88-0.75 (m, 9H), 0.66-0.41 (m, 1H).
237		152	[M+H]+ 495.2 NMR3: 8.75 (s, 1H), 8.62 (d, J = 2.3 Hz, 1H), 7.89 (s, 1H), 4.78 (d, J = 14.3 Hz, 2H), 3.80 (s, 1H), 3.69 (s, 2H), 3.52 (s, 1H), 3.47-3.34 (m, 1H), 3.22-2.93 (m, 4H), 2.31 (d, J = 12.9 Hz, 1H), 2.24 (s, 1H), 2.16-1.83 (m, 4H), 1.82-1.55 (m, 5H), 1.48 (t, J = 13.0 Hz, 1H), 0.98 (s, 9H).

238		122	$[M+H]^+$ 426.3
239		156	$[M+H]^+$ 490.4
240		122	$[M+H]^+$ 406.3
241		122	$[M+H]^+$ 479.3

242	 and its enantiomer	242	$[M+H]^+$ 420.3 Racemate
243		242	$[M+H]^+$ 420.4
244		242	$[M+H]^+$ 420.3
245		245	$[M+H]^+$ 402.6
246		122	$[M+H]^+$ 388.3

[0409] Biological Activity

Test Example 1: TRF homogeneous proximity assay

In order to screen for sortilin binding compounds with the ability to disrupt PGRN sortilin interaction an in vitro time resolved fluorescence (TRF) assay was employed. One way in which a TRF signal can be achieved at ex 337 em 490, 520 nm is when a terbium labelled TRF donor is held in close proximity to a fluorescein labelled acceptor. The combination of a terbium labelled anti-His antibody (Life Technologies), c-terminally 6xHis tagged sortilin protein and fluorescein labelled peptide substrate for sortilin generates a robust TRF signal which can be decreased in response to compounds which displace substrate binding. The bioassay established for compound screening utilizes a custom fluorescein labelled neurotensin peptide (5-fam-RQLYENKPRRPYIL) synthesized and labelled by Peptide Synthetics, which had an approximate Kd of 100 nM for the 6xHis tagged sortilin used in the assay. Assays were run in 16 μl volumes in Corning 384 well assay plates (Cat ID 4514) or Falcon(R) 96-well Clear Flat Bottom TC-treated Culture Microplate (Falcon, #353072). Compounds were prepared over a ten-point dilution curve in a final concentration of 50 mM Hepes pH7.5, 100 mM NaCl, 0.01% Triton x-100, 2.5% DMSO, 0.5 nM His-tagged sortilin, 100 nM peptide, 0.33 nM Tb ant-His antibody.
The prepared plates were incubated at room temperature for 2 hours on a shaking platform, before reading on the Pherastar FS (Integration start: 60 ms, integration time: 400 ms, 40 flashes with laser).
Table 4 below presents the results of the assay. Where the indicated example number encompasses a plurality of stereoisomers, unless explicitly stated, the assay result shown may be that for a mixture of isomers or for an individual isomer, which may be the most active individual isomer. Each result shown in Table 4 may be an average value from several assays.

[0410]

[Table 4]

Table 4 -- TRF assay results					
EX	TRF assay (IC_{50}/μM)	EX	TRF assay (IC_{50}/μM)	EX	TRF assay (IC_{50}/μM)
1	0.11	2	0.0181	3	0.00975
4	0.31	5	0.012	6	0.0343
7	0.01	8	0.0089	9	0.014
10	0.021	11	0.046	12	0.0858
13	0.0038	14	0.04	15	0.09
16	0.2	17	0.036	18	0.11
19	0.0041	20	0.046	21	0.033
22	0.0092	23	0.037	24	0.0275
25	0.012	26	0.0086	27	0.012
28	0.0077	29	0.037	30	0.004
31	0.02	32	0.025	33	0.02
34	0.0214	35	0.012	36	0.004
37	0.0105	38	0.017	39	0.03
40	0.019	41	0.025	42	0.025
43	0.029	44	0.021	45	0.011
46	0.022	47	0.023	48	0.019
49	0.049	50	0.034	51	0.021
52	0.016	53	0.011	54	0.011
55	0.016	56	0.044	57	0.016
58	0.043	59	0.092	60	0.015
61	0.016	62	0.0056	63	0.011
64	0.012	65	0.016	66	0.031
67	0.037	68	0.047	69	0.046
70	0.02	71	0.034	72	0.052
73	0.017	74	0.031	75	0.016
76	0.026	77	0.053	78	0.036
79	0.021	80	0.02	81	0.0034
82	0.094	83	0.024	84	0.0013
85	0.0057	86	0.0058	87	0.0035
88	0.0091	89	0.022	90	0.0056
91	0.0053	92	0.013	93	0.017
94	0.0045	95	0.0037	96	0.0016

