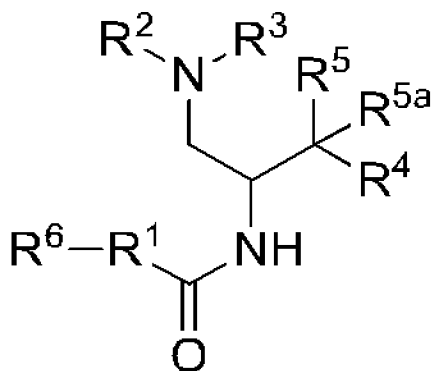




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(54) Titre : DERIVES N-(1-HYDROXY-3-(PYRROLIDINYL)PROPAN-2-YL)PYRROLIDINE-3-CARBOXAMIDE UTILES EN
TANT QU'INHIBITEURS DE LA GLUCOSYLCERAMIDE SYNTHASE
(54) Title: N-(1-HYDROXY-3-(PYRROLIDINYL)PROPAN-2-YL)PYRROLIDINE-3-CARBOXAMIDE DERIVATIVES AS
GLUCOSYLCERAMIDE SYNTHASE INHIBITORS



Formula I

(57) **Abrégé/Abstract:**

Described herein are compounds of Formula I, methods of making such compounds, pharmaceutical compositions and medicaments containing such compounds, and compounds I for use to treat or prevent diseases or conditions associated with the enzyme glucosylceramide synthase (GCS).



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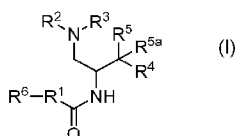
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(57) Abstract: Described herein are compounds of Formula I, methods of making such compounds, pharmaceutical compositions and medicaments containing such compounds, and compounds I for use to treat or prevent diseases or conditions associated with the enzyme glucosylceramide synthase (GCS).

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JUMBO APPLICATIONS / PATENTS

**THIS SECTION OF THE APPLICATION / PATENT CONTAINS MORE
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N-(1-HYDROXY-3-(PYRROLIDINYL)PROPAN-2-YL)PYRROLIDINE-3-CARBOXAMIDE DERIVATIVES AS GLUCOSYLCERAMIDE SYNTHASE INHIBITORS

[0001] The present application claims the benefit of priority of U.S. Provisional Application No. 61/897,110, filed October 29, 2013.

FIELD

[0002] Described herein are compounds, methods of making such compounds, pharmaceutical compositions and medicaments containing such compounds, and methods of using such compounds to treat or prevent diseases or conditions associated with the enzyme glucosylceramide synthase (GCS).

BACKGROUND

[0003] Glucosylceramide synthase (GCS) is a key enzyme which catalyzes the initial glycosylation step in the biosynthesis of glucosylceramide-based glycosphingolipids (GSLs) namely via the transfer of glucose from UDP-glucose (UDP-Glc) to ceramide to form glucosylceramide. GCS is a transmembrane, type III integral protein localized in the cis/medial golgi. Glycosphingolipids (GSLs) are believed to be integral in many cell membrane events, including cellular interactions, signaling, and trafficking. Synthesis of GSL structures has been shown (*Proc. Natl. Acad. Sci CUSA* **1999**, *96*(16), 9142-9147) to be essential for embryonic development and for the differentiation of some tissues. Ceramide plays a central role in sphingolipid metabolism, and downregulation of GCS activity has been shown to have marked effects on the sphingolipid pattern with diminished expression of glycosphingolipids. Sphingolipids have a role in physiological as well as pathological cardiovascular conditions. In particular, sphingolipids and their regulating enzymes appear to play a role in adaptive responses to chronic hypoxia in the neonatal rat heart (*Prostaglandins & Other Lipid Mediators* **2005**, *78*(1-4), 249-263).

[0004] GCS inhibitors have been proposed for the treatment of a variety of diseases (see, for example, WO2005068426). Such diseases include glycolipid storage diseases (e.g., Tay Sachs, Sandhoffs, GM1 gangliosidosis, Niemanns-Pick, and Fabry diseases), diseases associated with glycolipid accumulation (e.g., Gaucher disease), diseases that cause renal hypertrophy or hyperplasia such as diabetic nephropathy, diseases that cause hyperglycemia

or hyperinsulinemia, cancers in which glycolipid synthesis is abnormal, infectious diseases caused by organisms which use cell surface glycolipids as receptors, infectious diseases in which synthesis of glucosylceramide is essential or important, diseases in which excessive glycolipid synthesis occurs (e.g., atherosclerosis, polycystic kidney disease, and renal hypertrophy), neuronal disorders, neuronal injury, inflammatory diseases or disorders associated with macrophage recruitment and activation (e.g., rheumatoid arthritis, Crohn's disease, asthma and sepsis), pain (see WO2008011483 – neuropathic pain, inflammatory pain, headache pain, somatic pain, visceral pain, referred pain), cognitive disorders (see WO2008/109286 – agnosia; amnesia; aphasia; an apraxia; delirium; dementia including AIDS dementia complex, Binswanger's disease, dementia with Lewy Bodies, frontotemporal dementia, mild cognitive impairment, multi-infarct dementia, Pick's disease, semantic dementia, senile dementia, and vascular dementia; and learning disorders including Asperger's syndrome, attention deficit disorder, attention deficit hyperactivity disorder, autism, childhood disintegrative disorder, and Rett syndrome), neurodegenerative disorders (such as Alzheimer's disease, corticobasal degeneration, Creutzfeldt-Jacob disease, frontotemporal lobar degeneration, Huntington disease, multiple sclerosis, normal pressure hydrocephalus, organic chronic brain syndrome, Parkinson's disease, Pick disease, progressive supranuclear palsy, and senile dementia (Alzheimer type), glomerular disease, and diabetes mellitus and obesity (see WO 2006053043). Renal hypertrophy induced by diabetes is associated with enhanced synthesis of glycosphingolipids such as glucosylceramide and ganglioside GM₃ which accumulate in the kidney of rats (*J. Clin. Invest.* **1993**, 91(3), 797).

[0005] It has been shown that overexpression of GCS is implicated in multi-drug resistance and disrupts ceramide-induced apoptosis. For example, Turzanski et al. (*Experimental Hematology* **2005**, 33(1), 62-72) have shown that ceramide induces apoptosis in acute myeloid leukemia (AML) cells and that P-glycoprotein (p-gp) confers resistance to ceramide-induced apoptosis, with modulation of the ceramide-glucosylceramide pathway making a marked contribution to this resistance in TF-I cells. Thus, GCS inhibitors can be useful for treatment of proliferative disorders (such as cancer) by inducing apoptosis in diseased cells.

[0006] Sandhoff (or type 2 GM2 gangliosidosis) is caused by a deficiency in β -hexosaminidase A and B activity which leads to an accumulation of the ganglioside GM₂ and other glycolipids causing damage to the central nervous system and eventually is lethal (*PLoS One* **2011**, 6(6), e21758). Tay-Sachs disease (or GM₂ gangliosidosis) is caused by a

deficiency in β -hexosaminidase A which lead to an accumulation of gangliosides in the brain's nerve cells eventually leading to their premature death. Intravenous injection of the missing enzyme(s) is not a viable option as of the enzymes does cross the blood-brain barrier (*Genetics in Medicine* **2009**, 1(6), 425). Glucosylceramide synthase is a key enzyme in the synthesis of glucosylceramide and other glycosphingolipids. Its inhibition can decrease the amount of the glycosphingolipids which accumulate in Sandhoff disease.

[0007] Fabry disease is caused by loss of activity of the lysosomal hydrolase α -galactosidase which leads to an accumulation of glycosphingolipids (particularly globotriaosylceramide) causing pain, renal disease and failure, cerebral vascular disease, and myocardial infarction (*Kidney International* **2000**, 57, 446). One treatment strategy is to provide the defective enzyme to the patient; however, enzyme replacement therapy can only slow the progression of the disease and is not a cure. An alternative or complementary strategy is one where glucosylceramide synthase, a key enzyme in the synthesis of glycosphingolipids, is inhibited with a small molecule thus decreasing the amount of globotriaosylceramide and other glucosylceramide-based lipids that need to be broken down by hydrolase α -galactosidase.

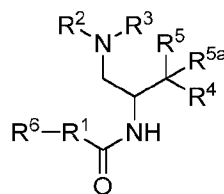
[0008] Gaucher disease is caused by a defect in the enzyme lysosomal glucocerebrosidase which is responsible for catalyzing the breakdown of glucosylceramide which then accumulates in tissues of affected people (*J. Org. Chem.* **2007**, 72(4), 1088) causing liver malfunction, skeletal disorders, painful bone lesions, hypersplenism, pancytopenia, and neurological symptoms (convulsions, hypertonia, mental retardation, apnea, dementia, and ocular muscle apraxia). One treatment strategy is to provide the defective enzyme to the patient; however, enzyme replacement therapy is not suitable for all patients and does not address the neurological manifestations of the disease for those with type 2 and type 3. An alternative or complementary strategy is one where glucosylceramide synthase is inhibited with small molecules thus decreasing the amount of glucosylceramide that needs to be broken down by glucocerebrosidase.

[0009] Nonalcoholic fatty liver disease (NALD) is a disease where fat accumulates in the liver of people who drink little or no alcohol and results in inflammation and scarring of the liver which can progress to liver failure. Inhibition of glucosylceramide synthase in ob/ob mice lowered glucose levels, lowered liver/body weight ratio, decreased the accumulation of triglycerides, and prevented and reversed steatosis (*Hepatology* **2009**, 50(1), 85-93). Thus GCS inhibitors are useful for the prevention and treatment of NALD.

[00010] Polycystic kidney disease (PKD) is a genetic disease characterized by noncancerous cysts which are filled with fluid and cause the kidneys to enlarge which can result in a decrease in quality of life (e.g., headaches, high blood pressure, back and side pain, colon problems, mitral valve prolapsed, and kidney stones) and can be life-threatening (e.g. kidney failure, aneurysm in the brain, and high blood pressure which can lead to heart disease and stroke). PKD can also damage the liver, spleen, pancreas, vasculature, testes, seminal vesicles, and intestines. Glucosylceramide and ganglioside GM₃ levels in the kidney are higher than in normal tissue (*Nat Med* **2010**, 16(7), 788). Thus, blocking the synthesis of glucosylceramide with an inhibitor of GCS can be useful in the treatment of PKD to reduce new cyst formation (partial or complete inhibition of cystogenesis), reduce cyst mass, reduce the size and number of cysts, and/or reduce the severity of the symptoms associated. All current treatments for PKD address symptoms and do not treat the underlying cause of the disease (*Nat Med* **2010**, 16(7), 788).

SUMMARY OF THE INVENTION

[00011] In one aspect, provided is a compound of Formula I:



Formula I

where

R¹ is cycloalkyl or heterocycloalkyl; wherein the heterocycloalkyl is attached to the C(O) group by a carbon atom and is optionally substituted with hydroxy;

R² is hydrogen, hydroxy, or alkyl; and R³ is alkyl, aminoalkyl, alkylaminoalkyl, or dialkylaminoalkyl; or R² and R³ together with the nitrogen to which they are attached form a 3-10 membered heterocycloalkyl ring which is optionally substituted with 1, 2, 3, or 4 R⁸; and wherein the -NR²R³ heterocycloalkyl is not morpholinyl;

R⁴ is aryl or heteroaryl each of which is optionally substituted with 1, 2, or 3 R⁹ groups;

R⁵ is halo, hydroxy, -N₃, -NH₂, -NHC(O)CH₃, -NH(OCH₃), or -NHC(O)H and R^{5a} is hydrogen, halo, alkyl, or deuterium; or R⁵ and R^{5a} together with the carbon to which they are attached form C(O) or C(NOH);

R⁶ is alkyl, alkoxycarbonyl, aryl, arylalkyl, arylcarbonyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, heteroarylalkyl, or -C(O)NR^{6a}R^{6b};

wherein each aryl and heteroaryl, whether alone or as part of another group, is optionally substituted with 1 or 2 R^{10} groups; and wherein each heterocycloalkyl and cycloalkyl, whether alone or as part of another group, is optionally substituted with 1 or 2 groups independently selected from hydroxy, halo, haloalkyl, alkoxy, alkyl, alkylcarbonyl, and alkoxy carbonyl;

R^{6a} is hydrogen or alkyl and R^{6b} is aryl or heteroaryl each of which is optionally substituted with 1 or 2 halo; or R^{6a} and R^{6b} together with the nitrogen to which they are attached form a heterocycloalkyl optionally substituted with alkyl, hydroxy, alkylcarbonyl, or alkoxy carbonyl;

each R^8 , when present, is independently deuterium, amino, alkylamino, dialkylamino, alkyl, hydroxy, alkoxy, halo, haloalkyl, or cycloalkyl;

each R^9 , when present, is independently cyano, nitro, amino, alkylamino, dialkylamino, halo, haloalkyl, alkyl, $-NR^{11}C(O)NR^{11a}R^{11b}$, hydroxy, alkoxy, haloalkoxy, hydroxyalkoxy, alkenyloxy, cycloalkyloxy, cycloalkylalkyloxy, cycloalkylthio, heterocycloalkyl, heterocycloalkyloxy, heterocycloalkylalkyloxy, or phenyl; where the phenyl is optionally substituted with 1 or 2 R^{9a} ; where each heterocycloalkyl, either alone or as part of another group, is optionally substituted with 1 or 2 groups independently selected from alkyl, hydroxy, alkylcarbonyl, and alkoxy carbonyl;

each R^{9a} , when present, is independently selected from alkyl, hydroxy, alkoxy, halo, haloalkyl, haloalkoxy, alkoxy carbonyl, amino, alkylamino, and dialkylamino;

each R^{10} , when present, is independently cyano, nitro, amino, alkylamino, dialkylamino, halo, haloalkyl, alkyl, alkenyl, alkynyl, $-NR^{11}C(O)NR^{11a}R^{11b}$, alkoxy carbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, cycloalkyl, hydroxy, alkoxy, haloalkoxy, hydroxyalkoxy, alkenyloxy, cycloalkyloxy, cycloalkylalkyloxy, cycloalkylthio, aryl, arylalkyl, aryloxy, heteroaryl, heteroarylalkyl, heteroaryloxy, heterocycloalkyl, heterocycloalkyloxy, or heterocycloalkylalkyloxy; where each aryl or heteroaryl either alone or as part of another group, are independently optionally substituted with 1, 2 or 3 R^{10a} ; and each heterocycloalkyl, either alone or as part of another group, is optionally substituted with 1 or 2 groups independently selected from alkyl, hydroxy, alkylcarbonyl, and alkoxy carbonyl groups;

each R^{10a} , when present, is independently selected from cyano, halo, alkyl, alkenyl, haloalkyl, hydroxyalkyl, and cycloalkyl; and

R^{11} , R^{11a} , and R^{11b} are independently hydrogen, alkyl, or cycloalkyl;

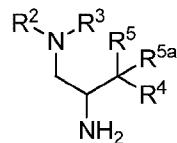
provided that when R^1 is cycloalkyl and R^6 is phenyl then the phenyl is substituted with 1 or 2 groups independently selected from cyano, nitro, amino, alkylamino, dialkylamino, haloalkyl, alkyl, $-NR^{11}C(O)NR^{11a}R^{11b}$, haloalkoxy, cycloalkyloxy, cycloalkylalkyloxy, heterocycloalkyl which is optionally substituted with 1 or 2 alkyl, heterocycloalkyloxy which is optionally substituted with 1 or 2 alkyl, or heterocycloalkylalkyloxy which is optionally substituted with 1 or 2 hydroxy; and optionally a tautomer, a single stereoisomer or mixture of stereoisomers thereof and additionally optionally a pharmaceutically acceptable salt thereof.

[00012] In a further aspect, provided is a pharmaceutical composition comprising 1) a Compound of Formula I optionally as a tautomer, a single stereoisomer or mixture of stereoisomers thereof and additionally optionally as a pharmaceutically acceptable salt thereof, and 2) a pharmaceutically acceptable excipient or pharmaceutically acceptable carrier.

[00013] In a further aspect, provided is a method of treating a disease or disorder comprising administering a Compound of Formula I, optionally as a tautomer, a single stereoisomer or mixture of stereoisomers thereof and additionally optionally as a pharmaceutically acceptable salt thereof, or the pharmaceutical composition thereof additionally comprising a pharmaceutically acceptable excipient or pharmaceutically acceptable carrier.

[00014] In a further aspect, it is provided a method of making a compound of Formula I, comprising:

- a) treating an intermediate of formula **100**



100

or a salt thereof, where R^2 , R^3 , R^4 , R^5 , and R^{5a} and all other groups are as defined in the Summary of the Invention or as in any of the embodiments described herein; with an intermediate of formula $R^6-R^1C(O)OH$ using standard amide coupling conditions to yield a Compound of Formula I where R^1 and R^6 are as defined in the Summary of the Invention or as in any of the embodiments described herein; and

- b) optionally separating individual isomers.

DETAILED DESCRIPTION

Abbreviations

Abbreviation	Meaning
ACN	acetonitrile
aq	aqueous
Boc	tert-butoxycarbonyl
CBz	
conc	concentrated
DAST	diethylaminosulfur trifluoride
DCM	dichloromethane
DIBAL	diisobutylaluminum hydride
DIPEA	diisopropylethylamine
DMF	dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethyl sulfoxide
DPPA	Diphenylphosphoryl azide
EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
h	hours
HATU	<i>O</i> -(7-azabenzotriazol-1-yl)- <i>N,N,N',N'</i> -tetramethyluronium hexafluorophosphate
HOBt	hydroxybenzotriazole
LDA	lithium diisopropyl amide
mg	milligram
mHz	megahertz
mL	milliliter
μL	microliter
MCPBA	meta-chloroperoxybenzoic acid
Ms	mesyl
NBS	N-bromosuccinimide
NMP	N-methyl pyrrolidone
NMR	nuclear magnetic resonance
PE	petroleum ether
rt or RT	room temperature
sat	saturated
TBAF	tetra-n-butylammonium fluoride
TBDMS	tert-butyldimethylsilyl
TEA	triethylamine
TES	triethylsilane
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography

Definitions

[00015] To facilitate understanding of the disclosure set forth herein, a number of terms are defined below. Generally, the nomenclature used herein and the laboratory procedures in organic chemistry, medicinal chemistry, and pharmacology described herein are those well-known and commonly employed in the art. Unless defined otherwise, all

technical and scientific terms used herein generally have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs.

[00016] As used throughout this application and the appended claims, the following terms have the following meanings:

[00017] “About” preceding a numerical value refers to a range of values $\pm 10\%$ of the value specified.

[00018] “Acceptable” with respect to a formulation, composition or ingredient, as used herein, means having no persistent detrimental effect on the general health of the subject being treated.