Table 4 – TRF assay results

EX	TRF assay (IC_{50}/μM)	EX	TRF assay (IC_{50}/μM)	EX	TRF assay (IC_{50}/μM)
97	0.012	98	0.013	99	0.0083
100	0.0025	101	0.003	102	0.0054
103	0.0029	104	0.0033	105	0.0071
106	0.0049	107	0.0034	108	0.0034
109	0.0056	110	0.003	111	0.015
112	0.0096	113	0.0039	114	0.003
115	0.035	116	0.012	117	0.001
118	0.003	119	0.0031	120	0.004
121	0.0067	122	0.0024	123	0.0026
124	0.01	125	0.0036	126	0.018
127	0.013	128	0.0043	129	0.0062
130	0.01	131	0.003	132	0.0088
133	0.011	134	0.0037	135	0.0072
136	0.0024	137	0.0042	138	0.0074
139	0.003	140	0.0028	141	0.0045
142	0.0047	143	0.008	144	0.003
145	0.0027	146	0.003	147	0.0022
148	0.015	149	0.00324	150	0.0086
151	0.0058	152	0.0028	153	0.0047
154	0.0063	155	0.003	156	0.0039
157	0.0038	158	0.0051	159	0.0021
160	0.001	161	0.0033	162	0.0056
163	0.0027	164	0.0058	165	0.0018
166	0.0052	167	0.003	168	0.0028
169	0.0018	170	0.0013	171	0.0031
172	0.0069	173	0.0029	174	0.009
175	0.0019	176	0.0024	177	0.0033
178	0.0036	179	0.0057	180	0.0046
181	0.0027	182	0.0048	183	0.0053
184	0.0063	185	0.0059	186	0.0071
187	0.0026	188	0.0069	189	0.0031
190	0.0093	191	0.18	192	0.056
193	0.049	194	0.023	195	0.11

Table 4 – TRF assay results					
EX	TRF assay (IC_{50}/μM)	EX	TRF assay (IC_{50}/μM)	EX	TRF assay (IC_{50}/μM)
196	0.017	197	0.018	198	0.022
199	0.01	200	0.0044	201	0.04
202	0.052	203	0.074	204	0.04
205	0.003	206	0.0175	207	0.021
208	0.017	209	0.025	210	0.015
211	0.044	212	0.29	213	0.078
214	0.018	215	0.0226	216	0.0046
217	0.0089	218	0.00454	219	0.003
220	0.034	221	0.008	222	0.0046
223	0.003	224	0.003	225	0.0023
226	0.0094	227	0.009	228	0.0057
229	0.003	230	0.003	231	0.001
232	0.02	233	0.056	234	0.0036
235	0.005	236	0.003	237	0.1

Table 4 - TRF assay results					
EX	TRF assay (IC_{50}/μM)	EX	TRF assay (IC_{50}/μM)	EX	TRF assay (IC_{50}/μM)
238	0.034	239	0.014	240	0.013
241	0.0096	245	0.174	246	0.0081

[0411] Test Example 2: Cell based progranulin modulation assay

Inhibition of PGRN-sortilin binding has been demonstrated to elevate endogenous extracellular PGRN levels. A human ELISA kit from Adipogen (# AG-45A-0018YEK-KI01) was employed to measure changes in extracellular PGRN from U251-MG cells following compound treatment for 72 hours.

Cells were cultured in RPMI 1640 (Life Technologies # 11875119), 10% FBS, Penicillin-Streptomycin at 37°C, 5% CO_2.

In 96 well plates, U251-MG cells were seeded at a density of 6.7 x 10^4 cells/well. 24 hours later the medium was changed to 100 μl of serum free Opti-MEM 1 Reduced Serum Medium (Life Technologies # 31985070) and test compounds, or controls, were added at 0.1% final DMSO concentration. The plates were then incubated at 37°C, 5% CO_2 for 72 hours before removing supernatants for analysis using an Adipogen human PGRN ELISA kit (# AG-45A-0018YEK-KI01) for evaluation of PGRN concentrations according to manufacturer protocols.

EC_{150} values were subsequently determined as the concentration providing as a 50% increase in extracellular PGRN levels relative to the DMSO control.

Table 5 below presents the results of the assay for those compounds demonstrating an EC_{150} of 1 μM or lower. Where the indicated example number encompasses a plurality of stereoisomers, unless explicitly stated, the assay result shown may be that for a mixture of isomers or for an individual isomer, which may be the most active individual isomer.

[0412]

[Table 5]

Table 5 – Cell based PGRN assay results					
EX	PGRN Modulation (EC_{150}/μM)	EX	PGRN Modulation (EC_{150}/μM)	EX	PGRN Modulation (EC_{150}/μM)
2	1.5	3	0.55	5	0.21
6	1.2	7	0.31	8	2.6
9	4.3	10	3.5	11	4.1
12	0.93	13	0.43	14	3.4
17	2.3	19	0.087	20	0.88
21	1.4	22	0.57	23	8
24	1	25	0.31	26	0.28
27	0.89	28	0.3	29	0.19
30	0.25	31	0.47	32	0.3
33	0.37	34	0.062	35	1.1
36	0.075	37	0.78	38	0.21
39	0.23	40	0.27	41	1.1
42	0.69	43	0.27	44	0.3
45	0.46	46	2.6	47	0.33
48	0.2	49	0.28	50	0.16
51	0.17	52	0.22	53	0.25
54	0.3	55	1.6	56	0.32
57	0.49	58	0.3	59	0.31
60	0.28	61	0.28	62	0.19
63	0.18	64	0.056	65	0.075
66	0.16	67	0.069	68	0.16
69	0.18	70	0.072	71	0.077
72	0.2	73	0.077	74	0.077
75	0.084	76	0.15	77	0.3
78	0.075	79	0.22	80	0.18
81	0.033	82	0.28	83	0.083
84	0.018	85	0.04	86	0.14
87	0.12	88	0.32	89	0.24
90	0.24	91	0.32	92	1.2