[00019] “Alkenyl” means a straight or branched hydrocarbon radical having from 2 to 8 carbon atoms and at least one double bond and includes ethenyl, propenyl, 1-but-3-enyl, 1-pent-3-enyl, 1-hex-5-enyl and the like. “Lower alkenyl” means an alkenyl group having one to six carbon atoms.

[00020] “Alkenyloxy” means an -OR group where R is alkenyl, as defined herein.

[00021] “Alkoxy” means an -OR group where R is alkyl, as defined herein. Illustrative examples include, but are not limited to, methoxy, ethoxy, propoxy, 2-propoxy, butoxy, tert-butoxy, pentyloxy, and hexyloxy.

[00022] “Alkoxycarbonyl” means a -C(O)R group where R is alkoxy, as defined herein.

[00023] “Alkyl” means a straight or branched saturated hydrocarbon radical containing from 1-10 carbon atoms, in another example 1-6 carbon atoms. Illustrative examples include, but are not limited to, methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, n-hexyl, 3-methylhexyl, 2,2-dimethylpentyl, 2,3-dimethylhexyl, n-heptyl, n-octyl, n-nonyl, and n-decyl.

[00024] “Alkylamino” means a -NHR radical where R is alkyl as defined herein, or an N-oxide derivative thereof, e.g., methylamino, ethylamino, *n*-, *iso*-propylamino, *n*-, *iso*-, *tert*-butylamino, or methylamino-N-oxide, and the like.

[00025] “Alkylaminoalkyl” means an alkyl group substituted with one or two alkylamino groups, as defined herein.

[00026] “Alkylaminocarbonyl” means a -C(O)R group where R is alkylamino, as defined herein.

[00027] “Alkylcarbonyl” means a -C(O)R group where R is alkyl, as defined herein.

[00028] “Alkynyl” means a straight or branched hydrocarbon radical having from 2 to 8 carbon atoms and at least one triple bond and includes ethynyl, propynyl, 1-but-3-ynyl, 1-

pent-3-ynyl, 1-hex-5-ynyl and the like. “Lower alkynyl” means an alkynyl group having one to six carbon atoms.

[00029] “Amino” means an -NH_2 group.

[00030] “Aminoalkyl” means an alkyl group substituted with at least one, for example one, two, or three, amino groups.

[00031] “Aminocarbonyl” means a -C(O)R group where R is amino, as defined herein.

[00032] “Aryl” means a monovalent six- to fourteen-membered, mono- or bi-carbocyclic ring, wherein the monocyclic ring is aromatic and at least one of the rings in the bicyclic ring is aromatic. Representative examples include phenyl, naphthyl, and indanyl, and the like.

[00033] “Arylalkyl” means an alkyl group, as defined herein, substituted with 1 or 2 aryl groups, as defined herein.

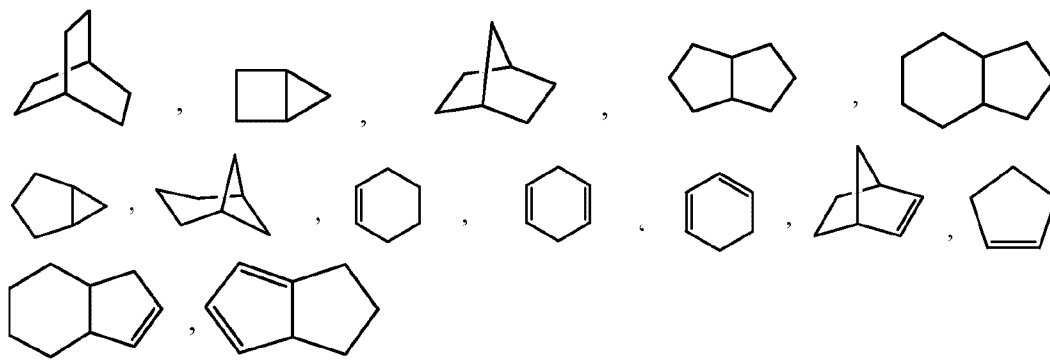
[00034] “Arylcarbonyl” means a -C(O)R group where R is aryl, as defined herein.

[00035] “Aryloxy” means an -OR group where R is aryl, as defined herein.

[00036] “Carboxy” means a -C(O)OH group.

[00037] “Cycloalkyl” means a monocyclic or fused bicyclic, saturated or partially unsaturated (but not aromatic), hydrocarbon radical of three to ten carbon ring atoms. Fused bicyclic hydrocarbon radical includes bridged rings. Cycloalkyl includes spirocycloalkyl rings. Unless stated otherwise, the valency of the group may be located on any atom of any ring within the radical, valency rules permitting. One or two ring carbon atoms may be replaced by a -C(O)- , -C(S)- , or -C(=NH)- group.

[00038] In certain embodiments, cycloalkyl groups include but are not limited to:



[00039] “Cycloalkylalkyl” means an alkyl group, as defined herein, substituted with at least one, in another example 1 or 2, cycloalkyl groups as defined herein.

[00040] “Cycloalkylalkyloxy” means an -OR group where R is a cycloalkylalkyl group as defined herein.

- [00041] “Cycloalkyloxy” means an -OR group where R is cycloalkyl, as defined herein.
- [00042] “Cycloalkylthio” means an -SR group where R is cycloalkyl, as defined herein.
- [00043] “Dialkylamino” means an -NRR’ radical where R and R’ are independently alkyl as defined herein, or an N-oxide derivative, or a protected derivative thereof, e.g., dimethylamino, diethylamino, *N,N*-methylpropylamino or *N,N*-methylethylamino, and the like.
- [00044] “Dialkylaminoalkyl” means an alkyl group substituted with at least one, for example one or two, dialkylamino group(s), as defined herein.
- [00045] “Dialkylaminocarbonyl” means a -C(O)R group where R is dialkylamino, as defined herein.
- [00046] “Halo” means a fluoro, chloro, bromo, or iodo group.
- [00047] “Haloalkoxy” means an alkoxy group, as defined herein, substituted with one or more halo atoms, in another example by 1, 2, or 3 halo atoms.
- [00048] “Haloalkyl” means an alkyl group substituted with one or more halo atoms, in another example by 1, 2, 3, 4, 5, or 6 halo atoms, in another example by 1, 2, or 3 halo atoms. Examples include, but are not limited to, trifluoromethyl, chloromethyl, and the like.
- [00049] “Heteroaryl” means monocyclic, fused bicyclic, or fused tricyclic, radical of 5 to 14 ring atoms containing one or more, in another example one, two, three, or four ring heteroatoms independently selected from -O-, -S(O)_n- (n is 0, 1, or 2), -N-, -N(H)-, and N-oxide, and the remaining ring atoms being carbon, wherein the ring comprising a monocyclic radical is aromatic and wherein at least one of the fused rings comprising a bicyclic or tricyclic radical is aromatic (but does not have to be a ring which contains a heteroatom, e.g. 2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl). One or two ring carbon atoms of any nonaromatic rings comprising a bicyclic or tricyclic radical may be replaced by a -C(O)-, -C(S)-, or -C(=NH)- group. Fused bicyclic radical includes bridged ring systems. Unless stated otherwise, the valency may be located on any atom of any ring of the heteroaryl group, valency rules permitting.
- [00050] In certain embodiments, heteroaryl includes, but is not limited to, triazolyl, tetrazolyl, pyrrolyl, imidazolyl, thienyl, furanyl, pyrazolyl, oxazolyl, isooxazolyl, oxadiazolyl, thiadiazolyl, indolyl, 2,3-dihydro-1*H*-indolyl (including, for example, 2,3-dihydro-1*H*-indol-2-yl or 2,3-dihydro-1*H*-indol-5-yl, and the like), indazolyl, phthalimidyl, benzimidazolyl, benzoxazolyl, benzofuranyl, benzothienyl, benzopyranyl,

benzothiazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, quinolinyl, isoquinolinyl, tetrahydroisoquinolinyl (including, for example, tetrahydroisoquinolin-4-yl or tetrahydroisoquinolin-6-yl, and the like), pyrrolo[3,2-*c*]pyridinyl (including, for example, pyrrolo[3,2-*c*]pyridin-2-yl or pyrrolo[3,2-*c*]pyridin-7-yl, and the like), pyrrolo[1,2-*b*]pyridazinyl, imidazo[1,2-*a*]pyridinyl, thiazolyl, benzo[*d*][1,3]dioxolyl, 2,3-dihydrobenzo[*b*][1,4]dioxinyl, furo[2,3-*d*]thiazolyl, thieno[2,3-*d*]oxazolyl, thieno[3,2-*b*]furanyl, furo[2,3-*d*]pyrimidinyl, furo[3,2-*b*]pyridinyl, furo[3,2-*c*]pyridinyl, 6,7-dihydro-5*H*-cyclopenta[*b*]pyridinyl, and 7,8-dihydro-6*H*-cyclopenta[*g*]quinoxaliny; and derivatives, N-oxide and protected derivatives thereof.

[00051] “Heteroarylalkyl” means an alkyl group, as defined herein, substituted with 1 or 2 heteroaryl groups, as defined herein.

[00052] “Heteroaryloxy” means an –OR group where R is heteroaryl, as defined herein.

[00053] “Heterocycloalkyl” means a saturated or partially unsaturated (but not aromatic) monovalent monocyclic group of 3 to 9 ring atoms or a saturated or partially unsaturated (but not aromatic) monovalent fused bicyclic group of 5 to 12 ring atoms in which one or more heteroatoms, for example one, two, three, or four ring heteroatoms, independently selected from –O–, –S(O)_{*n*}– (*n* is 0, 1, or 2), –N=, –NH–, and N-oxide, the remaining ring atoms being carbon. One or two ring carbon atoms may be replaced by a –C(O)–, –C(S)–, or –C(=NH)– group. Fused bicyclic radical includes bridged ring systems. Unless otherwise stated, the valency of the group may be located on any atom of any ring within the radical, valency rules permitting.

[00054] In certain embodiments, heterocycloalkyl includes, but is not limited to, azetidiny, pyrrolidinyl, 2-oxopyrrolidinyl, 2,5-dihydro-1*H*-pyrrolinyl, 2,5-dioxo-1*H*-pyrrolyl, 2,5-dioxo-pyrrolidinyl, 2,5-dihydro-1*H*-pyrrolyl, piperidinyl, 2-oxopiperidinyl, 4-piperidonyl, morpholinyl, piperazinyl, 2-oxopiperazinyl, dioxopiperazinyl, pyranyl, tetrahydropyranyl, tetrahydrothiopyranyl, 1,3-dioxinyl, 1,3-dioxanyl, 1,4-dioxinyl, 1,4-dioxanyl, thiomorpholinyl, thiamorpholinyl, perhydroazepinyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, 2,4-dioxo-imidazolidinyl, dihydropyridinyl, tetrahydropyridinyl, oxazolinyl, oxazolidinyl, isoxazolidinyl, thiazolinyl, thiazolidinyl, quinuclidinyl, isothiazolidinyl, octahydroindolyl, octahydroisoindolyl, decahydroisoquinolyl, tetrahydrofuryl, 2-azaspiro[3.3]heptanyl, 7-azabicyclo[2.2.1]heptanyl, and 8-azabicyclo[3.2.1]octanyl, and the derivatives thereof and N-oxide (for example 1-oxido-pyrrolidin-1-yl) or a protected derivative thereof.

[00055] “Heterocycloalkylalkyl” means an alkyl group substituted with at least one, in another example 1 or 2, heterocycloalkyl groups, as defined herein.

[00056] “Heterocycloalkylalkyloxy” means an –OR group where R is an heterocycloalkylalkyl group, as defined herein.

[00057] “Heterocycloalkyloxy” means an -OR group where R is heterocycloalkyl, as defined herein.

[00058] “Hydroxyalkoxy” means an alkoxy group, as defined herein, substituted with at least one, or in other embodiments 1, 2, or 3, hydroxy groups.

[00059] The term “protecting group” refers to a removable group which modifies the reactivity of a functional group, for example, a hydroxyl, ketone or amine, against undesirable reaction during synthetic procedures and to be later removed. Examples of hydroxy-protecting groups include, but not limited to, methylthiomethyl, tert-dimethylsilyl, tert-butyldiphenylsilyl, ethers such as methoxymethyl, and esters including acetyl, benzoyl, and the like. Examples of ketone protecting groups include, but not limited to, ketals, oximes, O-substituted oximes for example O-benzyl oxime, O-phenylthiomethyl oxime, 1-isopropoxycyclohexyl oxime, and the like. Examples of amine protecting groups include, but are not limited to, tert-butoxycarbonyl (Boc) and carbobenzyloxy (Cbz).

[00060] “Stereoisomers” include (but are not limited to) geometric isomers, enantiomers, diastereomers, and mixtures of geometric isomers, enantiomers or diastereomers. In some embodiments, individual stereoisomers of compounds are prepared synthetically from commercially available starting materials which contain asymmetric or chiral centers or by preparation of racemic mixtures followed by resolution. These methods of resolution are exemplified by (1) attachment of a mixture of enantiomers to a chiral auxiliary, separation of the resulting mixture of diastereomers by recrystallization or chromatography and liberation of the optically pure product from the auxiliary or (2) direct separation of the mixture of optical enantiomers on chiral chromatographic column.

[00061] As used herein, “amelioration” of the symptoms of a particular disorder by administration of a particular compound or pharmaceutical composition refers to any lessening of severity, delay in onset, slowing of progression, or shortening of duration, whether permanent or temporary, lasting or transient that can be attributed to or associated with administration of the compound or composition.

[00062] The term “carrier” includes pharmaceutically inert, inorganic or organic carriers for the production of pharmaceutical compositions. Lactose, corn starch, or derivatives thereof, talc, stearic acid or its salts and the like can be used, for example, as such

carriers for tablets, coated tablets, dragees and hard gelatin capsules. Suitable carriers for soft gelatin capsules are, for example, vegetable oils, waxes, fats, semi-solid and liquid polyols and the like. Depending on the nature of the active ingredient no carriers are, however, usually required in the case of soft gelatin capsules, other than the soft gelatin itself. Suitable carriers for the production of solutions and syrups are, for example, water, polyols, glycerol, vegetable oils and the like. Suitable carriers for suppositories are, for example, natural or hardened oils, waxes, fats, semi-liquid or liquid polyols and the like.

[00063] The term “diluent” refers to chemical compounds that are used to dilute the compound of interest prior to delivery. Diluents include chemicals used to stabilize compounds because they provide a more stable environment. Salts dissolved in buffered solutions (which also can provide pH control or maintenance) are utilized as diluents in some or any embodiments, including, but not limited to a phosphate buffered saline solution.

[00064] The terms “effective amount” or “therapeutically effective amount,” as used herein, refer to a sufficient amount of an agent or a compound being administered which will relieve to some extent one or more of the symptoms of the disease or condition being treated. The result includes reduction and/or alleviation of the signs, symptoms, or causes of a disease, or any other desired alteration of a biological system. For example, an “effective amount” for therapeutic uses is the amount of the composition comprising a compound as disclosed herein required to provide a clinically significant decrease in disease symptoms. An appropriate “effective” amount in any individual case is determined using any suitable technique, such as a dose escalation study.

[00065] “Excipient” or “pharmaceutically acceptable excipient” means a pharmaceutically-acceptable material, composition, or vehicle, such as a liquid or solid filler, diluent, solvent, or encapsulating material. In one embodiment, each component is “pharmaceutically acceptable” in the sense of being compatible with the other ingredients of a pharmaceutical formulation, and suitable for use in contact with the tissue or organ of humans and animals without excessive toxicity, irritation, allergic response, immunogenicity, or other problems or complications, commensurate with a reasonable benefit/risk ratio. *See, e.g., Remington: The Science and Practice of Pharmacy, 21st ed.*; Lippincott Williams & Wilkins: Philadelphia, PA, 2005; *Handbook of Pharmaceutical Excipients, 6th ed.*; Rowe *et al.*, Eds.; The Pharmaceutical Press and the American Pharmaceutical Association: 2009; *Handbook of Pharmaceutical Additives, 3rd ed.*; Ash and Ash Eds.; Gower Publishing Company: 2007; *Pharmaceutical Preformulation and Formulation, 2nd ed.*; Gibson Ed.; CRC Press LLC: Boca Raton, FL, 2009.

[00066] “Pharmaceutically acceptable salt” refers to a formulation of a compound that does not cause significant irritation to an organism to which it is administered and does not abrogate the biological activity and properties of the compound. In certain instances, pharmaceutically acceptable salts are obtained by reacting a compound described herein, with acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid and the like. In some instances, pharmaceutically acceptable salts are obtained by reacting a compound having acidic group described herein with a base to form a salt such as an ammonium salt, an alkali metal salt, such as a sodium or a potassium salt, an alkaline earth metal salt, such as a calcium or a magnesium salt, a salt of organic bases such as dicyclohexylamine, *N*-methyl-D-glucamine, tris(hydroxymethyl)methylamine, and salts with amino acids such as arginine, lysine, and the like, or by other methods previously determined. The pharmacologically acceptable salt is not specifically limited as far as it can be used in medicaments. Examples of a salt that the compound of the present invention forms with a base include the following: salts thereof with inorganic bases such as sodium, potassium, magnesium, calcium, and aluminum; salts thereof with organic bases such as methylamine, ethylamine and ethanolamine; salts thereof with basic amino acids such as lysine and ornithine; and ammonium salt. The salts may be acid addition salts, which are specifically exemplified by acid addition salts with the following: mineral acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, nitric acid, and phosphoric acid; organic acids such as formic acid, acetic acid, propionic acid, oxalic acid, malonic acid, succinic acid, fumaric acid, maleic acid, lactic acid, malic acid, tartaric acid, citric acid, methanesulfonic acid, and ethanesulfonic acid; acidic amino acids such as aspartic acid and glutamic acid.

[00067] The term “pharmaceutical composition” refers to a mixture of a compound described herein with other chemical components, such as carriers, stabilizers, diluents, dispersing agents, suspending agents, thickening agents, and/or excipients. The pharmaceutical composition facilitates administration of the compound to an organism. Multiple techniques of administering a compound exist in the art including, but not limited to: intravenous, oral, aerosol, parenteral, ophthalmic, pulmonary and topical administration.

[00068] “Subject” refers to an animal, including, but not limited to, a primate (*e.g.*, human), monkey, cow, pig, sheep, goat, horse, dog, cat, rabbit, rat, or mouse. The terms “subject” and “patient” are used interchangeably herein in reference, for example, to a mammalian subject, such as a human.

[00069] “Treat,” “treating,” and “treatment,” in the context of treating a disease or disorder, are meant to include alleviating or abrogating a disorder, disease, or condition, or one or more of the symptoms associated with the disorder, disease, or condition; or to slowing the progression, spread or worsening of a disease, disorder or condition or of one or more symptoms thereof. Often, the beneficial effects that a subject derives from a therapeutic agent do not result in a complete cure of the disease, disorder or condition.