Table 5 – Cell based PGRN assay results

EX	PGRN Modulation (EC_{150}/μM)	EX	PGRN Modulation (EC_{150}/μM)	EX	PGRN Modulation (EC_{150}/μM)
93	1.3	94	0.25	95	0.2
96	0.061	97	0.5	98	0.32
99	0.5	100	0.2	101	0.23
102	0.26	103	0.2	104	0.25
105	0.23	107	0.2	108	0.21
109	0.28	110	0.14	111	0.79
112	0.11	113	0.02	114	0.014
117	0.013	118	0.16	119	0.1
120	0.32	121	0.25	122	0.13
123	0.24	124	1.1	127	0.64
128	0.065	129	0.24	130	0.32
131	0.02	133	0.45	134	0.24
135	0.34	136	0.2	137	0.28
139	0.2	140	0.046	141	0.28
142	0.12	143	0.11	144	0.13
145	0.053	146	0.048	147	0.12
149	0.015	150	0.014	151	0.015
152	0.055	153	0.057	154	0.15
155	0.067	156	0.014	157	0.11
159	0.19	160	0.029	161	0.19
163	0.91	165	0.2	167	0.26
168	0.098	169	0.076	170	0.16
171	0.32	173	0.27	175	0.068
176	0.29	177	0.015	178	0.025
179	0.28	180	0.64	181	0.074
182	0.055	183	0.28	184	0.17
185	0.17	187	0.014	188	0.31
200	0.12	205	0.19	206	3.8
208	6.1	209	4	210	7.2
211	0.014	214	0.78	216	0.3

Table 5 – Cell based PGRN assay results					
EX	PGRN Modulation (EC_{150}/μM)	EX	PGRN Modulation (EC_{150}/μM)	EX	PGRN Modulation (EC_{150}/μM)
218	0.88	219	0.29	222	0.29

[0413] Test Example 3: Pharmacodynamics

Male Rats (Crl:CD(SD), The Jackson Laboratory Japan, eight weeks old) were orally administered with test compounds in 5% gum arabic (AG) in water or 1% hydroxypropyl methylcellulose (HPMC) in water as vehicle. Rats administered with vehicle only were used as a negative control. In each study, one control group and one or more test compound administered group(s) were prepared, but each group was only administered with one test compound at one concentration.

After several hours of administration, plasma, cerebrospinal fluid (CSF) and brains were collected. Intervals between administration and sampling range from 2 to 6 hours. Rats were anesthetized with isoflurane before and during sampling. CSF was collected from cisterna magna and centrifuged in Protein LoBind Tubes (Eppendorf) at 2290 rpm (Model 6200, KUBOTA Corporation) 4°C for 20 minutes to remove any impurity. Blood was then collected from inferior vena cava into EDTA coated tubes and centrifuged at 3000 rpm (Model 6200, KUBOTA Corporation) 4°C for 10 minutes to get plasma. Brains were collected after sacrifice and the front third of the right side of a brain was separated and homogenized together with saline 3 times the weight of brain tissue.

Test compound concentration in plasma, brain and CSF samples prepared following the description above were measured by liquid chromatograph-tandem mass spectrometer (LC-MS/MS). The mass spectrometer was operated in positive ion mode of the electrospray ionization (ESI) method. Unchanged substances and the internal standard (IS) were detected by selected reaction monitoring (SRM) transitions using selected precursor and product ions set. Samples from rats administered with compounds were tested.

Progranulin (PGRN) concentrations in the CSF of all rats were measured by ELISA (AG-45A-0043YEK-KI01, AdipoGen Life Sciences) following the protocol described above in PGRN modulation assay. Average PGRN concentrations in test compound administered groups and control groups were calculated separately. In each study, PGRN concentration in control group were assigned a relative value of 1. Statistical significance was calculated by t-test or Dunnett's test in accordance with the number of groups in one study. *$p<0.05$, **$p<0.01$

Example compounds demonstrated acceptable brain penetration and effects to increase PGRN level in CSF compared to control group.

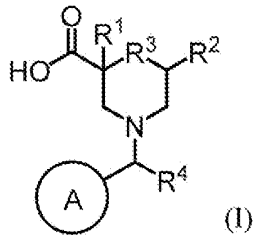
Industrial Applicability

[0414] A compound of formula (I), or a salt thereof, may have sortilin-binding inhibitory activity and is expected to be useful for treating, preventing, and/or diagnosing diseases or disorders associated with sortilin ligands.

Claims

[Claim 1] A compound of formula (I):

[Chem.1]



(I)

wherein:

R^1 is

1) H,

2) R^{11} optionally substituted with one or more R^{12}, or

3) -O-R^{11} optionally substituted with one or more R^{12},

R^{11} is C_{1-6} alkyl or C_{2-6} alkenyl,

R^{12} is each independently halogen, C_{1-6} alkyl-O-, C_{3-8} cycloalkyl, or saturated 3- to 8-membered monocyclic heterocyclyl comprising at least one heteroatom independently selected from the group consisting of nitrogen, oxygen, and sulfur, wherein R^{12} is optionally substituted with the same or different one or more halogen;

R^2 is

1) C_{1-6} alkyl optionally substituted with the same or different one or more halogen, hydroxy, or cyano,

2) C_{3-8} cycloalkyl optionally substituted with the same or different one or more C_{1-6} alkyl, halogen, or cyano, or

3) $Si(C_{1-6}\text{ alkyl})_3$;

R^3 is CH_2 or O;

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

Ring A is optionally substituted partially unsaturated or unsaturated 7- to 15-membered bicyclic or tricyclic heterocyclyl comprising at least one heteroatom independently selected from the group consisting of nitrogen, oxygen, and sulfur;

or a salt thereof.

[Claim 2] The compound according to claim 1, or a salt thereof, wherein R^2 is

1) C_{2-6} alkyl optionally substituted with the same or different one or more halogen, hydroxy or cyano, or

2) C_{3-8} cycloalkyl optionally substituted with the same or different one

or more C_{1-6} alkyl;
provided that the compound is not
5-(1,1-dimethylethyl)-1-(pyrazolo[1,5-a]pyridin-4-ylmethyl)-3-piperidinecarboxylic acid,
5-(1,1-dimethylethyl)-1-(imidazo[2,1-b]thiazol-6-ylmethyl)-3-piperidinecarboxylic acid,
5-(1,1-dimethylethyl)-1-(imidazo[1,2-a]pyridin-5-ylmethyl)-3-piperidinecarboxylic acid,
5-(1,1-dimethylethyl)-1-(imidazo[1,2-a]pyridin-3-ylmethyl)-3-piperidinecarboxylic acid,
5-(1,1-dimethylethyl)-1-(imidazo[2,1-b]thiazol-2-ylmethyl)-3-piperidinecarboxylic acid,
5-(1,1-dimethylethyl)-1-(imidazo[2,1-b]thiazol-6-ylmethyl)-3-piperidinecarboxylic acid,
5-(1,1-dimethylethyl)-1-(pyrazolo[1,5-a]pyridin-4-ylmethyl)-3-piperidinecarboxylic acid, or
1-[(7,8-dihydro-5H-pyrano[4,3-b]pyridin-3-yl)methyl]-5-(1,1-dimethylethyl)-3-piperidinecarboxylic acid.

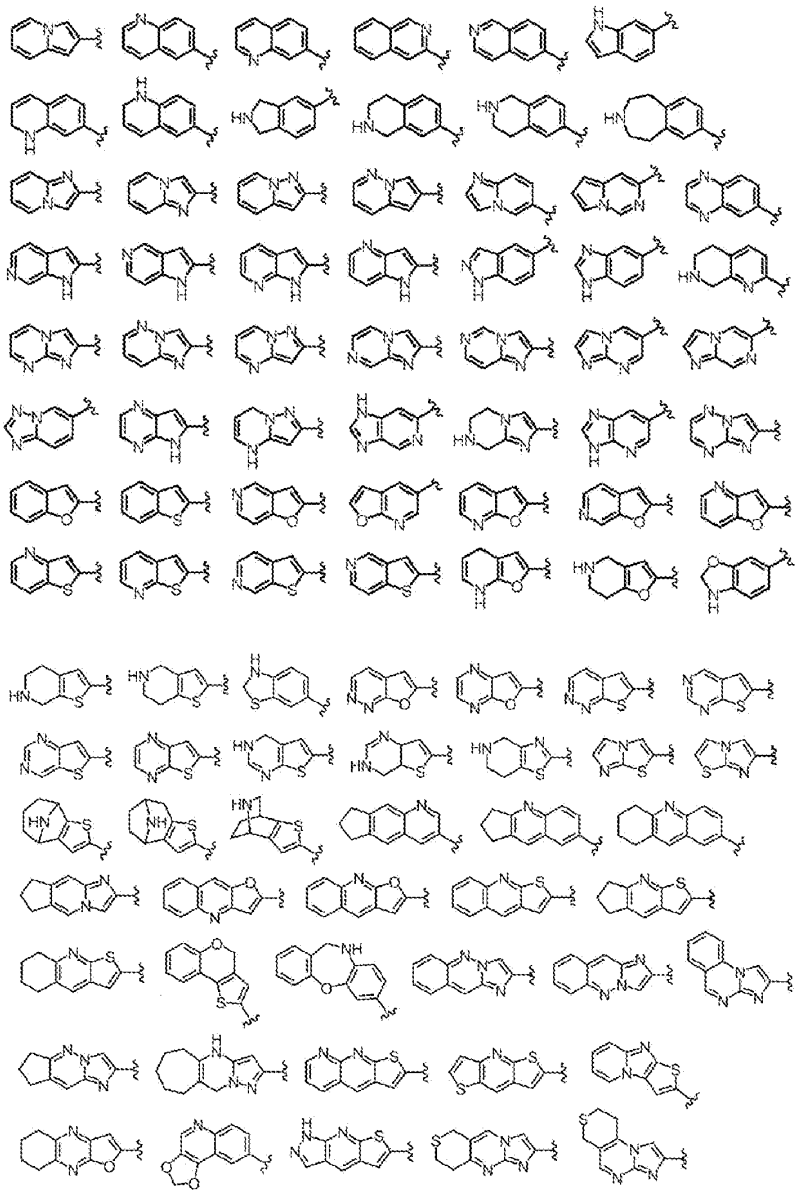
[Claim 3] The compound according to claim 1 or 2, or a salt thereof, wherein
Ring A is optionally substituted with one or more R^5;
R^5 is each independently selected from the group consisting of:
1) halogen,
2) cyano,
3) oxo,
4) C_{1-6} alkyl,
5) C_{2-6} alkynyl,
6) C_{3-8} cycloalkyl,
7) C_{3-8} cycloalkenyl,
8) C_{6-10} aryl,
9) 4- to 10-membered monocyclic or bicyclic heterocyclyl,
10) -O-R^{5a}, and
11) -N(R^{5b})(R^{5c}),
wherein R^{5a}, R^{5b}, and R^{5c} are each independently selected from H, C_{1-6} alkyl, or C_{6-10} aryl;
R^5 is optionally substituted with one or more R^{51},
R^{51} is each independently selected from the group consisting of:
1) halogen,
2) C_{1-6} alkyl optionally substituted with one or more halogen,

3) C_{3-8} cycloalkyl,
4) C_{6-10} aryl,
5) 5- to 10-membered monocyclic heterocyclyl,
6) oxo,
7) -O-R^{51a}, and
8) -N(R^{51b})(R^{51c}),
wherein R^{51a}, R^{51b}, and R^{51c} are each independently selected from H or C_{1-6} alkyl.