Embodiments

[00070] The following paragraphs present a number of embodiments of the compounds disclosed herein. In each instance the embodiment includes both the recited compound(s) as well as a single stereoisomer or mixture of stereoisomers thereof, as well as a pharmaceutically acceptable salt thereof. The compounds include the *N*-oxides or pharmaceutically acceptable salts thereof. In some situations, the compounds exist as tautomers. All tautomers are included within the scope of the compounds presented herein.

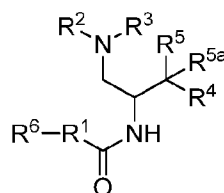
[00071] The compounds described herein, as well as their corresponding pharmaceutically acceptable salts thereof, can exist in isotopically-labeled form, in which one or more atoms of the compounds are replaced by an atom having the same atomic number but an atomic mass different from the atomic mass usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, sulfur, fluorine, and chloride, such as ^2H (deuterium), ^3H (tritium), ^{13}C , ^{14}C , ^{15}N , ^{17}O , ^{18}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F , and ^{36}Cl , respectively. Isotopically labeled compounds of the present invention, as well as pharmaceutically acceptable salts thereof, generally can be prepared by carrying out the procedures disclosed in the Schemes and/or in the Examples and Preparations herein, by substituting a readily available isotopically labeled reagent for a non-isotopically labeled reagent.

[00072] In the compounds of the invention, unless otherwise stated, any atom not specifically designated as a particular isotope is meant to represent any stable isotope of that atom at its natural abundance. When a position is designated as “H” or “hydrogen,” the position is to be understood to have hydrogen at its naturally abundant isotopic composition, with the understanding that some variation of natural isotopic abundance occurs in a synthesized compound depending upon the origin of chemical materials used in the synthesis. When a particular position is designated as “D” or “deuterium,” it is to be understood that the abundance of deuterium at that position is substantially greater than the natural abundance of

deuterium, with is 0.015%, and typically has at least 50% deuterium incorporation at that position.

[00073] The methods disclosed herein also include methods of treating diseases by administering deuterated compounds of the invention or other isotopically-labeled compounds of the invention alone or as pharmaceutical compositions. In some of these situations, substitution of hydrogen atoms with heavier isotopes such as deuterium can afford certain therapeutic advantages resulting from greater metabolic stability (for example, increased in vivo half-life or reduced dosage requirements). Moreover, certain isotopically-labeled compounds, for example those into which radioactive isotopes such as ^3H and ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays such as positron emission tomography (PET). Tritiated (^3H) and carbon-14 (^{14}C) isotopes are useful for these embodiments.

[00074] In embodiment, provided is a compound of Formula I:



Formula I

where

R^1 is cycloalkyl or R^1 is heterocycloalkyl; wherein the heterocycloalkyl is attached to the $\text{C}(\text{O})$ group by a carbon atom and is optionally substituted with hydroxy;

R^2 is hydrogen, hydroxy, or alkyl; and R^3 is alkyl, aminoalkyl, alkylaminoalkyl, or dialkylaminoalkyl; or R^2 and R^3 together with the nitrogen to which they are attached form a 3-10 membered heterocycloalkyl ring which is optionally substituted with 1, 2, 3, or 4 R^8 ; and wherein the $-\text{NR}^2\text{R}^3$ heterocycloalkyl is not morpholinyl;

R^4 is aryl or heteroaryl each of which is optionally substituted with 1, 2, or 3 R^9 groups;

R^5 is halo, $-\text{OH}$, $-\text{N}_3$, $-\text{NH}_2$, $-\text{NHC}(\text{O})\text{CH}_3$, $-\text{NH}(\text{OCH}_3)$, or $-\text{NHC}(\text{O})\text{H}$ and R^{5a} is hydrogen, halo, alkyl, or deuterium; or R^5 and R^{5a} together with the carbon to which they are attached form $\text{C}(\text{O})$ or $\text{C}(\text{NOH})$;

R^6 is alkyl, alkoxycarbonyl, aryl, arylalkyl, arylcarbonyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, heteroarylalkyl, or $-\text{C}(\text{O})\text{NR}^{6a}\text{R}^{6b}$; wherein the aryl and the heteroaryl, whether alone or as part of arylalkyl or heteroarylalkyl, are optionally substituted with 1 or 2 R^{10} groups; and wherein the

heterocycloalkyl and cycloalkyl, whether alone or as part of cycloalkylalkyl or heterocycloalkylalkyl, are optionally substituted with 1 or 2 groups independently selected from hydroxy, halo, haloalkyl, alkoxy, alkyl, alkylcarbonyl, and alkoxycarbonyl; R^{6a} is hydrogen or alkyl and R^{6b} is aryl or heteroaryl each of which is optionally substituted with 1 or 2 halo; or R^{6a} and R^{6b} together with the nitrogen to which they are attached form a heterocycloalkyl optionally substituted with alkyl, hydroxy, alkylcarbonyl, or alkoxycarbonyl;

each R^8 , when present, is independently deuterium, amino, alkylamino, dialkylamino, alkyl, hydroxy, alkoxy, halo, haloalkyl, or cycloalkyl;

each R^9 , when present, is independently cyano, nitro, amino, alkylamino, dialkylamino, halo, haloalkyl, alkyl, $-NR^{11}C(O)NR^{11a}R^{11b}$, hydroxy, alkoxy, haloalkoxy, hydroxyalkoxy, alkenyloxy, cycloalkyloxy, cycloalkylalkyloxy, cycloalkylthio, heterocycloalkyl, heterocycloalkyloxy, or heterocycloalkylalkyloxy; where each heterocycloalkyl, either alone or as part of another group, is optionally substituted with 1 or 2 groups independently selected from alkyl, hydroxy, alkylcarbonyl, and alkoxycarbonyl groups;

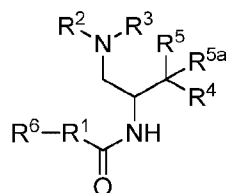
each R^{10} , when present, is independently is cyano, nitro, amino, alkylamino, dialkylamino, halo, haloalkyl, alkyl, $-NR^{11}C(O)NR^{11a}R^{11b}$, hydroxy, alkoxy, haloalkoxy, cycloalkyloxy, cycloalkylalkyloxy, aryl, aryloxy, heteroaryloxy, heterocycloalkyl, heterocycloalkyloxy, or heterocycloalkylalkyloxy; where each aryl or heteroaryl either alone or as part of another group, are independently optionally substituted with 1 or 2 halo or alkyl; and each heterocycloalkyl, either alone or as part of another group, is optionally substituted with 1 or 2 groups independently selected from alkyl, hydroxy, alkylcarbonyl, and alkoxycarbonyl groups;

R^{11} , R^{11a} , and R^{11b} are independently hydrogen, alkyl, or cycloalkyl;

provided that when R^1 is cycloalkyl and R^6 is phenyl then the phenyl is substituted with 1 or 2 groups independently selected from cyano, nitro, amino, alkylamino, dialkylamino, haloalkyl, alkyl, $-NR^{11}C(O)NR^{11a}R^{11b}$, haloalkoxy, cycloalkyloxy, cycloalkylalkyloxy, heterocycloalkyl which is optionally substituted with 1 or 2 alkyl, heterocycloalkyloxy which is optionally substituted with 1 or 2 alkyl, or heterocycloalkylalkyloxy which is optionally substituted with 1 or 2 hydroxy; and

optionally a tautomer, a single stereoisomer or mixture of stereoisomers thereof and additionally optionally a pharmaceutically acceptable salt thereof.

[00075] In one embodiment, provided is a compound of Formula I:



Formula I

where

- R^1 is cycloalkyl or R^1 is heterocycloalkyl attached to the C(O) group by a carbon atom;
 R^2 is hydrogen, hydroxy, or alkyl; and R^3 is alkyl, aminoalkyl, alkylaminoalkyl, or dialkylaminoalkyl; or R^2 and R^3 together with the nitrogen to which they are attached form a 3-10 membered heterocycloalkyl ring which is optionally substituted with 1, 2, 3, or 4 R^8 ; and wherein the $-NR^2R^3$ heterocycloalkyl is not morpholinyl;
 R^4 is aryl or heteroaryl each of which is optionally substituted with 1, 2, or 3 R^9 groups;
 R^5 is halo, -OH, -N₃, -NH₂, -NHC(O)CH₃, -NH(OCH₃), or -NHC(O)H and R^{5a} is hydrogen, halo, alkyl, or deuterium; or R^5 and R^{5a} together with the carbon to which they are attached form C(O) or C(NO₂);
 R^6 is alkoxycarbonyl, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, heteroarylalkyl, or -C(O)NR^{6a}R^{6b}; wherein the aryl and the heteroaryl, whether alone or as part of arylalkyl or heteroarylalkyl, are optionally substituted with 1 or 2 R^{10} groups; and wherein the heterocycloalkyl and cycloalkyl, whether alone or as part of cycloalkylalkyl or heterocycloalkylalkyl, are optionally substituted with 1 or 2 groups independently selected from hydroxy, halo, haloalkyl, alkoxy, alkyl, alkylcarbonyl, and alkoxycarbonyl;
 R^{6a} is hydrogen or alkyl and R^{6b} is aryl or heteroaryl each of which is optionally substituted with 1 or 2 halo; or R^{6a} and R^{6b} together with the nitrogen to which they are attached form a heterocycloalkyl optionally substituted with alkyl, hydroxy, alkylcarbonyl, or alkoxycarbonyl;
each R^8 , when present, is independently deuterium, amino, alkylamino, dialkylamino, alkyl, hydroxy, alkoxy, halo, haloalkyl, or cycloalkyl;
each R^9 , when present, is independently cyano, nitro, amino, alkylamino, dialkylamino, halo, haloalkyl, alkyl, -NR¹¹C(O)NR^{11a}R^{11b}, hydroxy, alkoxy, haloalkoxy, cycloalkyloxy, cycloalkylalkyloxy, heterocycloalkyl, heterocycloalkyloxy, or heterocycloalkylalkyloxy; where each heterocycloalkyl, either alone or as part of another group, is optionally

substituted with 1 or 2 groups independently selected from alkyl, hydroxy, alkylcarbonyl, and alkoxy carbonyl groups;

each R^{10} , when present, is independently R^9 ; and

R^{11} , R^{11a} , and R^{11b} are independently hydrogen, alkyl, or cycloalkyl;

provided that when R^1 is cycloalkyl and R^6 is phenyl then the phenyl is substituted with 1 or 2 groups independently selected from cyano, nitro, amino, alkylamino, dialkylamino, haloalkyl, alkyl, $-NR^{11}C(O)NR^{11a}R^{11b}$, haloalkoxy, cycloalkyloxy, cycloalkylalkyloxy, heterocycloalkyl which is optionally substituted with 1 or 2 alkyl, heterocycloalkyloxy which is optionally substituted with 1 or 2 alkyl, or heterocycloalkylalkyloxy which is optionally substituted with 1 or 2 hydroxy; and

optionally a tautomer, a single stereoisomer or mixture of stereoisomers thereof and additionally optionally a pharmaceutically acceptable salt thereof.

[00076] In some or any embodiments, the compound of Formula I is that where

R^1 is $N-(R^6)$ -azetidiny, $N-(R^6)$ -pyrrolidiny, or $N-(R^6)$ -piperidiny, each of which is attached to the C(O) by a carbon atom, and is optionally substituted with hydroxy;

R^2 and R^3 together with the nitrogen to which they are attached form a 4-6 membered heterocycloalkyl ring with 1 or 2 nitrogen atoms, which is optionally substituted with 1 or 2 R^8 ;

R^4 is aryl or heteroaryl each of which is optionally substituted with 1 or 2 R^9 groups;

R^5 is -OH and R^{5a} is hydrogen;

R^6 is alkyl, aryl, arylalkyl, arylcarbonyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, or heteroarylalkyl; wherein the aryl and the heteroaryl, whether alone or as part of another group, are optionally substituted with 1 or 2 R^{10} groups; and wherein the heterocycloalkyl and cycloalkyl, whether alone or as part of another group, are optionally substituted with 1 or 2 groups independently selected from hydroxy, halo, haloalkyl, alkoxy, and alkyl;

each R^8 , when present, is independently hydrogen, alkyl, hydroxy, alkoxy, halo, or haloalkyl;

each R^9 , when present, is independently cyano, nitro, halo, haloalkyl, alkyl, hydroxy, alkoxy, haloalkoxy, hydroxyalkoxy, alkenyloxy, cycloalkyloxy, cycloalkylalkyloxy, cycloalkylthio, heterocycloalkyl, heterocycloalkyloxy, or heterocycloalkylalkyloxy; where each heterocycloalkyl, either alone or as part of another group, is optionally substituted with 1 or 2 groups independently selected from alkyl, hydroxy, alkylcarbonyl, and alkoxy carbonyl groups;

each R¹⁰, when present, is independently is cyano, halo, haloalkyl, alkyl, hydroxy, alkoxy, haloalkoxy, cycloalkyloxy, cycloalkylalkyloxy, aryl, aryloxy, heteroaryloxy, heterocycloalkyl, heterocycloalkyloxy, or heterocycloalkylalkyloxy; where each aryl or heteroaryl either alone or as part of another group, are independently optionally substituted with 1 or 2 halo or alkyl groups; and each heterocycloalkyl, either alone or as part of another group, is optionally substituted with 1 or 2 groups independently selected from alkyl and hydroxy; and

optionally a tautomer, a single stereoisomer or mixture of stereoisomers thereof and additionally optionally a pharmaceutically acceptable salt thereof.

[00077] In some or any embodiments, the compound of Formula I is that where

R¹ is *N*-(R⁶)-pyrrolidinyl, attached to the C(O) by a carbon atom, and is optionally substituted with hydroxy;

R² and R³ together with the nitrogen to which they are attached form a azetidiny, pyrrolidinyl, or piperidinyl ring;

R⁴ is aryl or heteroaryl each of which is optionally substituted with 1 or 2 R⁹ groups;

R⁵ is -OH and R^{5a} is hydrogen;

R⁶ is alkyl, aryl, arylalkyl, arylcarbonyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, or heteroaryl; wherein the aryl and the heteroaryl, whether alone or as part of arylalkyl or heteroarylalkyl, are optionally substituted with 1 or 2 R¹⁰ groups; and wherein the heterocycloalkyl is optionally substituted with hydroxy;

each R⁹, when present, is independently halo, haloalkyl, alkyl, alkoxy, haloalkoxy, hydroxyalkoxy, alkenyloxy, cycloalkyloxy, cycloalkylthio, heterocycloalkyl, heterocycloalkyloxy, or heterocycloalkylalkyloxy; where each heterocycloalkyl, either alone or as part of another group, is optionally substituted with an alkyl group;

each R¹⁰, when present, is independently is cyano, halo, haloalkyl, alkyl, haloalkoxy, cycloalkyloxy, aryl, aryloxy, or heteroaryloxy; where each aryl or heteroaryl either alone or as part of another group, are independently optionally substituted with 1 or 2 halo or alkyl; and optionally a tautomer, a single stereoisomer or mixture of stereoisomers thereof and additionally optionally a pharmaceutically acceptable salt thereof.

[00078] In some or any embodiments, the compound of Formula I is that where

R¹ is cycloalkyl or R¹ is heterocycloalkyl attached to the C(O) group by a carbon atom;

R² and R³ together with the nitrogen to which they are attached form a 4-7 membered

heterocycloalkyl ring which is optionally substituted with 1, 2, 3, or 4 R⁸;

R⁴ is aryl or heteroaryl each of which is optionally substituted with 1, 2, or 3 R⁹ groups;

R⁵ is -OH and R^{5a} is hydrogen;

R⁶ is alkoxycarbonyl, aryl arylalkyl; cycloalkyl; heterocycloalkyl; heterocycloalkylalkyl optionally substituted with 1 or 2 hydroxy; heteroaryl; or -C(O)NR^{6a}R^{6b}; wherein the aryl and the heteroaryl, whether alone or as part of arylalkyl or heteroarylalkyl, are optionally substituted with 1 or 2 R¹⁰ groups; and wherein the heterocycloalkyl, heterocycloalkylalkyl, and cycloalkyl are optionally substituted with 1 or 2 groups independently selected from hydroxy and alkyl;

R^{6a} is hydrogen or alkyl and R^{6b} is aryl optionally substituted with halo;

each R⁸, when present, is independently deuterium or alkyl;

each R⁹, when present, is independently halo, alkyl, alkoxy, cycloalkyloxy, heterocycloalkyl which is optionally substituted with 1 or 2 alkyl, heterocycloalkyloxy which is optionally substituted with 1 or 2 alkyl, or heterocycloalkylalkyloxy which is optionally substituted with 1 or 2 hydroxy;

each R¹⁰, when present, is independently; and

provided that when R¹ is cycloalkyl and R⁶ is aryl then the aryl is substituted with 1 or 2 groups independently selected from haloalkyl, haloalkoxy, cycloalkyloxy; and optionally a tautomer, a single stereoisomer or mixture of stereoisomers thereof and additionally optionally a pharmaceutically acceptable salt thereof.

[00079] In some or any embodiments, the compound of Formula I is that where R¹ is cycloalkyl; and all groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In some or any embodiments, the compound of Formula I is that where R¹ is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or bicyclo[1.1.1]pentyl; and all groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein.

[00080] In some or any embodiments, the compound of Formula I is that where R¹ is heterocycloalkyl attached to the C(O) group by a carbon atom; and all groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In some or any embodiments, the compound of Formula I is that where R¹ is heterocycloalkyl attached to the C(O) group by a carbon atom and attached to R⁶ via a nitrogen atom; and all groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In some or any embodiments, the compound of Formula I is that where R¹ is azetidiny, pyrrolidinyl, or piperidinyl, each of which is attached to the C(O) by a carbon atom; and all groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In some or any embodiments, the compound of

Formula I is that where R^1 is $N-(R^6)$ -azetidiny, $N-(R^6)$ -pyrrolidinyl, or $N-(R^6)$ -piperidinyl, each of which is attached to the C(O) by a carbon atom; and all groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In some or any embodiments, the compound of Formula I is that where R^1 is $N-(R^6)$ -pyrrolidinyl attached to the C(O) by a carbon atom; and all groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In some or any embodiments, the compound of Formula I is that where R^1 is $N-(R^6)$ -azetidin-3-yl, $N-(R^6)$ -pyrrolidin-3-yl, or $N-(R^6)$ -piperidin-3-yl, each of which is attached to the C(O) by a carbon atom; and all groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In some or any embodiments, the compound of Formula I is that where R^1 is $N-(R^6)$ -azetidin-3-yl attached to the C(O) by a carbon atom; and all groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein.