[Claim 4] The compound according to any one of claims 1 to 3, or a salt thereof, wherein Ring A is partially unsaturated or unsaturated 9- to 14-membered bicyclic or tricyclic heterocyclyl comprising 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, oxygen, and sulfur and is optionally substituted with the same or different 1 to 4 R^5.

[Claim 5] The compound according to any one of claims 1 to 4, or a salt thereof, wherein Ring A is any one of the heterocyclyl selected from the following groups:

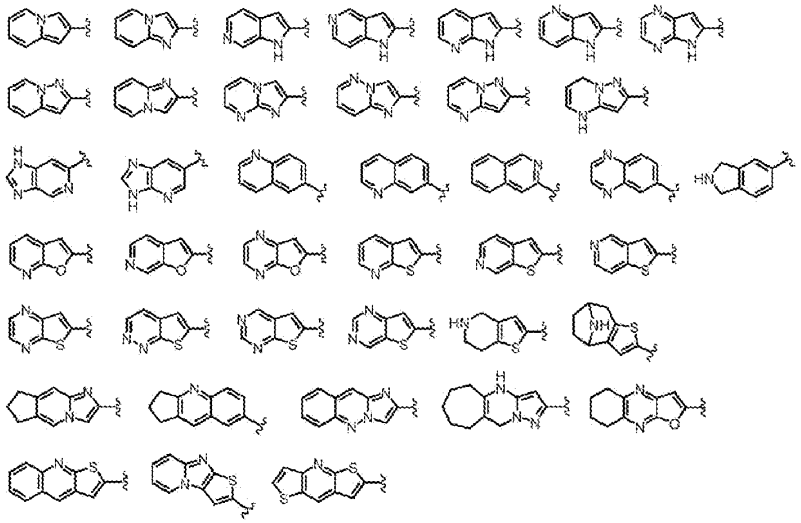
[Chem.2]



and is optionally substituted with the same or different 1 to 4 R^5.

[Claim 6] The compound according to any one of claims 1 to 5, or a salt thereof, wherein Ring A is any one of the heterocyclyl selected from the following groups:

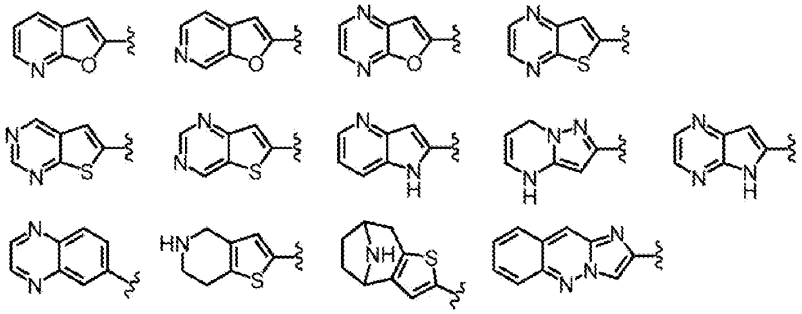
[Chem.3]



and is optionally substituted with the same or different 1 to 4 R^5.

[Claim 7] The compound according to any one of claims 1 to 6, or a salt thereof, wherein Ring A is any one of the heterocyclyl selected from the following groups:

[Chem.4]



and is optionally substituted with the same or different 1 to 3 R^5.

[Claim 8] The compound according to any one of claims 1 to 7, or a salt thereof, wherein R^4 is H or methyl.

[Claim 9] The compound according to any one of claims 1 to 8, or a salt thereof, wherein R^2 is C_{2-6} alkyl, halogen- or hydroxy-substituted C_{2-6} alkyl, or C_{1-6} alkyl-substituted C_{3-6} cycloalkyl.

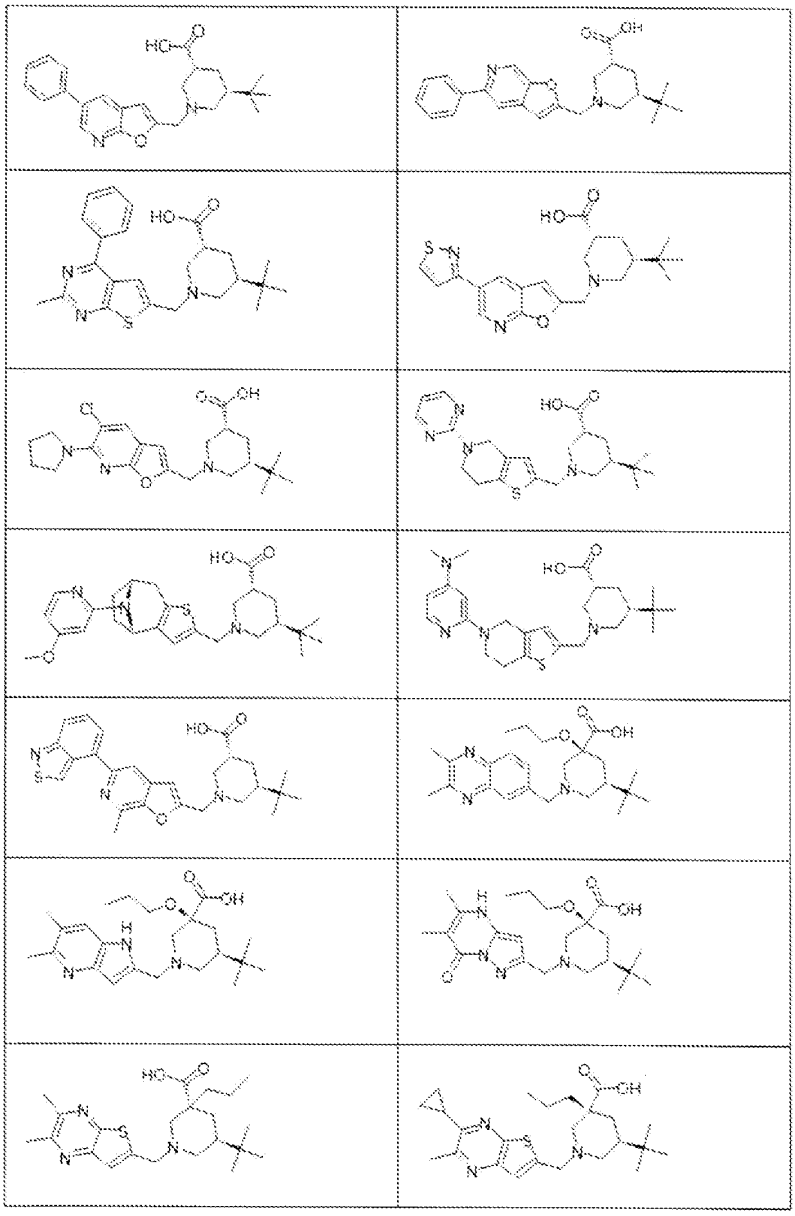
[Claim 10] The compound according to any one of claims 1 to 9, or a salt thereof, wherein R^{12} is each independently halogen, C_{1-6} alkyl-O-, C_{3-6} cycloalkyl, or saturated 3- to 8-membered monocyclic heterocyclyl.

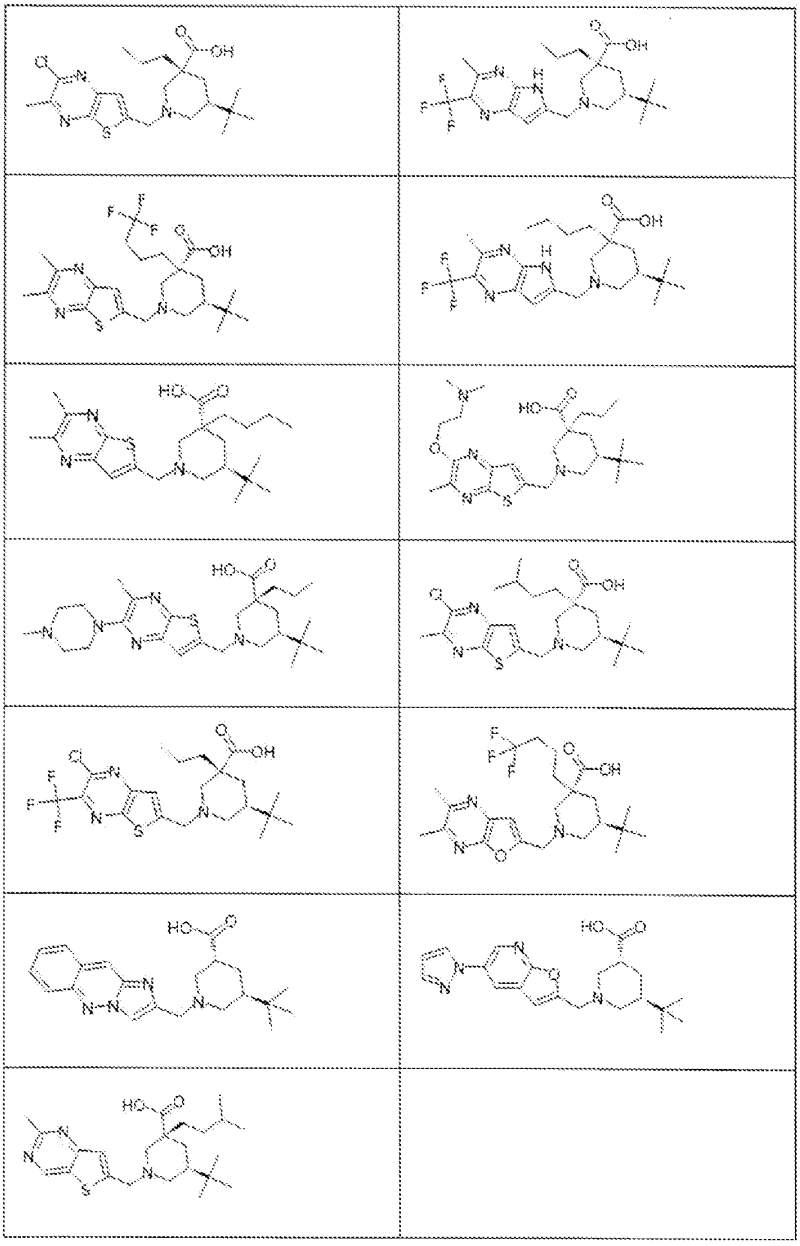
[Claim 11] The compound according to any one of claims 1 to 10, or a salt thereof, wherein R^{11} is C_{1-6} alkyl optionally substituted with one or more R^{12},

and R^{12} is each independently halogen.