[00081] In some or any embodiments, the compound of Formula I is that where R^2 and R^3 together with the nitrogen to which they are attached form a 3-10 membered heterocycloalkyl ring which is optionally substituted with 1, 2, 3, or 4 R^8 ; and all groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In some or any embodiments, the compound of Formula I is that where R^2 and R^3 together with the nitrogen to which they are attached form a 4-7 membered heterocycloalkyl ring which is optionally substituted with 1, 2, 3, or 4 R^8 ; and all groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In some or any embodiments, the compound of Formula I is that where R^2 and R^3 together with the nitrogen to which they are attached form azetidiny, pyrrolidinyl, or piperidinyl, each of which is optionally substituted with 1, 2, 3, or 4 R^8 ; and all groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In some or any embodiments, the compound of Formula I is that where R^2 and R^3 together with the nitrogen to which they are attached form azetidiny or pyrrolidinyl group, each of which is optionally substituted with 1, 2, 3, or 4 R^8 ; and all groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein.

[00082] In some or any embodiments, the compound of Formula I is that where R^4 is aryl optionally independently substituted with 1 or 2 halo, alkoxy, cycloalkyloxy, heterocycloalkyloxy, hydroxyalkoxy, heterocycloalkyl, or heterocycloalkylalkoxy; or heteroaryl optionally independently substituted with halo or haloalkyl; and all groups are as defined in the Summary of the Invention or as defined in any of the embodiments described

herein. In some or any embodiments, the compound of Formula I is that where R^4 is aryl optionally independently substituted with 1 or 2 halo, cycloalkyloxy, or heterocycloalkyloxy; or heteroaryl optionally independently substituted with halo; and all groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein.

[00083] In some or any embodiments, the compound of Formula I is that where R^4 is phenyl or 2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl, where the phenyl is optionally independently substituted with 1 or 2 halo, alkoxy, cycloalkyloxy, heterocycloalkyloxy, hydroxyalkoxy, heterocycloalkyl, or heterocycloalkylalkoxy, and the 2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl is optionally substituted with halo or haloalkyl; and all groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In some or any embodiments, the compound of Formula I is that where R^4 is phenyl or 2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl, where the phenyl is optionally independently substituted with 1 or 2 halo, cycloalkyloxy, or heterocycloalkyloxy, and the 2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl is optionally substituted with halo; and all groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein.

[00084] In some or any embodiments, the compound of Formula I is that where R^4 is aryl optionally substituted with 1, 2, or 3 R^9 groups; and all groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In some or any embodiments, the compound of Formula I is that where R^4 is phenyl optionally substituted with 1, 2, or 3 R^9 groups; and all groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In some or any embodiments, the compound of Formula I is that where R^4 is phenyl optionally substituted with 1, 2, or 3 R^9 groups where each R^9 , when present, is independently halo, alkoxy, cycloalkyloxy, heterocycloalkyl, heterocycloalkyloxy optionally substituted with alkyl, heterocycloalkylalkyloxy optionally substituted with hydroxy; and all groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein.

[00085] In some or any embodiments, the compound of Formula I is that where R^4 is heteroaryl optionally substituted with 1, 2, or 3 R^9 groups; and all groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In some or any embodiments, the compound of Formula I is that where R^4 is pyridinyl or 2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl, optionally substituted with 1 or 2 R^9 groups; and all groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In some or any embodiments, the compound of Formula I is that where R^4

is pyridinyl or 2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl, optionally substituted with 1 or 2 R⁹ groups where each R⁹, when present, is independently selected from halo, alkyl, alkoxy, cycloalkyloxy; and all groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein.

[00086] In some or any embodiments, the compound of Formula I is that where R⁵ and R^{5a} are halo; and all groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein.

[00087] In some or any embodiments, the compound of Formula I is that where R⁵ is -OH and R^{5a} is hydrogen; and all groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein.

[00088] In some or any embodiments, the compound of Formula I is that where R⁶ is alkyl, aryl, arylalkyl, arylcarbonyl, cycloalkyl, cycloalkylalkyl, heterocylcoalkyl, heterocycloalkylalkyl, heteroaryl, or heteroarylalkyl; wherein the aryl and the heteroaryl, whether alone or as part of another group, are optionally substituted with 1 or 2 R¹⁰ groups; and wherein the heterocycloalkyl and cycloalkyl, whether alone or as part of another group, are optionally substituted with 1 or 2 groups independently selected from hydroxy, halo, haloalkyl, alkoxy, and alkyl; and all groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In some or any embodiments, the compound of Formula I is that where R⁶ is aryl, arylalkyl, arylcarbonyl, heterocylcoalkyl, heterocycloalkylalkyl, or heteroaryl; wherein the aryl and the heteroaryl, whether alone or as part of arylalkyl or heteroarylalkyl, are optionally substituted with 1 or 2 R¹⁰ groups; and wherein the heterocycloalkyl is optionally substituted with hydroxy; and all groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In some or any embodiments, the compound of Formula I is that where R⁶ is aryl or heteroaryl, wherein the aryl is optionally independently substituted with 1 or 2 halo, alkyl, cycloalkyloxy, or heterocycloalkyloxy; and the heteroaryl is optionally independently substituted with 1 or 2 halo, alkyl, or cycloalkyloxy; and all groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein.

[00089] In some or any embodiments, the compound of Formula I is that where R⁶ is alkoxycarbonyl; and all groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In some or any embodiments, the compound of Formula I is that where R⁶ is *tert*-butoxycarbonyl; and all groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein.

[00090] In some or any embodiments, the compound of Formula I is that where R⁶ is aryl optionally substituted with 1 or 2 R¹⁰ groups; and all groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In some or any embodiments, the compound of Formula I is that where R⁶ is phenyl or naphthyl optionally substituted with 1 or 2 R¹⁰ groups; and all groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In some or any embodiments, the compound of Formula I is that where R⁶ is phenyl optionally substituted with 1 or 2 R¹⁰ groups; and all groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In some or any embodiments, the compound of Formula I is that where R⁶ is phenyl optionally substituted with 1 or 2 R¹⁰ groups where each R¹⁰, when present, is independently selected from halo, haloalkyl, haloalkoxy, and cycloalkyloxy; and all groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In some or any embodiments, the compound of Formula I is that where R⁶ is naphthyl optionally substituted with 1 or 2 halo; and all groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein.

[00091] In some or any embodiments, the compound of Formula I is that where R⁶ is heteroaryl optionally substituted with 1 or 2 R¹⁰ groups; and all groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In some or any embodiments, the compound of Formula I is that where R⁶ is pyridinyl, thiazolyl, benzothiazolyl, or 4,5,6,7-tetrahydrobenzo[d]thiazolyl, each of which is optionally substituted with 1 or 2 R¹⁰ groups; and all groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In some or any embodiments, the compound of Formula I is that where R⁶ is pyridinyl, thiazolyl, benzothiazolyl, or 4,5,6,7-tetrahydrobenzo[d]thiazolyl, each of which is optionally substituted with 1 or 2 halo; and all groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein.

[00092] In some or any embodiments, the compound of Formula I is that where R⁶ is arylalkyl where the aryl is optionally substituted with 1 or 2 R¹⁰ groups; and all groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In some or any embodiments, the compound of Formula I is that where R⁶ is phenylalkyl where the phenyl is optionally substituted with 1 or 2 R¹⁰ groups; and all groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In some or any embodiments, the compound of Formula I is that where R⁶

is phenylalkyl where the phenyl is optionally substituted with 1 or 2 halo; and all groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In some or any embodiments, the compound of Formula I is that where R^6 is naphthylmethyl, phenylmethyl or phenethyl where the phenyl is optionally substituted with 1 or 2 R^{10} groups; and all groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In some or any embodiments, the compound of Formula I is that where R^6 is phenylmethyl where the phenyl is optionally substituted with 1 or 2 R^{10} groups; and all groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein.

[00093] In some or any embodiments, the compound of Formula I is that where R^6 is heteroarylalkyl where the heteroaryl is optionally substituted with 1 or 2 R^{10} groups; and all groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In some or any embodiments, the compound of Formula I is that where R^6 is pyridinylalkyl where the heteroaryl is optionally substituted with 1 or 2 R^{10} groups; and all groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In some or any embodiments, the compound of Formula I is that where R^6 is pyridinylmethyl where the heteroaryl is optionally substituted with 1 or 2 R^{10} groups; and all groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein.

[00094] In some or any embodiments, the compound of Formula I is that where R^6 is cycloalkyl where the cycloalkyl is optionally substituted with 1 or 2 groups independently selected from hydroxy, halo, haloalkyl, alkoxy, alkyl, alkylcarbonyl, and alkoxy carbonyl; and all groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In some or any embodiments, the compound of Formula I is that where R^6 is cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl each of which is optionally substituted with 1 or 2 groups independently selected from hydroxy, halo, haloalkyl, alkoxy, alkyl, alkylcarbonyl, and alkoxy carbonyl; and all groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In some or any embodiments, the compound of Formula I is that where R^6 is cyclopentyl or cyclohexyl each of which is optionally substituted with 1 or 2 groups independently selected from hydroxy, halo, haloalkyl, alkoxy, alkyl, alkylcarbonyl, and alkoxy carbonyl; and all groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In some or any embodiments, the compound of Formula I is that where R^6 is unsubstituted cyclopropyl, unsubstituted cyclobutyl, unsubstituted

cyclopentyl, or unsubstituted cyclohexyl; and all groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In some or any embodiments, the compound of Formula I is that where R^6 is unsubstituted cyclopentyl or unsubstituted cyclohexyl; and all groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein.

[00095] In some or any embodiments, the compound of Formula I is that where R^6 is cycloalkylalkyl where the cycloalkyl is optionally substituted with 1 or 2 groups independently selected from hydroxy, halo, haloalkyl, alkoxy, alkyl, alkylcarbonyl, and alkoxy carbonyl; and all groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In some or any embodiments, the compound of Formula I is that where R^6 is cycloalkylmethyl where the cycloalkyl is optionally substituted with 1 or 2 groups independently selected from hydroxy, halo, haloalkyl, alkoxy, alkyl, alkylcarbonyl, and alkoxy carbonyl; and all groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In some or any embodiments, the compound of Formula I is that where R^6 is unsubstituted cyclopropylmethyl, unsubstituted cyclobutylmethyl, unsubstituted cyclopentylmethyl, or unsubstituted cyclohexylmethyl; and all groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In some or any embodiments, the compound of Formula I is that where R^6 is unsubstituted cyclopentylmethyl or unsubstituted cyclohexylmethyl; and all groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein.

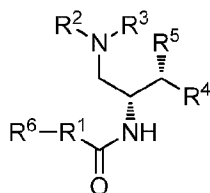
[00096] In some or any embodiments, the compound of Formula I is that where R^6 is heterocycloalkyl where the heterocycloalkyl is optionally substituted with 1 or 2 groups independently selected from hydroxy, halo, haloalkyl, alkoxy, alkyl, alkylcarbonyl, and alkoxy carbonyl; and all groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In some or any embodiments, the compound of Formula I is that where R^6 is unsubstituted tetrahydropyranyl; and all groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein.

[00097] In some or any embodiments, the compound of Formula I is that where R^6 is heterocycloalkylalkyl where the heterocycloalkyl is optionally substituted with 1 or 2 groups independently selected from hydroxy, halo, haloalkyl, alkoxy, alkyl, alkylcarbonyl, and alkoxy carbonyl; and all groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In some or any embodiments, the compound of Formula I is that where R^6 is heterocycloalkylmethyl where the heterocycloalkyl is optionally

substituted with 1 or 2 groups independently selected from hydroxy, halo, haloalkyl, alkoxy, alkyl, alkylcarbonyl, and alkoxy carbonyl; and all groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In some or any embodiments, the compound of Formula I is that where R^6 is tetrahydropyranylmethyl optionally substituted with 1 or 2 groups independently selected from hydroxy, halo, haloalkyl, alkoxy, alkyl, alkylcarbonyl, and alkoxy carbonyl; and all groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In some or any embodiments, the compound of Formula I is that where R^6 is tetrahydropyranylmethyl optionally substituted with 1 or 2 hydroxy; and all groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein.

[00098] In some or any embodiments, the compound of Formula I is that where R^6 is $-C(O)NR^{6a}R^{6b}$; and all groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In some or any embodiments, the compound of Formula I is that where R^6 is $-C(O)NR^{6a}R^{6b}$ where R^{6a} is hydrogen; and all groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In some or any embodiments, the compound of Formula I is that where R^6 is $-C(O)NR^{6a}R^{6b}$ where R^{6a} is hydrogen and R^{6b} is aryl or heteroaryl each of which is optionally substituted with halo; and all groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In some or any embodiments, the compound of Formula I is that where R^6 is $-C(O)NR^{6a}R^{6b}$ where R^{6a} is hydrogen and R^{6b} is phenyl optionally substituted with 1 or 2 halo; and all groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein.

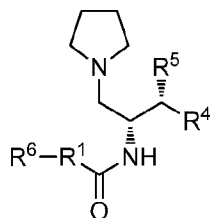
[00099] In some or any embodiments, the compound of Formula I is according to Formula I(a):



Formula I(a)

where all groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein.

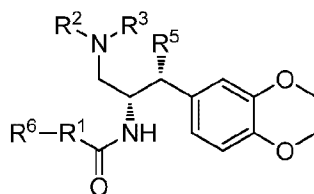
[000100] In some or any embodiments, the compound of Formula I is according to Formula I(b):



Formula I(b)

where all groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein.

[000101] In some or any embodiments, the compound of Formula I is according to Formula I(c):



Formula I(c)

where all groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In some or any embodiments, the compound of Formula I is according to Formula I(c) where:

R¹ is pyrrolidinyl attached to the C(O) by a carbon atom, and is optionally substituted with hydroxy;

R² and R³ together with the nitrogen to which they are attached form a azetidiny, pyrrolidinyl, or piperidinyl ring, which is optionally substituted with 1 or 2 R⁸;

R⁵ is -OH and R^{5a} is hydrogen;

R⁶ is aryl, arylalkyl, arylcarbonyl, cycloalkyl, cycloalkylalkyl, heterocylcoalkyl, heterocycloalkylalkyl, heteroaryl, or heteroarylalkyl; wherein the aryl and the heteroaryl, whether alone or as part of another group, are optionally substituted with 1 or 2 R¹⁰ groups; and wherein the heterocycloalkyl and cycloalkyl, whether alone or as part of another group, are optionally substituted with 1 or 2 groups independently selected from hydroxy, halo, haloalkyl, alkoxy, and alkyl; or R² and R³ together with the nitrogen to which they are attached form a azetidiny or pyrrolidinyl ring; and R⁶ is phenyl or naphthyl optionally substituted with chloro or fluoro.

[000102] In some or any embodiments, the compound of Formula I is according to Formula I(a) or I(c) and R^2 and R^3 together with the nitrogen to which they are attached form a 3-10 membered heterocycloalkyl ring which is optionally substituted with 1, 2, 3, or 4 R^8 ; and all groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein.

[000103] In some or any embodiments, the compound of Formula I is according to Formula I(a), I(b), or I(c) and R^5 is hydroxy; and all groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein.

[000104] In some or any embodiments, the compound of Formula I is according to Formula I(a), I(b), or I(c) and R^1 is cycloalkyl; and all groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein.

[000105] In some or any embodiments, the compound of Formula I is according to Formula I(a), I(b), or I(c) and R^1 is heterocycloalkyl attached to the C(O) by a carbon atom; and all groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein.

[000106] In some or any embodiments, the compound of Formula I is according to Formula I(a) or I(c) and R^2 and R^3 together with the nitrogen to which they are attached form a 3-10 membered heterocycloalkyl ring which is optionally substituted with 1, 2, 3, or 4 R^8 ; R^1 is heterocycloalkyl attached to the C(O) by a carbon atom; and all groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein.

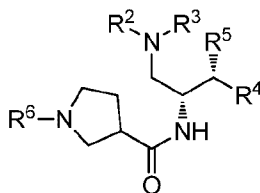
[000107] In some or any embodiments, the compound of Formula I is according to Formula I(a) or I(c) and R^2 and R^3 together with the nitrogen to which they are attached form a 3-10 membered heterocycloalkyl ring which is optionally substituted with 1, 2, 3, or 4 R^8 ; R^1 is heterocycloalkyl attached to the C(O) by a carbon atom; R^5 is hydroxy; and all groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein.

[000108] In some or any embodiments, the compound of Formula I is according to Formula I(b) and R^5 is hydroxy; and all groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein.

[000109] In some or any embodiments, the compound of Formula I is according to Formula I(b) and R^1 is heterocycloalkyl attached to the C(O) by a carbon atom, R^5 is hydroxy, and all groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein.

[000110] In some or any embodiments, the compound of Formula I is according to Formula I(a) or I(c) and R^2 and R^3 together with the nitrogen to which they are attached form a 3-10 membered heterocycloalkyl ring which is optionally substituted with 1, 2, 3, or 4 R^8 ; R^5 is hydroxy; and all groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein.

[000111] In some or any embodiments, the compound of Formula I is according to Formula I(d):



Formula I(d)

where all groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In some or any embodiments, the compound of Formula I is according to Formula I(d) where:

R^2 and R^3 together with the nitrogen to which they are attached form a azetidiny, pyrrolidinyl, or piperidinyl ring;

R^4 is aryl or heteroaryl each of which is optionally substituted with 1 or 2 R^9 groups;

R^5 is -OH and R^{5a} is hydrogen;

R^6 is alkyl, aryl, arylalkyl, arylcarbonyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, or heteroaryl; wherein the aryl and the heteroaryl, whether alone or as part of arylalkyl or heteroarylalkyl, are optionally substituted with 1 or 2 R^{10} groups; and wherein the heterocycloalkyl is optionally substituted with hydroxy;

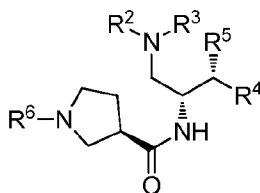
each R^9 , when present, is independently halo, haloalkyl, alkyl, alkoxy, haloalkoxy, hydroxyalkoxy, alkenyloxy, cycloalkyloxy, cycloalkylthio, heterocycloalkyl, heterocycloalkyloxy, or heterocycloalkylalkyloxy; where each heterocycloalkyl, either alone or as part of another group, is optionally substituted with an alkyl group;

each R^{10} , when present, is independently is cyano, halo, haloalkyl, alkyl, haloalkoxy, cycloalkyloxy, aryl, aryloxy, or heteroaryloxy; where each aryl or heteroaryl either alone or as part of another group, are independently optionally substituted with 1 or 2 halo or alkyl; and optionally a tautomer, a single stereoisomer or mixture of stereoisomers thereof and additionally optionally a pharmaceutically acceptable salt thereof.