[Claim 12] The compound according to claim 1, or a salt thereof, selected from the following formulae:

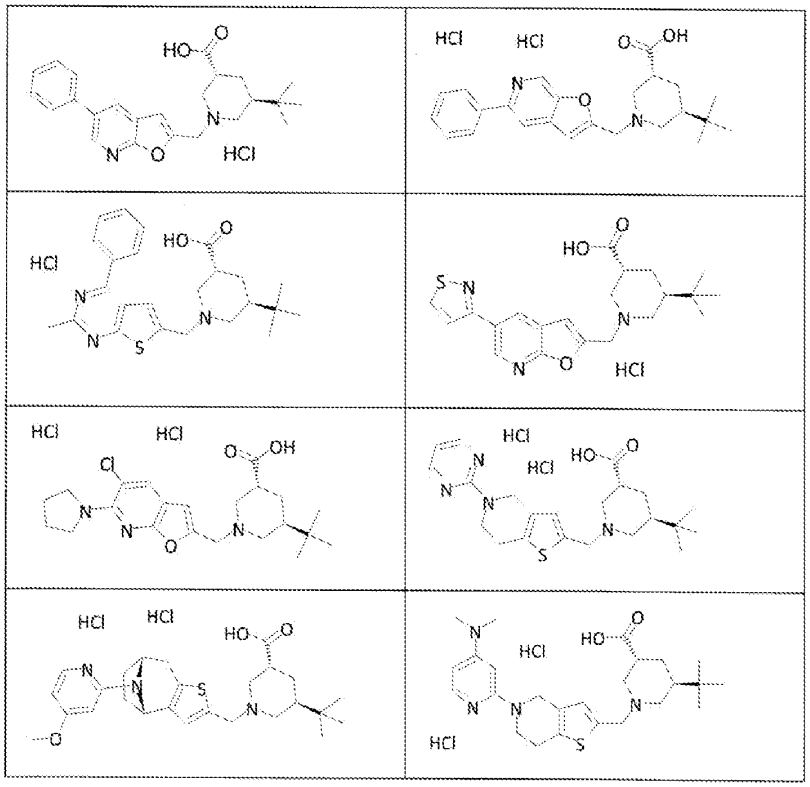
[Chem.5]

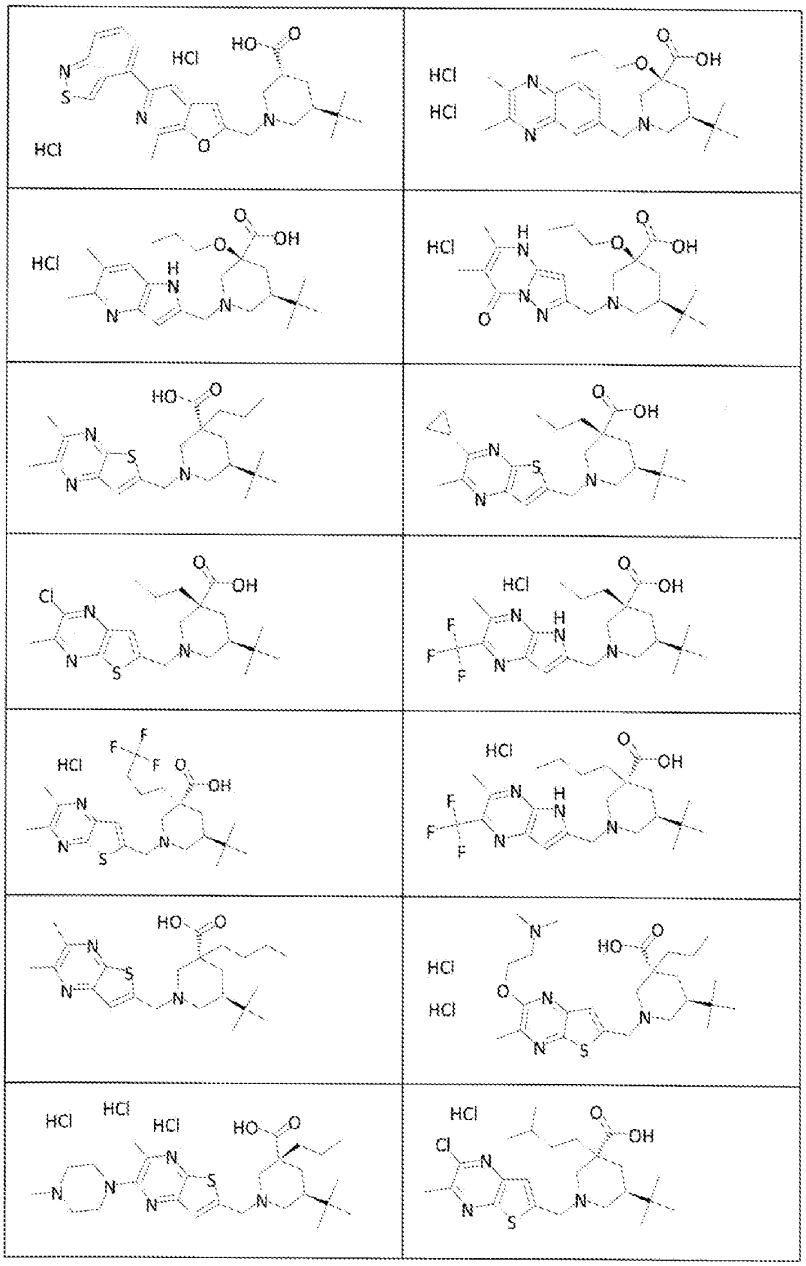


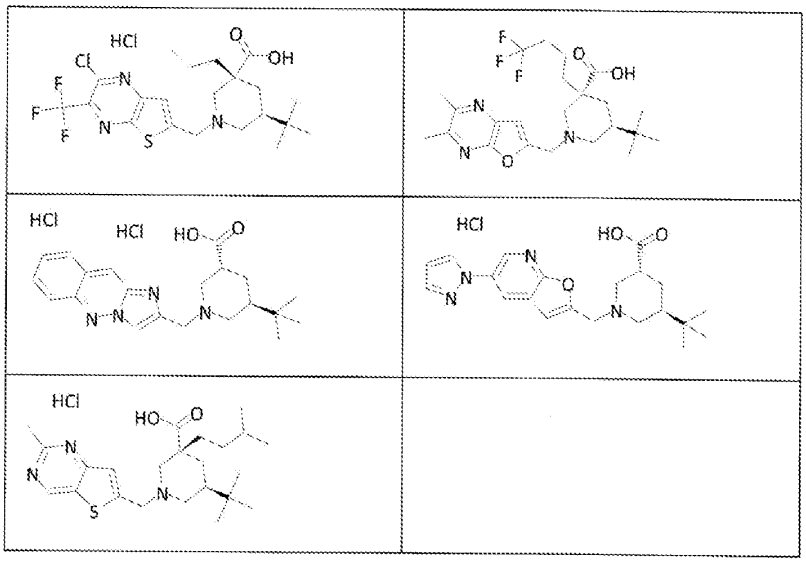


[Claim 13] The compound according to claim 1 selected from the following formulae:

[Chem.6]







[Claim 14] A pharmaceutical composition comprising a compound according to any one of claims 1 to 13, or a salt thereof, and a pharmaceutically acceptable carrier or excipient.

[Claim 15] The compound according to any one of claims 1 to 13, or a salt thereof, for use as a medicament.

[Claim 16] Use of a compound according to any one of claims 1 to 13, or a salt thereof, in the manufacture of a medicament.

[Claim 17] The compound according to any one of claims 1 to 13, or a salt thereof, composition, compound for use, or use according to any one of claims 14 to 16, for use in the treatment, prophylaxis, or diagnosis of a disease or disorder, wherein the disease or disorder is selected from the group consisting of inflammatory diseases including rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), systemic sclerosis (SSc), inflammatory bowel disease (IBD), psoriasis, type 1 diabetes mellitus (T1DM), and multiple sclerosis (MS); cancers including progranulin-induced metastatic breast cancer, lung metastases, and pancreatic cancer cell invasion; wounds (i.e., wound healing) and traumatic brain injury; CNS diseases such as stroke, schizophrenia-like psychosis, schizophrenia, or bipolar disorder (BPD); atypical parkinsonism, such as corticobasal syndrome (CBS), and progressive supranuclear palsy (PSP); spinocerebellar ataxia 3 (SCA3), limbic-predominant age-related TDP-43 encephalopathy (LATE), and Huntington's diseases (HD); age-related macular degeneration (AMD), retinal degeneration,

and other neurodegenerative diseases of the eye; atherosclerosis; neurodegenerative diseases such as frontotemporal dementia (FTD), frontotemporal lobar degeneration (FTLD), neuronal ceroid lipofuscinosis (NCL, a lysosomal storage disease), Niemann-Pick disease type A (NPA), Niemann-Pick disease type B (NPB), Niemann-Pick disease type C (NPC), amyotrophic lateral sclerosis (ALS), C9ORF72-associated ALS/FTD, sporadic ALS, Alzheimer's disease (AD), Gaucher disease types 2 and 3, Parkinson's disease (PD), and major depression; pain; and hearing loss.

[Claim 18] A method of treatment, prophylaxis, or diagnosis of a disease or disorder, comprising administering to a subject in need thereof a compound according to any one of claims 1 to 13, or a salt thereof, wherein the disease or disorder is selected from the group consisting of inflammatory diseases including rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), systemic sclerosis (SSc), inflammatory bowel disease (IBD), psoriasis, type 1 diabetes mellitus (T1DM), and multiple sclerosis (MS); cancers including progranulin-induced metastatic breast cancer, lung metastases, and pancreatic cancer cell invasion; wounds (i.e., wound healing) and traumatic brain injury; CNS diseases such as stroke, schizophrenia-like psychosis, schizophrenia, or bipolar disorder (BPD); atypical parkinsonism, such as corticobasal syndrome (CBS), and progressive supranuclear palsy (PSP); spinocerebellar ataxia 3 (SCA3), limbic-predominant age-related TDP-43 encephalopathy (LATE), and Huntington's diseases (HD); age-related macular degeneration (AMD), retinal degeneration, and other neurodegenerative diseases of the eye; atherosclerosis; neurodegenerative diseases such as frontotemporal dementia (FTD), frontotemporal lobar degeneration (FTLD), neuronal ceroid lipofuscinosis (NCL, a lysosomal storage disease), Niemann-Pick disease type A (NPA), Niemann-Pick disease type B (NPB), Niemann-Pick disease type C (NPC), amyotrophic lateral sclerosis (ALS), C9ORF72-associated ALS/FTD, sporadic ALS, Alzheimer's disease (AD), Gaucher disease types 2 and 3, Parkinson's disease (PD), and major depression; pain; and hearing loss.

[Claim 19] The compound, or a salt thereof, composition, compound for use, use, or method according to claim 17 or 18, wherein the disease or disorder is selected from frontotemporal dementia, Alzheimer's disease, Parkinson's disease or amyotrophic lateral sclerosis.