[000112] In some or any embodiments, the compound of Formula I is according to Formula I(d) where R^2 and R^3 together with the nitrogen to which they are attached form a azetidiny or pyrrolidinyl ring; R^4 is phenyl or 2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl, where the phenyl is optionally independently substituted with 1 or 2 halo, cycloalkyloxy, or heterocycloalkyloxy, and the 2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl is optionally substituted with halo; and R^6 is aryl or heteroaryl, each optionally substituted with chloro, fluoro, or alkyl; or R^6 is phenyl or naphthyl optionally independently substituted with chloro or fluoro.

[000113] In some or any embodiments, the compound of Formula I(d) is that where R^2 and R^3 together with the nitrogen to which they are attached form a 3-10 membered heterocycloalkyl ring which is optionally substituted with 1, 2, 3, or 4 R^8 ; and all groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In some or any embodiments, the compound of Formula I(d) is that where R^5 is hydroxy; and all groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In some or any embodiments, the compound of Formula I(d) is that where R^4 is 2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl; and all groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein.

[000114] In some or any embodiments, the compound of Formula I is according to Formula I(d1):

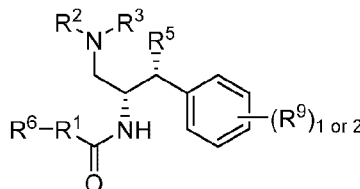


Formula I(d1)

[000115] where all groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In some or any embodiments, the compound of Formula I(d1) is that where R^2 and R^3 together with the nitrogen to which they are attached form a 3-10 membered heterocycloalkyl ring which is optionally substituted with 1, 2, 3, or 4 R^8 ; and all groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In some or any embodiments, the compound of Formula I(d1) is that where R^5 is hydroxy; and all groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In some or any embodiments, the compound of Formula I(d1) is that where R^4 is 2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl; and all

groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein.

[000116] In some or any embodiments, the compound of Formula I is according to Formula I(d2):



Formula I(d2)

where all groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In some or any embodiments, the compound of Formula I(d2) is that where R¹ is pyrrolidinyl attached to the C(O) by a carbon atom, and is optionally substituted with hydroxy; R² and R³ together with the nitrogen to which they are attached form azetidiny or pyrrolidinyl; R⁵ is -OH and R^{5a} is hydrogen; and each R⁹ is independently halo, hydroxyalkoxy, cycloalkyloxy, heterocycloalkyloxy, or heterocycloalkylalkyloxy; and R⁶ is aryl or heteroaryl, each optionally substituted with chloro, fluoro, or alkyl; or R⁶ is phenyl optionally independently substituted with chloro or fluoro. In some or any embodiments, the compound of Formula I(d2) is that where:

R¹ is *N*-(R⁶)-azetidiny, *N*-(R⁶)-pyrrolidinyl, or *N*-(R⁶)-piperidinyl, each of which is attached to the C(O) by a carbon atom, and is optionally substituted with hydroxy;

R² and R³ together with the nitrogen to which they are attached form a 4-6 membered heterocycloalkyl ring with 1 or 2 nitrogen atoms;

R⁵ is -OH and R^{5a} is hydrogen;

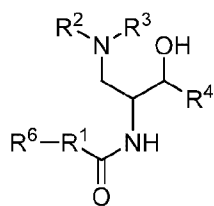
R⁶ is alkyl, aryl, arylalkyl, arylcarbonyl, cycloalkyl, cycloalkylalkyl, heterocylcoalkyl, heterocycloalkylalkyl, heteroaryl, or heteroarylalkyl; wherein the aryl and the heteroaryl, whether alone or as part of another group, are optionally substituted with 1 or 2 R¹⁰ groups; and wherein the heterocycloalkyl and cycloalkyl, whether alone or as part of another group, are optionally substituted with 1 or 2 groups independently selected from hydroxy, halo, haloalkyl, alkoxy, and alkyl;

each R⁹, when present, is independently cyano, nitro, halo, haloalkyl, alkyl, hydroxy, alkoxy, haloalkoxy, hydroxyalkoxy, alkenyloxy, cycloalkyloxy, cycloalkylalkyloxy, cycloalkylthio, heterocycloalkyl, heterocycloalkyloxy, or heterocycloalkylalkyloxy; where each heterocycloalkyl, either alone or as part of another group, is optionally substituted with

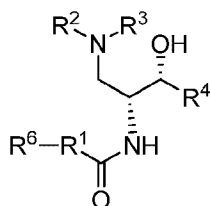
1 or 2 groups independently selected from alkyl, hydroxy, alkylcarbonyl, and alkoxy carbonyl groups;

each R^{10} , when present, is independently is cyano, halo, haloalkyl, alkyl, hydroxy, alkoxy, haloalkoxy, cycloalkyloxy, cycloalkylalkyloxy, aryl, aryloxy, heteroaryloxy, heterocycloalkyl, heterocycloalkyloxy, or heterocycloalkylalkyloxy; where each aryl or heteroaryl either alone or as part of another group, are independently optionally substituted with 1 or 2 halo or alkyl groups; and each heterocycloalkyl, either alone or as part of another group, is optionally substituted with 1 or 2 groups independently selected from alkyl and hydroxy; and optionally a tautomer, a single stereoisomer or mixture of stereoisomers thereof and additionally optionally a pharmaceutically acceptable salt thereof.

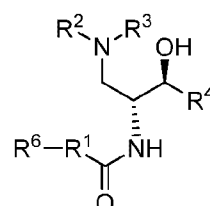
[000117] In some or any embodiments, the compound of Formula I is according to Formula I(e), Formula I(e1), or Formula I(e2):



Formula I(e)



Formula I(e1)



Formula I(e2)

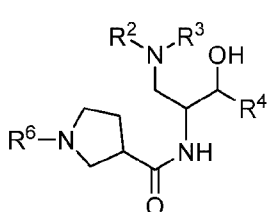
where all groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein. In some or any embodiments, the compound of Formula I is according to Formula I(c) where:

R^1 is pyrrolidinyl attached to the $C(O)$ by a carbon atom, and is optionally substituted with hydroxy;

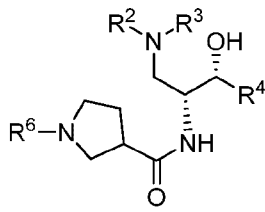
R^2 and R^3 together with the nitrogen to which they are attached form a azetidiny, pyrrolidinyl, or piperidinyl ring, which is optionally substituted with 1 or 2 R^8 ;

R^6 is aryl, arylalkyl, arylcarbonyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, or heteroarylalkyl; wherein the aryl and the heteroaryl, whether alone or as part of another group, are optionally substituted with 1 or 2 R^{10} groups; and wherein the heterocycloalkyl and cycloalkyl, whether alone or as part of another group, are optionally substituted with 1 or 2 groups independently selected from hydroxy, halo, haloalkyl, alkoxy, and alkyl; or R^2 and R^3 together with the nitrogen to which they are attached form a azetidiny or pyrrolidinyl ring; and R^6 is phenyl or naphthyl optionally substituted with chloro or fluoro.

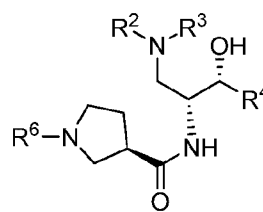
[000118] In some or any embodiments, the compound of Formula I is according to Formula I(f), Formula I(f1), or Formula I(f2):



Formula I(f)



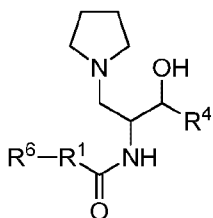
Formula I(f1)



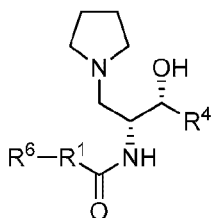
Formula I(f2)

where all groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein.

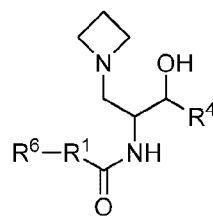
[000119] In some or any embodiments, the compound of Formula I is according to Formula I(g), Formula I(g1), Formula I(h), or Formula I(h1):



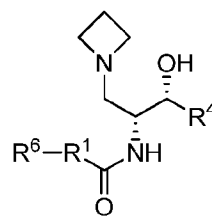
Formula I(g)



Formula I(g1)



Formula I(h)

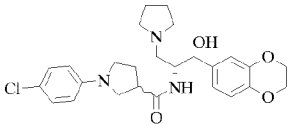
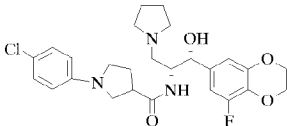


Formula I(h1)

where all groups are as defined in the Summary of the Invention or as defined in any of the embodiments described herein.

[000120] In some or any embodiments, the compound of Formula I is according to the compounds in Table 1:

Table 1.

Example No.	Name	Structure
1C	1-(4-chlorophenyl)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)pyrrolidine-3-carboxamide	
2A	1-(4-chlorophenyl)-N-((1R,2R)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)pyrrolidine-3-carboxamide	

Example No.	Name	Structure
3A	N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(4-chlorophenyl)pyrrolidine-3-carboxamide	
1	(R)-1-(4-chlorophenyl)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)pyrrolidine-3-carboxamide	
1D	(S)-1-(4-chlorophenyl)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)pyrrolidine-3-carboxamide	
5D	N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-((4-hydroxytetrahydro-2H-pyran-4-yl)methyl)pyrrolidine-3-carboxamide	
6	N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(4-(trifluoromethyl)phenyl)pyrrolidine-3-carboxamide	
8D	(S)-1-(3,4-dichlorophenyl)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)pyrrolidine-3-carboxamide	

Example No.	Name	Structure
8	(R)-1-(3,4-dichlorophenyl)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)pyrrolidine-3-carboxamide	
9D	N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(tetrahydro-2H-pyran-4-yl)pyrrolidine-3-carboxamide	
10	N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(4-(trifluoromethoxy)phenyl)pyrrolidine-3-carboxamide	
5	(R)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-((4-hydroxytetrahydro-2H-pyran-4-yl)methyl)pyrrolidine-3-carboxamide	
5E	(S)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-((4-hydroxytetrahydro-2H-pyran-4-yl)methyl)pyrrolidine-3-carboxamide	
11	1-cyclopentyl-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)pyrrolidine-3-carboxamide	

Example No.	Name	Structure
12D	(S)-1-(2,4-dichlorophenyl)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)pyrrolidine-3-carboxamide	
12	(R)-1-(2,4-dichlorophenyl)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)pyrrolidine-3-carboxamide	
13	(R)-1-(4-chlorophenyl)-N-((1R,2R)-1-(6-cyclopropoxypyridin-3-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)pyrrolidine-3-carboxamide	
13C	(S)-1-(4-chlorophenyl)-N-((1R,2R)-1-(6-cyclopropoxypyridin-3-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)pyrrolidine-3-carboxamide	
14C	N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(6-fluoronaphthalen-2-yl)pyrrolidine-3-carboxamide	
2	(R)-1-(4-chlorophenyl)-N-((1R,2R)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)pyrrolidine-3-carboxamide	

Example No.	Name	Structure
2B	(S)-1-(4-chlorophenyl)-N-((1R,2R)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)pyrrolidine-3-carboxamide	
3	(S)-N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(4-chlorophenyl)pyrrolidine-3-carboxamide	
3B	(R)-N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(4-chlorophenyl)pyrrolidine-3-carboxamide	
9	(R)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(tetrahydro-2H-pyran-4-yl)pyrrolidine-3-carboxamide	
9E	(S)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(tetrahydro-2H-pyran-4-yl)pyrrolidine-3-carboxamide	
15C	1-(4-chlorobenzyl)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)pyrrolidine-3-carboxamide	
14D	(R)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(6-fluoronaphthalen-2-yl)pyrrolidine-3-carboxamide	

Example No.	Name	Structure
14	(S)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(6-fluoronaphthalen-2-yl)pyrrolidine-3-carboxamide	
36F	N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl)pyrrolidine-3-carboxamide	
17D	(S)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(thiazol-2-yl)pyrrolidine-3-carboxamide	
19	1-(4-chloro-3-cyclopropoxyphenyl)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)pyrrolidine-3-carboxamide	
20D	1-(3-chloro-4-cyclopropoxyphenyl)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)pyrrolidine-3-carboxamide	
22C	N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(pyridin-2-yl)pyrrolidine-3-carboxamide	

Example No.	Name	Structure
17	(R)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(thiazol-2-yl)pyrrolidine-3-carboxamide	
21E	1-(4-chlorophenethyl)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)pyrrolidine-3-carboxamide	
15	(R)-1-(4-chlorobenzyl)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)pyrrolidine-3-carboxamide	
15D	(S)-1-(4-chlorobenzyl)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)pyrrolidine-3-carboxamide	
36	(R)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl)pyrrolidine-3-carboxamide	
36G	(S)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl)pyrrolidine-3-carboxamide	
20	(R)-1-(3-chloro-4-cyclopropoxyphenyl)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)pyrrolidine-3-carboxamide	

Example No.	Name	Structure
20E	(S)-1-(3-chloro-4-cyclopropoxyphenyl)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)pyrrolidine-3-carboxamide	
23	(R)-N-((1R,2R)-1-(3-chloro-4-isopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(4-chlorophenyl)pyrrolidine-3-carboxamide	
23B	(S)-N-((1R,2R)-1-(3-chloro-4-isopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(4-chlorophenyl)pyrrolidine-3-carboxamide	
24B	N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(4-fluorophenyl)pyrrolidine-3-carboxamide	
25	(R)-N-((1R,2R)-3-(azetidin-1-yl)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxypropan-2-yl)-1-(4-chlorophenyl)pyrrolidine-3-carboxamide	
25B	(S)-N-((1R,2R)-3-(azetidin-1-yl)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxypropan-2-yl)-1-(4-chlorophenyl)pyrrolidine-3-carboxamide	

Example No.	Name	Structure
26	1-cyclohexyl-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)pyrrolidine-3-carboxamide	
27	(R)-N-((1R,2R)-1-(6-cyclopropoxy-pyridin-3-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(4-fluorophenyl)pyrrolidine-3-carboxamide	
27C	(S)-N-((1R,2R)-1-(6-cyclopropoxy-pyridin-3-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(4-fluorophenyl)pyrrolidine-3-carboxamide	
28C	1-(5-chloropyridin-2-yl)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)pyrrolidine-3-carboxamide	
22	(R)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(pyridin-2-yl)pyrrolidine-3-carboxamide	
22D	(S)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(pyridin-2-yl)pyrrolidine-3-carboxamide	
29	(R)-1-(4-chlorophenyl)-N-((1R,2R)-1-hydroxy-1-(6-isopropoxy-pyridin-3-yl)-3-(pyrrolidin-1-yl)propan-2-yl)pyrrolidine-3-carboxamide	

Example No.	Name	Structure
29B	(S)-1-(4-chlorophenyl)-N-((1R,2R)-1-hydroxy-1-(6-isopropoxypyridin-3-yl)-3-(pyrrolidin-1-yl)propan-2-yl)pyrrolidine-3-carboxamide	
30	1-butyl-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)pyrrolidine-3-carboxamide	
31	(R)-1-(4-fluorophenyl)-N-((1R,2R)-1-hydroxy-1-(6-isopropoxypyridin-3-yl)-3-(pyrrolidin-1-yl)propan-2-yl)pyrrolidine-3-carboxamide	
31B	(S)-1-(4-fluorophenyl)-N-((1S,2R)-1-hydroxy-1-(6-isopropoxypyridin-3-yl)-3-(pyrrolidin-1-yl)propan-2-yl)pyrrolidine-3-carboxamide	
32	(R)-N-((1R,2R)-1-(3-chloro-4-((tetrahydro-2H-pyran-4-yl)oxy)phenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(4-fluorophenyl)pyrrolidine-3-carboxamide	
32A	(S)-N-((1R,2R)-1-(3-chloro-4-((tetrahydro-2H-pyran-4-yl)oxy)phenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(4-fluorophenyl)pyrrolidine-3-carboxamide	
21	(R)-1-(4-chlorophenethyl)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)pyrrolidine-3-carboxamide	

Example No.	Name	Structure
21F	(S)-1-(4-chlorophenethyl)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)pyrrolidine-3-carboxamide	
28	(R)-1-(5-chloropyridin-2-yl)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)pyrrolidine-3-carboxamide	
28D	(S)-1-(5-chloropyridin-2-yl)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)pyrrolidine-3-carboxamide	
54	(R)-N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(pyridin-2-yl)pyrrolidine-3-carboxamide	
33	(R)-1-(4-chlorophenyl)-N-((1R,2R)-1-hydroxy-3-(pyrrolidin-1-yl)-1-(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)propan-2-yl)pyrrolidine-3-carboxamide	
33A	(S)-1-(4-chlorophenyl)-N-((1R,2R)-1-hydroxy-3-(pyrrolidin-1-yl)-1-(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)propan-2-yl)pyrrolidine-3-carboxamide	
34	(R)-1-(4-fluorophenyl)-N-((1R,2R)-1-hydroxy-3-(pyrrolidin-1-yl)-1-(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)propan-2-yl)pyrrolidine-3-carboxamide	

Example No.	Name	Structure
34A	(S)-1-(4-fluorophenyl)-N-((1R,2R)-1-hydroxy-3-(pyrrolidin-1-yl)-1-(6-(2,2,2-trifluoroethoxy)pyridin-3-yl)propan-2-yl)pyrrolidine-3-carboxamide	
24	(R)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(4-fluorophenyl)pyrrolidine-3-carboxamide	
24C	(S)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(4-fluorophenyl)pyrrolidine-3-carboxamide	
35	(R)-N-((1R,2R)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(4-fluorophenyl)pyrrolidine-3-carboxamide	
35A	(S)-N-((1R,2R)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(4-fluorophenyl)pyrrolidine-3-carboxamide	
44C	(S)-1-(4-chlorophenyl)-N-((1R,2R)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(piperidin-1-yl)propan-2-yl)pyrrolidine-3-carboxamide	
44	(R)-1-(4-chlorophenyl)-N-((1R,2R)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(piperidin-1-yl)propan-2-yl)pyrrolidine-3-carboxamide	

Example No.	Name	Structure
43D	1-(4-chlorophenyl)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(piperidin-1-yl)propan-2-yl)pyrrolidine-3-carboxamide	
54A	(S)-N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(pyridin-2-yl)pyrrolidine-3-carboxamide	
45	(R)-N-((1R,2R)-1-(3-chloro-4-((tetrahydro-2H-pyran-4-yl)oxy)phenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(4-chlorophenyl)pyrrolidine-3-carboxamide	
45A	(S)-N-((1R,2R)-1-(3-chloro-4-((tetrahydro-2H-pyran-4-yl)oxy)phenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(4-chlorophenyl)pyrrolidine-3-carboxamide	
55A	1-(2,3-dihydro-1H-inden-2-yl)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)pyrrolidine-3-carboxamide	
56D	1-(2-cyclopropoxypyridin-4-yl)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)pyrrolidine-3-carboxamide	
46A	N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(piperidin-1-yl)propan-2-yl)-1-(4-fluorophenyl)pyrrolidine-3-carboxamide	

Example No.	Name	Structure
47A	N-((1R,2R)-3-(azetidin-1-yl)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxypropan-2-yl)-1-(6-fluoronaphthalen-2-yl)pyrrolidine-3-carboxamide	
48	(R)-N-((1R,2R)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(pyridin-2-yl)pyrrolidine-3-carboxamide	
48A	(S)-N-((1R,2R)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(pyridin-2-yl)pyrrolidine-3-carboxamide	
49	(R)-N-((1R,2R)-1-(3-chloro-4-((1-methylpiperidin-4-yl)oxy)phenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(4-chlorophenyl)pyrrolidine-3-carboxamide	
49A	(S)-N-((1R,2R)-1-(3-chloro-4-((1-methylpiperidin-4-yl)oxy)phenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(4-chlorophenyl)pyrrolidine-3-carboxamide	
50	(R)-N-((1R,2R)-1-(3-chloro-4-((tetrahydro-2H-pyran-4-yl)oxy)phenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(6-fluoronaphthalen-2-yl)pyrrolidine-3-carboxamide	
50A	(S)-N-((1R,2R)-1-(3-chloro-4-((tetrahydro-2H-pyran-4-yl)oxy)phenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(6-fluoronaphthalen-2-yl)pyrrolidine-3-carboxamide	

Example No.	Name	Structure
51	(R)-1-(4-chlorophenyl)-N-((1R,2R)-1-(2,2-dimethylchroman-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)pyrrolidine-3-carboxamide	
51A	(S)-1-(4-chlorophenyl)-N-((1R,2R)-1-(2,2-dimethylchroman-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)pyrrolidine-3-carboxamide	
43	(R)-1-(4-chlorophenyl)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(piperidin-1-yl)propan-2-yl)pyrrolidine-3-carboxamide	
43E	(S)-1-(4-chlorophenyl)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(piperidin-1-yl)propan-2-yl)pyrrolidine-3-carboxamide	
56	(R)-1-(2-cyclopropoxypyridin-4-yl)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)pyrrolidine-3-carboxamide	
56E	(S)-1-(2-cyclopropoxypyridin-4-yl)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)pyrrolidine-3-carboxamide	
52	(R)-N-((1R,2R)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(6-fluoronaphthalen-2-yl)pyrrolidine-3-carboxamide	

Example No.	Name	Structure
52A	(S)-N-((1R,2R)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(6-fluoronaphthalen-2-yl)pyrrolidine-3-carboxamide	
55	(R)-1-(2,3-dihydro-1H-inden-2-yl)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)pyrrolidine-3-carboxamide	
55B	(S)-1-(2,3-dihydro-1H-inden-2-yl)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)pyrrolidine-3-carboxamide	
46	(R)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(piperidin-1-yl)propan-2-yl)-1-(4-fluorophenyl)pyrrolidine-3-carboxamide	
46B	(S)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(piperidin-1-yl)propan-2-yl)-1-(4-fluorophenyl)pyrrolidine-3-carboxamide	
53C	1-(benzo[b]thiophen-6-yl)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)pyrrolidine-3-carboxamide	
47	(R)-N-((1R,2R)-3-(azetidin-1-yl)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxypropan-2-yl)-1-(6-fluoronaphthalen-2-yl)pyrrolidine-3-carboxamide	

Example No.	Name	Structure
47B	(S)-N-((1R,2R)-3-(azetidin-1-yl)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxypropan-2-yl)-1-(6-fluoronaphthalen-2-yl)pyrrolidine-3-carboxamide	
57A	(S)-N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(5-chloropyridin-2-yl)pyrrolidine-3-carboxamide	
57	(R)-N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(5-chloropyridin-2-yl)pyrrolidine-3-carboxamide	
58	(R)-1-(6-cyclopropoxypyridin-3-yl)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)pyrrolidine-3-carboxamide	
58D	(S)-1-(6-cyclopropoxypyridin-3-yl)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)pyrrolidine-3-carboxamide	
59	(R)-N-((1R,2R)-1-(3-chloro-4-(oxetan-3-yloxy)phenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(4-chlorophenyl)pyrrolidine-3-carboxamide	
60	(R)-N-((1R,2R)-1-(4-(2-(azetidin-1-yl)ethoxy)-3-chlorophenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(4-chlorophenyl)pyrrolidine-3-carboxamide	

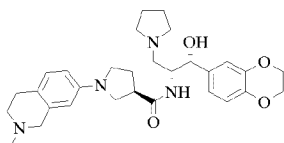
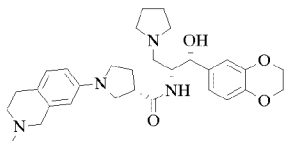
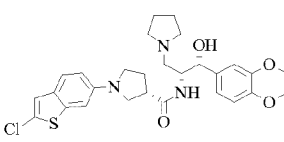
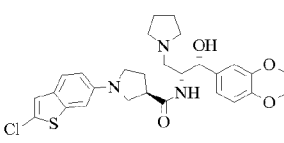
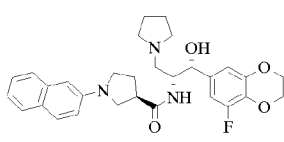
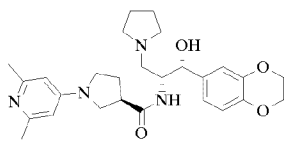
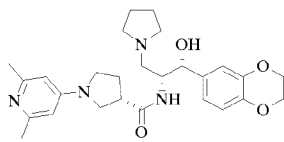
Example No.	Name	Structure
60A	(S)-N-((1R,2R)-1-(4-(2-(azetidin-1-yl)ethoxy)-3-chlorophenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(4-chlorophenyl)pyrrolidine-3-carboxamide	
61C	N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(1-methyl-1H-indazol-6-yl)pyrrolidine-3-carboxamide	
62	(R)-1-(4-chlorophenyl)-N-((1R,2R)-1-hydroxy-1-(6-(oxetan-3-yloxy)pyridin-3-yl)-3-(pyrrolidin-1-yl)propan-2-yl)pyrrolidine-3-carboxamide	
63C	N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)pyrrolidine-3-carboxamide	
64	N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(2,2-dimethylchroman-6-yl)pyrrolidine-3-carboxamide	
65	(R)-1-(4-chlorophenyl)-N-((1R,2R)-1-(4-cyclopropoxy-3-fluorophenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)pyrrolidine-3-carboxamide	
66	(R)-N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(piperidin-1-yl)propan-2-yl)-1-(4-chlorophenyl)pyrrolidine-3-carboxamide	

Example No.	Name	Structure
67C	(S)-N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(naphthalen-2-yl)pyrrolidine-3-carboxamide	
68C	(S)-N-((1R,2S)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(quinolin-2-yl)pyrrolidine-3-carboxamide	
61	(R)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(1-methyl-1H-indazol-6-yl)pyrrolidine-3-carboxamide	
61D	(S)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(1-methyl-1H-indazol-6-yl)pyrrolidine-3-carboxamide	
69	(R)-N-((1R,2R)-1-(4-cyclopropoxy-3-fluorophenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(4-fluorophenyl)pyrrolidine-3-carboxamide	
69A	(S)-N-((1R,2R)-1-(4-cyclopropoxy-3-fluorophenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(4-fluorophenyl)pyrrolidine-3-carboxamide	
70	(R)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(naphthalen-2-yl)pyrrolidine-3-carboxamide	

Example No.	Name	Structure
70A	(S)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(naphthalen-2-yl)pyrrolidine-3-carboxamide	
71E	N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(2,2-dimethylchroman-7-yl)pyrrolidine-3-carboxamide	
72A	N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(quinolin-2-yl)pyrrolidine-3-carboxamide	
73	(R)-N-((1R,2R)-3-(azetidin-1-yl)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxypropan-2-yl)-1-(4-chlorophenyl)pyrrolidine-3-carboxamide	
67	(R)-N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(naphthalen-2-yl)pyrrolidine-3-carboxamide	
53	(R)-1-(benzo[b]thiophen-6-yl)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)pyrrolidine-3-carboxamide	
53D	(S)-1-(benzo[b]thiophen-6-yl)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)pyrrolidine-3-carboxamide	

Example No.	Name	Structure
74	(R)-N-((1R,2R)-1-(3-chloro-4-morpholinophenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(4-chlorophenyl)pyrrolidine-3-carboxamide	
74C	(S)-N-((1R,2R)-1-(3-chloro-4-morpholinophenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(4-chlorophenyl)pyrrolidine-3-carboxamide	
75	(R)-N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(3-(pyridin-2-yloxy)phenyl)pyrrolidine-3-carboxamide	
75E	(S)-N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(3-(pyridin-2-yloxy)phenyl)pyrrolidine-3-carboxamide	
76D	1-(2-chlorobenzo[b]thiophen-6-yl)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)pyrrolidine-3-carboxamide	
77	N-[2-(2H,3H-benzo[e]1,4-dioxan-6-yl)(1R,2R)-2-hydroxy-1-(pyrrolidinylmethyl)ethyl][1-(4-chlorophenyl)pyrrolidin-3-yl]carboxamide	
78	(R)-N-((1R,2R)-3-(azetidin-1-yl)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxypropan-2-yl)-1-(4-chlorophenyl)pyrrolidine-3-carboxamide	

Example No.	Name	Structure
72	(R)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(quinolin-2-yl)pyrrolidine-3-carboxamide	
72B	(S)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(quinolin-2-yl)pyrrolidine-3-carboxamide	
71	(R)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(2,2-dimethylchroman-7-yl)pyrrolidine-3-carboxamide	
71F	(S)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(2,2-dimethylchroman-7-yl)pyrrolidine-3-carboxamide	
79A	N-((1R,2R)-3-(azetidin-1-yl)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxypropan-2-yl)-1-(6-fluoronaphthalen-2-yl)pyrrolidine-3-carboxamide	
80G	N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(5,6,7,8-tetrahydronaphthalen-2-yl)pyrrolidine-3-carboxamide	
68	(R)-N-((1R,2R)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(quinolin-2-yl)pyrrolidine-3-carboxamide	

Example No.	Name	Structure
63	(R)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)pyrrolidine-3-carboxamide	
63D	(S)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)pyrrolidine-3-carboxamide	
76E	(S)-1-(2-chlorobenzo[b]thiophen-6-yl)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)pyrrolidine-3-carboxamide	
76	(R)-1-(2-chlorobenzo[b]thiophen-6-yl)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)pyrrolidine-3-carboxamide	
81	(R)-N-((1R,2R)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(naphthalen-2-yl)pyrrolidine-3-carboxamide	
82	(R)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(2,6-dimethylpyridin-4-yl)pyrrolidine-3-carboxamide	
82E	(S)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(2,6-dimethylpyridin-4-yl)pyrrolidine-3-carboxamide	

Example No.	Name	Structure
83C	N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(quinoxalin-6-yl)pyrrolidine-3-carboxamide	
84	(R)-N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(6-fluoronaphthalen-2-yl)pyrrolidine-3-carboxamide	
84A	(S)-N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(6-fluoronaphthalen-2-yl)pyrrolidine-3-carboxamide	
79	(R)-N-((1R,2R)-3-(azetidin-1-yl)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxypropan-2-yl)-1-(6-fluoronaphthalen-2-yl)pyrrolidine-3-carboxamide	
79B	(S)-N-((1R,2R)-3-(azetidin-1-yl)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxypropan-2-yl)-1-(6-fluoronaphthalen-2-yl)pyrrolidine-3-carboxamide	
80	(R)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(5,6,7,8-tetrahydronaphthalen-2-yl)pyrrolidine-3-carboxamide	
80H	(S)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(5,6,7,8-tetrahydronaphthalen-2-yl)pyrrolidine-3-carboxamide	

Example No.	Name	Structure
85	(R)-N-((1R,2R)-3-(azetidin-1-yl)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxypropan-2-yl)-1-(naphthalen-2-yl)pyrrolidine-3-carboxamide	
86	(R)-N-((1R,2R)-3-(azetidin-1-yl)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxypropan-2-yl)-1-(naphthalen-2-yl)pyrrolidine-3-carboxamide	
87	(R)-N-((1R,2R)-1-(3-chloro-4-(2-hydroxy-2-methylpropoxy)phenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(4-chlorophenyl)pyrrolidine-3-carboxamide	
88C	1-(1-chloro-6-fluoronaphthalen-2-yl)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)pyrrolidine-3-carboxamide	
89F	N-((1R,2R)-3-(azetidin-1-yl)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxypropan-2-yl)-1-(6-chloronaphthalen-2-yl)pyrrolidine-3-carboxamide	
90	(R)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(1,5-naphthyridin-3-yl)pyrrolidine-3-carboxamide	
90D	(S)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(1,5-naphthyridin-3-yl)pyrrolidine-3-carboxamide	

Example No.	Name	Structure
92	(R)-1-(benzo[b]thiophen-6-yl)-N-((1R,2R)-1-(3-chloro-4-((tetrahydro-2H-pyran-4-yl)oxy)phenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)pyrrolidine-3-carboxamide	
83	(R)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(quinoxalin-6-yl)pyrrolidine-3-carboxamide	
83D	(S)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(quinoxalin-6-yl)pyrrolidine-3-carboxamide	
88	(R)-1-(1-chloro-6-fluoronaphthalen-2-yl)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)pyrrolidine-3-carboxamide	
88D	(S)-1-(1-chloro-6-fluoronaphthalen-2-yl)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)pyrrolidine-3-carboxamide	
89	(R)-N-((1R,2R)-3-(azetidin-1-yl)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxypropan-2-yl)-1-(6-chloronaphthalen-2-yl)pyrrolidine-3-carboxamide	
89G	(S)-N-((1R,2R)-3-(azetidin-1-yl)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxypropan-2-yl)-1-(6-chloronaphthalen-2-yl)pyrrolidine-3-carboxamide	

Example No.	Name	Structure
93	(R)-N-((1R,2R)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(5,6,7,8-tetrahydronaphthalen-2-yl)pyrrolidine-3-carboxamide	
93A	(S)-N-((1R,2R)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(5,6,7,8-tetrahydronaphthalen-2-yl)pyrrolidine-3-carboxamide	
91	(R)-1-(benzo[b]thiophen-6-yl)-N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)pyrrolidine-3-carboxamide	
94	(R)-N-((1R,2R)-1-(3-chloro-4-((tetrahydro-2H-pyran-4-yl)oxy)phenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(naphthalen-2-yl)pyrrolidine-3-carboxamide	
95	(R)-N-((1R,2R)-3-(azetidin-1-yl)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxypropan-2-yl)-1-(6-fluoronaphthalen-2-yl)pyrrolidine-3-carboxamide	
96	(R)-N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(4-fluorophenyl)pyrrolidine-3-carboxamide	
97	(R)-1-(benzo[b]thiophen-6-yl)-N-((1R,2R)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)pyrrolidine-3-carboxamide	

Example No.	Name	Structure
97C	(S)-1-(benzo[b]thiophen-6-yl)-N-((1R,2R)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)pyrrolidine-3-carboxamide	
98	(R)-N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(5,6,7,8-tetrahydronaphthalen-2-yl)pyrrolidine-3-carboxamide	
98A	(S)-N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(5,6,7,8-tetrahydronaphthalen-2-yl)pyrrolidine-3-carboxamide	
99C	1-(6-chloroquinolin-2-yl)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)pyrrolidine-3-carboxamide	
100	(R)-N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(6-chloroquinolin-2-yl)pyrrolidine-3-carboxamide	
101	(R)-N-((1R,2R)-1-(3-chloro-4-((tetrahydro-2H-pyran-4-yl)oxy)phenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(2-chlorobenzo[b]thiophen-6-yl)pyrrolidine-3-carboxamide	
102	(R)-N-((1R,2R)-1-(3-chloro-4-(2-hydroxy-2-methylpropoxy)phenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(6-fluoronaphthalen-2-yl)pyrrolidine-3-carboxamide	

Example No.	Name	Structure
103	(R)-1-(4-chloro-3-(pyridin-2-yloxy)phenyl)-N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)pyrrolidine-3-carboxamide	
104	(R)-1-(6-chloroquinolin-2-yl)-N-((1R,2R)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)pyrrolidine-3-carboxamide	
105	(R)-1-(4-chloro-3-(pyridin-2-yloxy)phenyl)-N-((1R,2R)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)pyrrolidine-3-carboxamide	
106	(R)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(quinolin-7-yl)pyrrolidine-3-carboxamide	
107	(R)-N-((1R,2R)-1-(3-chloro-4-(2-hydroxy-2-methylpropoxy)phenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(naphthalen-2-yl)pyrrolidine-3-carboxamide	
99	(R)-1-(6-chloroquinolin-2-yl)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)pyrrolidine-3-carboxamide	
99D	(S)-1-(6-chloroquinolin-2-yl)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)pyrrolidine-3-carboxamide	

Example No.	Name	Structure
108	(R)-N-((1R,2R)-3-(azetidin-1-yl)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxypropan-2-yl)-1-(2-chlorobenzo[b]thiophen-6-yl)pyrrolidine-3-carboxamide	
109	(R)-N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(2-chlorobenzo[b]thiophen-6-yl)pyrrolidine-3-carboxamide	
110	(R)-1-(4-chloro-3-(pyridin-2-yloxy)phenyl)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)pyrrolidine-3-carboxamide	
111	(R)-1-(2-chlorobenzo[b]thiophen-6-yl)-N-((1R,2R)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)pyrrolidine-3-carboxamide	
112	(R)-N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(6-(4-chlorophenoxy)pyridin-2-yl)pyrrolidine-3-carboxamide	
113	(R)-1-(6-(4-chlorophenoxy)pyridin-2-yl)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)pyrrolidine-3-carboxamide	
114	(R)-1-(6-(4-chlorophenoxy)pyridin-2-yl)-N-((1R,2R)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)pyrrolidine-3-carboxamide	

Example No.	Name	Structure
115	(R)-N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(6-(4-fluorophenoxy)pyridin-2-yl)pyrrolidine-3-carboxamide	
116	(R)-N-((1R,2R)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(6-(4-fluorophenoxy)pyridin-2-yl)pyrrolidine-3-carboxamide	
117	(R)-N-((1R,2R)-1-(3-chloro-4-(oxetan-3-yloxy)phenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(6-fluoronaphthalen-2-yl)pyrrolidine-3-carboxamide	
118	(R)-N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(2-chloro-5-(pyridin-2-yloxy)phenyl)pyrrolidine-3-carboxamide	
119	(R)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(6-(4-fluorophenoxy)pyridin-2-yl)pyrrolidine-3-carboxamide	
121	(R)-1-benzoyl-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)pyrrolidine-3-carboxamide	
120	(R)-1-benzoyl-N-((1R,2R)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)pyrrolidine-3-carboxamide	

Example No.	Name	Structure
122	(R)-N-((1R,2R)-3-(azetidin-1-yl)-1-(3-chloro-4-(oxetan-3-yloxy)phenyl)-1-hydroxypropan-2-yl)-1-(6-fluoronaphthalen-2-yl)pyrrolidine-3-carboxamide	
123	(R)-N-((1R,2R)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(6-(4-fluorophenyl)pyridin-2-yl)pyrrolidine-3-carboxamide	
124	(R)-N-((1R,2R)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(6-(4-fluorophenyl)pyridin-2-yl)pyrrolidine-3-carboxamide	
125	(R)-N-((1R,2R)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(1-methyl-1H-indazol-5-yl)pyrrolidine-3-carboxamide	
127	(R)-N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(1-methyl-1H-indazol-5-yl)pyrrolidine-3-carboxamide	
128	(R)-1-(4-chloro-3-(4-fluorophenoxy)phenyl)-N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)pyrrolidine-3-carboxamide	
129	(R)-1-benzoyl-N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)pyrrolidine-3-carboxamide	

Example No.	Name	Structure
126	(R)-N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(6-(4-fluorophenyl)pyridin-2-yl)pyrrolidine-3-carboxamide	
130	(R)-1-(4-chlorophenyl)-N-((1R,2R)-1-(5-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)pyrrolidine-3-carboxamide	
131	(R)-1-(4-chloro-3-((6-methylpyridin-2-yl)oxy)phenyl)-N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)pyrrolidine-3-carboxamide	
132	(R)-N-((1R,2R)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(1-methyl-1H-indazol-6-yl)pyrrolidine-3-carboxamide	
133	(R)-N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(1-methyl-1H-indazol-6-yl)pyrrolidine-3-carboxamide	
134	(R)-N-((1R,2R)-3-(azetidin-1-yl)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxypropan-2-yl)-1-(1-methyl-1H-indazol-6-yl)pyrrolidine-3-carboxamide	
135	(R)-N-((1R,2R)-1-(4-(tert-butoxy)-3-chlorophenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(4-chlorophenyl)pyrrolidine-3-carboxamide	

Example No.	Name	Structure
136	(R)-1-(4-chloro-3-(cyclohexyloxy)phenyl)-N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)pyrrolidine-3-carboxamide	
137	(R)-1-(4-chlorophenyl)-N-((1R,2R)-1-hydroxy-3-(pyrrolidin-1-yl)-1-(8-(trifluoromethyl)-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)propan-2-yl)pyrrolidine-3-carboxamide	
138	(R)-1-(6-chloro-4'-fluoro-[1,1'-biphenyl]-3-yl)-N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)pyrrolidine-3-carboxamide	
139	(R)-1-(4-(tert-butyl)phenyl)-N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)pyrrolidine-3-carboxamide	
140	(R)-N-((1R,2R)-1-(3-chloro-4-cyclobutoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(4-chlorophenyl)pyrrolidine-3-carboxamide	
141	(R)-N-((1R,2R)-1-(3-chloro-4-(cyclopentyloxy)phenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(4-chlorophenyl)pyrrolidine-3-carboxamide	
142	(R)-1-(4-(tert-butyl)phenyl)-N-((1R,2R)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)pyrrolidine-3-carboxamide	

Example No.	Name	Structure
143	(R)-N-((1R,2R)-1-(benzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(4-chlorophenyl)pyrrolidine-3-carboxamide	
144	(R)-1-(5-chloro-6-(4-fluorophenyl)pyridin-2-yl)-N-((1R,2R)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)pyrrolidine-3-carboxamide	
145	(R)-N-((1R,2R)-1-(3-chloro-4-(cyclopropylthio)phenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(4-chlorophenyl)pyrrolidine-3-carboxamide	
146	(R)-N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(5-chloro-6-(4-fluorophenyl)pyridin-2-yl)pyrrolidine-3-carboxamide	
147	(R)-N-((1R,2R)-1-(3-chloro-4-(vinylloxy)phenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(4-chlorophenyl)pyrrolidine-3-carboxamide	
148	(R)-N-((1R,2R)-1-(4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(4-fluorophenyl)pyrrolidine-3-carboxamide	
149	(R)-N-((1R,2R)-1-(4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-phenylpyrrolidine-3-carboxamide	

Example No.	Name	Structure
150	(R)-N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-phenylpyrrolidine-3-carboxamide	
151	(R)-N-((1R,2R)-1-(4-cyclopropoxy-3-fluorophenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-phenylpyrrolidine-3-carboxamide	
152	(R)-N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(4-cyanophenyl)pyrrolidine-3-carboxamide	
152C	(R)-N-((1S,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(4-cyanophenyl)pyrrolidine-3-carboxamide	
153	(R)-N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(p-tolyl)pyrrolidine-3-carboxamide	
154	(S)-1-(4-chlorophenyl)-N-((1R,2R)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-3-hydroxypyrrolidine-3-carboxamide	
154C	(R)-1-(4-chlorophenyl)-N-((1R,2R)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-3-hydroxypyrrolidine-3-carboxamide	

Example No.	Name	Structure
155	(R)-1-(4-chlorophenyl)-N-((1R,2R)-1-(4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)pyrrolidine-3-carboxamide	
156	(R)-1-(4-chlorophenyl)-N-((1R,2R)-1-(4-chlorophenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)pyrrolidine-3-carboxamide	
157	(R)-1-(benzo[b]thiophen-6-yl)-N-((1R,2R)-1-(4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)pyrrolidine-3-carboxamide	
158	(R)-N-((1R,2R)-3-(azetidin-1-yl)-1-(4-cyclopropoxyphenyl)-1-hydroxypropan-2-yl)-1-(benzo[b]thiophen-6-yl)pyrrolidine-3-carboxamide	
159	(R)-N-((1R,2R)-3-(azetidin-1-yl)-1-(4-cyclopropoxyphenyl)-1-hydroxypropan-2-yl)-1-(6-fluoronaphthalen-2-yl)pyrrolidine-3-carboxamide	
159C	(S)-N-((1R,2R)-3-(azetidin-1-yl)-1-(4-cyclopropoxyphenyl)-1-hydroxypropan-2-yl)-1-(6-fluoronaphthalen-2-yl)pyrrolidine-3-carboxamide	
160	(R)-1-(4-chlorophenyl)-N-((1R,2R)-1-(4-(difluoromethoxy)phenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)pyrrolidine-3-carboxamide	

Example No.	Name	Structure
161	(R)-N-((1R,2R)-1-(4-(difluoromethoxy)phenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-phenylpyrrolidine-3-carboxamide	
162	(R)-N-((1R,2R)-1-(4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(6-fluoronaphthalen-2-yl)pyrrolidine-3-carboxamide	

[000121] In some or any embodiments, the compound is selected from Table 1.

[000122] In some or any embodiments, the compound is selected from the group consisting of the compounds of Examples 1, 1C, 1D, 2, 2A, 2B, 5, 5D, 5E, 8, 8C, 8D, 9, 9D, 9E, 11, 12, 12D, 14, 14C, 14D, 15, 15C, 15D, 17, 17D, 19, 20, 20D, 20E, 21, 21E, 21F, 22, 22C, 22D, 24, 24B, 24C, 25, 25B, 26, 28, 28C, 28D, 30, 35, 35A, 36, 36F, 36G, 43, 43D, 43E, 44, 44C, 46, 46A, 46B, 47, 47A, 47B, 48, 48A, 52, 52A, 53, 53C, 53D, 55, 55A, 55B, 56, 56D, 56E, 58, 58D, 61, 61C, 61D, 63, 63C, 63D, 64, 68, 68C, 70, 70A, 71, 71E, 71F, 72, 72A, 72B, 76, 76D, 76E, 77, 78, 79, 79A, 79B, 80, 80G, 80H, 81, 82, 82E, 83, 83C, 83D, 85, 88, 88C, 88D, 89, 89F, 89G, 90, 90D, 93, 93A, 97, 97C, 99, 99C, 99D, 104, 105, 106, 108, 110, 111, 113, 114, 116, 119, 120, 121, 123, 124, 125, 130, 132, 134, 137, 142, 144, 154, and 154C.

[000123] In some or any embodiments, the compound is selected from the group consisting of the compounds of Examples 3, 3A, 3B, 6, 10, 23, 23B, 32, 32A, 45, 45A, 49, 49A, 50, 50A, 54, 54A, 57, 57A, 59, 60, 60A, 65, 66, 67, 67C, 69, 69A, 73, 74, 74C, 75, 75E, 84, 84A, 86, 87, 91, 92, 94, 95, 96, 98, 98A, 100, 101, 102, 103, 107, 109, 112, 115, 117, 118, 122, 126, 127, 128, 129, 131, 133, 135, 136, 138, 139, 140, 141, 145, 146, 147, 148, 149, 150, 151, 152, 152C, 153, 155, 156, 157, 158, 159, 159A, 160, 161, and 162.

[000124] In some or any embodiments, the compound is selected from the group consisting of the compounds of Examples 1, 1C, 1D, 2, 2A, 2B, 3, 3A, 3B, 6, 8, 8C, 8D, 10, 12, 12D, 13, 13C, 14, 14C, 14D, 19, 20, 20D, 20E, 23, 23B, 24, 24B, 24C, 25, 25B, 27, 27C, 29, 29B, 31, 31B, 32, 32A, 33, 33A, 34, 34A, 35, 35A, 43, 43D, 43E, 44, 44C, 45, 45A, 46, 46A, 46B, 47, 47A, 47B, 49, 49A, 50, 50A, 51, 51A, 52, 52A, 59, 60, 60A, 62, 65, 66, 67,

67C, 69, 69A, 70, 70A, 73, 74, 74C, 75, 75E, 77, 78, 79, 79A, 79B, 81, 84, 84A, 85, 86, 87, 88, 88C, 88D, 89, 89F, 89G, 94, 95, 96, 102, 103, 105, 107, 110, 117, 118, 122, 128, 130, 131, 135, 136, 137, 138, 139, 140, 141, 142, 143, 145, 147, 148, 149, 150, 151, 152, 152C, 153, 154, 154C, 155, 156, 159, 159A, 160, 161, and 162.

[000125] In some or any embodiments, the compound is selected from the group consisting of the compounds of Examples 17, 17D, 22, 22C, 22D, 28, 28C, 28D, 48, 48A, 53, 53C, 53D, 54, 54A, 56, 56D, 56E, 57, 57A, 58, 58D, 61, 61C, 61D, 68, 68C, 72, 72A, 72B, 76, 76D, 76E, 82, 82E, 83, 83C, 83D, 90, 90D, 91, 92, 97, 97C, 99, 99C, 99D, 100, 101, 104, 106, 108, 109, 111, 112, 113, 114, 115, 116, 119, 123, 124, 125, 126, 127, 132, 133, 134, 144, 146, 157, and 158.

[000126] In some or any embodiments, the compound is selected from the group consisting of the compounds of Examples 5, 5D, 5E, 9, 9D, 9E, 11, 26, 30, 36, 36F, 36G, 55, 55A, 55B, 63, 63C, 63D, 64, 71, 71E, 71F, 80, 80G, 80H, 93, 93A, 98, and 98A.

[000127] In some or any embodiments, the compound is selected from the group consisting of the compounds of Examples 13, 13C, 27, 27C, 29, 29B, 31, 31B, 33, 33A, 34, 34A, and 62.

[000128] In some or any embodiments, the compound is selected from the group consisting of the compounds of Examples 15, 15C, 15D, 21, 21E, 21F, 120, 121, and 129.4.

[000129] In some or any embodiments, provided is a pharmaceutical composition comprising 1) a Compound of Formula I, (b), I(c), or a compound in Table 1 optionally as a tautomer, a single stereoisomer or mixture of stereoisomers thereof and additionally optionally as a pharmaceutically acceptable salt thereof, and 2) a pharmaceutically acceptable excipient or pharmaceutically acceptable carrier.

Pharmaceutical Composition/Formulation

[000130] In some or any embodiments, optionally in combination with any or all of the above various embodiments, provided herein is a pharmaceutical composition comprising of a compound of Formula I, I(a), I(b), I(c), I(d), I(d1), I(d2), I(e), I(e1), I(e2), I(f), I(f1), I(f2), I(g), I(g1), I(h), I(h1), or a compound of Table 1 or stereoisomers, or a pharmaceutically acceptable salt, and one or more pharmaceutically acceptable carrier(s), excipient(s), binder(s) or diluent(s). The pharmaceutical compositions can, moreover, contain preservatives, solubilizers, stabilizers, wetting agents, emulsifiers, sweeteners, colorants, flavorants, salts for varying the osmotic pressure, buffers, coating agents or antioxidants.

[000131] In some or any embodiments, disclosed herein is a pharmaceutical composition comprising a compound, pharmaceutically acceptable salt, pharmaceutically acceptable *N*-oxide, pharmaceutically active metabolite, pharmaceutically acceptable prodrug, or pharmaceutically acceptable solvate of any of the compounds disclosed herein. In some embodiments, the pharmaceutical compositions further comprises a pharmaceutically acceptable diluent, excipient or binder.

[000132] In some or any embodiments, pharmaceutical compositions are formulated in any manner, including using one or more physiologically acceptable carriers comprising excipients and/or auxiliaries which facilitate processing of the active compounds into pharmaceutical preparations. In some embodiments, proper formulation is dependent upon the route of administration chosen. In various embodiments, any techniques, carriers, and excipients are used as suitable.

[000133] A pharmaceutical composition, as used herein, refers to a mixture of a compound described herein with other chemical components, such as carriers, stabilizers, diluents, dispersing agents, suspending agents, thickening agents, and/or excipients. In some or any embodiments, a pharmaceutical composition facilitates administration of the compound to an organism. In some embodiments, practicing the methods of treatment or use provided herein, includes administering or using a pharmaceutical composition comprising a therapeutically effective amount of a compound provided herein. In specific embodiments, the methods of treatment provided for herein include administering such a pharmaceutical composition to a mammal having a disease or condition to be treated. In one embodiment, the mammal is a human. In some embodiments, the therapeutically effective amount varies widely depending on the severity of the disease, the age and relative health of the subject, the potency of the compound used and other factors. In various embodiments, the compounds described herein are used singly or in combination with one or more therapeutic agents as components of mixtures.

[000134] In a some or any embodiment, it is provided a method of forming a composition, comprising providing a compound and forming the composition. In some embodiments, the composition further comprises a pharmaceutically acceptable carrier. In some embodiments of the composition, optionally in combination with any or all of the above various embodiments, the composition is formulated in a formulation for local or systemic delivery. Examples of such formulations are formulations for oral administration, injection, topical administration, pulmonary administration, or implant. In some or any embodiments, the compound is according to any of the various embodiments described above or below.

[000135] In some or any embodiments, the pharmaceutical compositions provided herein are formulated for intravenous injections. In certain aspects, the intravenous injection formulations provided herein are formulated as aqueous solutions, and, in some embodiments, in physiologically compatible buffers such as Hank's solution, Ringer's solution, or physiological saline buffer. In certain embodiments, the pharmaceutical compositions provided herein are formulated for transmucosal administration. In some aspects, transmucosal formulations include penetrants appropriate to the barrier to be permeated. In certain embodiments, the pharmaceutical compositions provided herein are formulated for other parenteral injections, appropriate formulations include aqueous or nonaqueous solutions, and in one embodiment, with physiologically compatible buffers or excipients.

[000136] In some or any embodiments, the pharmaceutical compositions provided herein are formulated for oral administration. In certain aspects, the oral formulations provided herein comprise compounds described herein that are formulated with pharmaceutically acceptable carriers or excipients. Such carriers enable the compounds described herein to be formulated as tablets, powders, pills, dragees, capsules, liquids, gels, syrups, elixirs, slurries, suspensions and the like, for oral ingestion by a patient to be treated.

[000137] In some or any embodiments, pharmaceutical preparations for oral use are obtained by mixing one or more solid excipient with one or more of the compounds described herein, optionally grinding the resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients include, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as: for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methylcellulose, microcrystalline cellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose; or others such as: polyvinylpyrrolidone (PVP or povidone) or calcium phosphate. If desired, disintegrating agents are optionally added, such as the cross-linked croscarmellose sodium, polyvinylpyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate.

[000138] In some or any embodiments, provided herein is a pharmaceutical composition formulated as dragee cores with suitable coatings. In some or any embodiments, concentrated sugar solutions are used in forming the suitable coating, and optionally contain gum arabic, talc, polyvinylpyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. In some embodiments,

dyestuffs and/or pigments are added to tablets, dragees and/or the coatings thereof for, e.g., identification or to characterize different combinations of active compound doses.

[000139] In some or any embodiments, pharmaceutical preparations which are used include orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. In some embodiments, the push-fit capsules contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In some or any embodiments, in soft capsules, the active compounds are dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers are optionally added. In some or any embodiments, the formulations for oral administration are in dosages suitable for such administration.

[000140] In some or any embodiments, the pharmaceutical compositions provided herein are formulated for buccal or sublingual administration. In some or any embodiments, buccal or sublingual compositions take the form of tablets, lozenges, or gels formulated in a conventional manner. In some or any embodiments, parenteral injections involve bolus injection or continuous infusion. In some embodiments, formulations for injection are presented in unit dosage form, *e.g.*, in ampoules or in multi-dose containers, with an added preservative. In some embodiments, the pharmaceutical composition described herein is in a form suitable for parenteral injection as a sterile suspensions, solutions or emulsions in oily or aqueous vehicles, and optionally contains formulatory agents such as suspending, stabilizing and/or dispersing agents. Pharmaceutical formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form. In some embodiments, suspensions of the active compounds are prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. In some or any embodiments, aqueous injection suspensions contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspensions also contain suitable stabilizers or agents which increase the solubility of the compounds to allow for the preparation of highly concentrated solutions. In alternative embodiments, the active ingredient is in powder form for constitution with a suitable vehicle, *e.g.*, sterile pyrogen-free water, before use.

[000141] In some embodiments, the compounds described herein are administered topically. In specific embodiments, the compounds described herein are formulated into a variety of topically administrable compositions, such as solutions, suspensions, lotions, gels,

pastes, medicated sticks, balms, creams or ointments. Such pharmaceutical compounds optionally contain solubilizers, stabilizers, tonicity enhancing agents, buffers and/or preservatives.

[000142] In some or any embodiments, the pharmaceutical compositions provided herein are formulated for transdermal administration of compounds described herein. In some embodiments, administration of such compositions employs transdermal delivery devices and transdermal delivery patches. In some or any embodiments, the compositions are lipophilic emulsions or buffered, aqueous solutions, dissolved and/or dispersed in a polymer or an adhesive. Such patches include those constructed for continuous, pulsatile, or on demand delivery of pharmaceutical agents. In some embodiments, transdermal delivery of the compounds described herein is accomplished by use of iontophoretic patches and the like. In some or any embodiments, transdermal patches provide controlled delivery of the compounds provided herein, such as, for example, compounds of Formula (I). In some or any embodiments, the rate of absorption is slowed by using rate-controlling membranes or by trapping the compound within a polymer matrix or gel. Conversely, absorption enhancers are optionally used to increase absorption. Absorption enhancer and carrier include absorbable pharmaceutically acceptable solvents that assist in passage of the compound through the skin. For example, transdermal devices are in the form of a bandage comprising a backing member, a reservoir containing the compound optionally with carriers, optionally a rate controlling barrier to deliver the compound to the skin of the host at a controlled and predetermined rate over a prolonged period of time, and means to secure the device to the skin.

[000143] In some or any embodiments, the pharmaceutical compositions provided herein are formulated for administration by inhalation. In some or any embodiments, in such pharmaceutical compositions formulated for inhalation, the compounds described herein are in a form as an aerosol, a mist or a powder. In some embodiments, pharmaceutical compositions described herein are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebuliser, with the use of a suitable propellant, *e.g.*, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In certain aspects of a pressurized aerosol, the dosage unit is determined by providing a valve to deliver a metered amount. In some or any embodiments, capsules and cartridges of, such as, by way of example only, gelatin for use in an inhaler or insufflator is formulated containing a powder mix of the compound described herein and a suitable powder base such as lactose or starch.

[000144] In some embodiments, the compounds described herein are formulated in rectal compositions such as enemas, rectal gels, rectal foams, rectal aerosols, suppositories, jelly suppositories, or retention enemas. In some or any embodiments, rectal compositions optionally contain conventional suppository bases such as cocoa butter or other glycerides, as well as synthetic polymers such as polyvinylpyrrolidone, PEG, and the like. In some or any suppository forms of the compositions, a low-melting wax such as, but not limited to, a mixture of fatty acid glycerides, optionally in combination with cocoa butter is first melted.

[000145] In various embodiments provided herein, the pharmaceutical compositions are formulated in a conventional manner using one or more physiologically acceptable carriers comprising excipients and auxiliaries which facilitate processing of the active compounds into pharmaceutically acceptable preparations. In some or any embodiments, proper formulation is dependent upon the route of administration chosen. In various embodiments, any of the techniques, carriers, and excipients is used as suitable. In some embodiments, pharmaceutical compositions comprising a compound described herein are manufactured in a conventional manner, such as, by way of example only, by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or compression processes.

[000146] In some or any embodiments, the pharmaceutical compositions include at least one pharmaceutically acceptable carrier, diluent or excipient and a compound described herein described herein as an active ingredient in free-acid or free-base form, or in a pharmaceutically acceptable salt form. In addition, the methods and pharmaceutical compositions described herein include the use of *N*-oxides, crystalline forms (also known as polymorphs), as well as active metabolites of these compounds having the same type of activity. In some situations, compounds described herein exist as tautomers. All tautomers are included within the scope of the compounds presented herein. Additionally, included herein are the solvated and unsolvated forms of the compounds described herein. Solvated compounds include those that are solvated with pharmaceutically acceptable solvents such as water, ethanol, and the like. The solvated forms of the compounds presented herein are also considered to be disclosed herein. In some embodiments, the pharmaceutical compositions described herein include other medicinal or pharmaceutical agents, carriers, adjuvants, such as preserving, stabilizing, wetting or emulsifying agents, solution promoters, salts for regulating the osmotic pressure, and/or buffers. In additional embodiments, the pharmaceutical compositions described herein also contain other therapeutically valuable substances.

[000147] Methods for the preparation of compositions containing the compounds described herein include formulating the compounds with one or more inert, pharmaceutically acceptable excipients or carriers to form a solid, semi-solid or liquid. Solid compositions include, but are not limited to, powders, tablets, dispersible granules, capsules, cachets, and suppositories. Liquid compositions include solutions in which a compound is dissolved, emulsions comprising a compound, or a solution containing liposomes, micelles, or nanoparticles comprising a compound as disclosed herein. Semi-solid compositions include, but are not limited to, gels, suspensions and creams. In various embodiments, the compositions are in liquid solutions or suspensions, solid forms suitable for solution or suspension in a liquid prior to use, or as emulsions. These compositions optionally contain minor amounts of nontoxic, auxiliary substances, such as wetting or emulsifying agents, pH buffering agents, and so forth.

[000148] In some embodiments, a composition comprising a compound described herein takes the form of a liquid where the agents are present in solution, in suspension or both. In some embodiments, when the composition is administered as a solution or suspension a first portion of the agent is present in solution and a second portion of the agent is present in particulate form, in suspension in a liquid matrix. In some embodiments, a liquid composition includes a gel formulation. In other embodiments, the liquid composition is aqueous.

[000149] Useful aqueous suspension optionally contain one or more polymers as suspending agents. Useful polymers include water-soluble polymers such as cellulosic polymers, *e.g.*, hydroxypropyl methylcellulose, and water-insoluble polymers such as cross-linked carboxyl-containing polymers. Useful compositions optionally comprise an mucoadhesive polymer, selected for example from carboxymethylcellulose, carbomer (acrylic acid polymer), poly(methylmethacrylate), polyacrylamide, polycarbophil, acrylic acid/butyl acrylate copolymer, sodium alginate and dextran.

[000150] Useful compositions optionally include solubilizing agents to aid in the solubility of a compound described herein. The term “solubilizing agent” generally includes agents that result in formation of a micellar solution or a true solution of the agent. Solubilizing agents include certain acceptable nonionic surfactants, for example polysorbate 80, and ophthalmically acceptable glycols, polyglycols, *e.g.*, polyethylene glycol 400, and glycol ethers.

[000151] Useful compositions optionally include one or more pH adjusting agents or buffering agents, including acids such as acetic, boric, citric, lactic, phosphoric and

hydrochloric acids; bases such as sodium hydroxide, sodium phosphate, sodium borate, sodium citrate, sodium acetate, sodium lactate and tris-hydroxymethylaminomethane; and buffers such as citrate/dextrose, sodium bicarbonate and ammonium chloride. Such acids, bases and buffers are included in an amount required to maintain pH of the composition in an acceptable range.

[000152] Useful compositions optionally include one or more salts in an amount required to bring osmolality of the composition into an acceptable range. Such salts include those having sodium, potassium or ammonium cations and chloride, citrate, ascorbate, borate, phosphate, bicarbonate, sulfate, thiosulfate or bisulfite anions; suitable salts include sodium chloride, potassium chloride, sodium thiosulfate, sodium bisulfite and ammonium sulfate.

[000153] Certain useful compositions optionally include one or more preservatives to inhibit microbial activity. Suitable preservatives include mercury-containing substances such as merfen and thiomersal; stabilized chlorine dioxide; and quaternary ammonium compounds such as benzalkonium chloride, cetyltrimethylammonium bromide and cetylpyridinium chloride.

[000154] Some useful compositions optionally include one or more surfactants to enhance physical stability or for other purposes. Suitable nonionic surfactants include polyoxyethylene fatty acid glycerides and vegetable oils, *e.g.*, polyoxyethylene (60) hydrogenated castor oil; and polyoxyethylene alkylethers and alkylphenyl ethers, *e.g.*, octoxynol 10, octoxynol 40.

[000155] Certain useful compositions optionally one or more antioxidants to enhance chemical stability where required. Suitable antioxidants include, by way of example only, ascorbic acid and sodium metabisulfite.

[000156] In some embodiments, aqueous suspension compositions are packaged in single-dose non-reclosable containers. In alternative embodiments, multiple-dose reclosable containers are used, in which case it is typical to include a preservative in the composition.

[000157] In various embodiments, any delivery system for hydrophobic pharmaceutical compounds is employed. Liposomes and emulsions are examples of delivery vehicles or carriers for hydrophobic drugs. In some or any embodiments, certain organic solvents such as *N*-methylpyrrolidone are employed. In some embodiments, the compounds are delivered using a sustained-release system, such as semipermeable matrices of solid hydrophobic polymers containing the therapeutic agent. Various sustained-release materials are utilized in the embodiments herein. In some or any embodiments, sustained-release capsules release the compounds for a few weeks up to over 100 days. In some embodiments, depending on the

chemical nature and the biological stability of the therapeutic reagent, additional strategies for protein stabilization are employed.

[000158] In some or any embodiments, the formulations or compositions described herein benefit from and/or optionally comprise antioxidants, metal chelating agents, thiol containing compounds and other general stabilizing agents. Examples of such stabilizing agents, include, but are not limited to: (a) about 0.5% to about 2% w/v glycerol, (b) about 0.1% to about 1% w/v methionine, (c) about 0.1% to about 2% w/v monothioglycerol, (d) about 1 mM to about 10 mM EDTA, (e) about 0.01% to about 2% w/v ascorbic acid, (f) 0.003% to about 0.02% w/v polysorbate 80, (g) 0.001% to about 0.05% w/v. polysorbate 20, (h) arginine, (i) heparin, (j) dextran sulfate, (k) cyclodextrins, (l) pentosan polysulfate and other heparinoids, (m) divalent cations such as magnesium and zinc; or (n) combinations thereof.

Methods of Dosing and Treatment Regimens

[000159] In some or any embodiments, the method can be conducted in living bodies of mammals. In such a case, the compounds may be administered to the mammals.

[000160] In some or any embodiments, the compounds described herein are used in the preparation or manufacture of medicaments for the treatment of diseases or conditions that are mediated by the enzyme GCS or in which inhibition of the enzyme GCS ameliorates the disease or condition. In some embodiments, a method for treating any of the diseases or conditions described herein in a subject in need of such treatment, involves administration of pharmaceutical compositions containing at least one compound described herein, or a pharmaceutically acceptable salt, pharmaceutically acceptable *N*-oxide, pharmaceutically active metabolite, pharmaceutically acceptable prodrug, or pharmaceutically acceptable solvate thereof, in therapeutically effective amounts to said subject.

[000161] In some or any embodiments, provided is a method of treating or ameliorating a medical condition, comprising administering to a subject in need thereof a compound according to any of the various embodiments described herein or a pharmaceutical composition according to any of the various embodiments described herein.

[000162] In some or any embodiments, provided herein is a method of treating or ameliorating a disease ameliorated by the inhibition of GCS comprising administering to a subject in need of treatment a therapeutically-effective amount of a compound of Formula I, I(a), I(b), I(c), I(d), I(d1), I(d2), I(e), I(e1), I(e2), I(f), I(f1), I(f2), I(g), I(g1), I(h), I(h1), or a compound in Table 1 optionally as a tautomer, a single stereoisomer or mixture of stereoisomers thereof and additionally optionally as a pharmaceutically acceptable salt

thereof. In some or any embodiments, the disease is selected from glycolipid storage diseases (e.g., Tay Sachs, Sandhoffs, GM1 gangliosidosis – including type, type 2 and type 3, Niemanns-Pick, and Fabry diseases); diseases associated with glycolipid accumulation (e.g., Gaucher disease); diseases that cause renal hypertrophy or hyperplasia such as diabetic nephropathy; diseases that cause hyperglycemia or hyperinsulemia; cancers in which glycolipid synthesis is abnormal; infectious diseases caused by organisms which use cell surface glycolipids as receptors or in which synthesis of glucosylceramide is essential or important; a metabolic disorder such as atherosclerosis, polycystic kidney disease, renal hypertrophy, diabetes mellitus, and obesity; cancer such as breast cancer, renal adenocarcinoma, brain cancer, neuroblastoma, lung cancer, intestinal cancer, pancreas and prostate cancer; neuronal disorders; neuronal injury; inflammatory diseases or disorders (e.g., rheumatoid arthritis, Crohn's disease, asthma and sepsis), and diabetes mellitus and obesity. In another embodiment, the disease is a gangliosidosis with central nervous system involvement, e.g. Gaucher's type 2, Gaucher's type 3, Gaucher's type 1 in which patients are at a higher risk for peripheral neuropathy and parkinsonian features, Sandhoff, infantile Sandhoff with peripheral neuropathy, GM1 gangliosidosis type 1, GM1 gangliosidosis type 2, GM1 gangliosidosis type, Tay-Sachs, and GM2 gangliosidosis, AB variant. In another embodiment the compounds of Formula I, I(a), I(b), I(c), I(d), I(d1), I(d2), I(e), I(e1), I(e2), I(f), I(f1), I(f2), I(g), I(g1), I(h), I(h1), or a compound in Table 1 optionally as a tautomer, a single stereoisomer or mixture of stereoisomers thereof and additionally optionally as a pharmaceutically acceptable salt thereof is one which crosses the blood brain barrier.

[000163] In any of the aforementioned embodiments are further embodiments that include single administrations of the effective amount of the compound, including further embodiments in which the compound is administered to the subject (i) once; (ii) multiple times over the span of one day; (iii) continually; or (iv) continuously.

[000164] In any of the aforementioned embodiments are further embodiments in which administration is enteral, parenteral, or both, and wherein:

- (a) the effective amount of the compound is systemically administered to the subject;
- (b) the effective amount of the compound is administered orally to the subject;
- (c) the effective amount of the compound is intravenously administered to the subject;
- (d) the effective amount of the compound is administered by inhalation;
- (e) the effective amount of the compound is administered by nasal administration;
- (f) the effective amount of the compound is administered by injection to the subject;
- (g) the effective amount of the compound is administered topically (dermal) to the subject;
- (h) the effective amount of the compound is administered by ophthalmic administration; and/or
- (i) the effective amount of the compound is administered rectally to the subject.

[000165] In some or any embodiments, the compositions containing the compound(s) described herein are administered for prophylactic and/or therapeutic treatments. In some or any therapeutic applications, the compositions are administered to a patient already suffering from a disease or condition, in an amount sufficient to cure or at least partially arrest the symptoms of the disease or condition. In some embodiments, amounts effective for this use will depend on the severity and course of the disease or condition, previous therapy, the patient's health status, weight, and response to the drugs, and the judgment of the treating physician. In certain instances, it is considered appropriate for the caregiver to determine such therapeutically effective amounts by routine experimentation (including, but not limited to, a dose escalation clinical trial).

[000166] In some or any prophylactic applications, compositions containing the compounds described herein are administered to a patient susceptible to or otherwise at risk of a particular disease, disorder or condition. In some embodiments, the amount administered is defined to be a "prophylactically effective amount or dose." In some or any embodiments of this use, the precise amounts of compound administered depend on the patient's state of health, weight, and the like. In some embodiments, it is considered appropriate for the caregiver to determine such prophylactically effective amounts by routine experimentation (*e.g.*, a dose escalation clinical trial). In some or any embodiments, when used in a patient, effective amounts for this use will depend on the severity and course of the disease, disorder or condition, previous therapy, the patient's health status and response to the drugs, and the judgment of the treating physician.

[000167] In some or any embodiments are further embodiments that include multiple administrations of the effective amount of the compound, including further embodiments wherein:

- (i) the compound is administered in a single dose;
- (ii) the time between multiple administrations is every 6 hours;
- (iii) the compound is administered to the subject every 8 hours.

[000168] In further or alternative embodiments, the method includes a drug holiday, wherein the administration of the compound is temporarily suspended or the dose of the compound being administered is temporarily reduced; at the end of the drug holiday, dosing of the compound is resumed. In some embodiments, the length of the drug holiday varies from 2 days to 1 year.

[000169] In certain instances, a patient's condition does not improve or does not significantly improve following administration of a compound or composition described herein and, upon the doctor's discretion the administration of the compounds is optionally administered chronically, that is, for an extended period of time, including throughout the duration of the patient's life in order to ameliorate or otherwise control or limit the symptoms of the patient's disease or condition.

[000170] In certain cases wherein the patient's status does improve or does not substantially improve, upon the doctor's discretion the administration of the compounds are optionally given continuously; alternatively, the dose of drug being administered is optionally temporarily reduced or temporarily suspended for a certain length of time (*i.e.*, a "drug holiday"). In some or any embodiments, the length of the drug holiday varies between 2 days and 1 year, including by way of example only, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 10 days, 12 days, 15 days, 20 days, 28 days, 35 days, 50 days, 70 days, 100 days, 120 days, 150 days, 180 days, 200 days, 250 days, 280 days, 300 days, 320 days, 350 days, or 365 days. The dose reduction during a drug holiday includes a reduction from about 10% to about 100%, including, by way of example only, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, or about 100%.

[000171] In some or any embodiments, once improvement of the patient's conditions has occurred, a maintenance dose is administered if necessary. In some embodiments, the dosage, e.g., of the maintenance dose, or the frequency of administration, or both, are reduced, as a function of the symptoms, to a level at which the improved disease, disorder or

condition is retained. In some or any embodiments, however, patients are optionally given intermittent treatment on a long-term basis upon any recurrence of symptoms.

[000172] In some or any embodiments, the amount of a given agent that corresponds to an effective amount varies depending upon factors such as the particular compound, disease or condition and its severity, the identity (*e.g.*, weight) of the subject or host in need of treatment. In some embodiments, the effective amount is, nevertheless, determined according to the particular circumstances surrounding the case, including, *e.g.*, the specific agent that is administered, the route of administration, the condition being treated, and the subject or host being treated. In some or any embodiments, however, doses employed for adult human treatment is in the range of about 0.02 to about 5000 mg per day, in a specific embodiment about 1 to about 1500 mg per day. In various embodiments, the desired dose is conveniently presented in a single dose or as divided doses administered simultaneously (or over a short period of time) or at appropriate intervals, for example as two, three, four or more sub-doses per day.

[000173] In some or any embodiments, the pharmaceutical compositions described herein are in a unit dosage form suitable for single administration of precise dosages. In some instances, in unit dosage form, the formulation is divided into unit doses containing appropriate quantities of one or more compound. In some or any embodiments, the unit dosage is in the form of a package containing discrete quantities of the formulation. Non-limiting examples are packaged tablets or capsules, and powders in vials or ampoules. In some embodiments, aqueous suspension compositions are packaged in single-dose non-reclosable containers. In alternative embodiments, multiple-dose reclosable containers are used, in which case it is typical to include a preservative in the composition. By way of example only, formulations for parenteral injection are, in some embodiments, presented in unit dosage form, which include, but are not limited to ampoules, or in multi-dose containers, with an added preservative.

[000174] In some or any embodiments, the daily dosages appropriate for the compounds described herein are from about 0.01 to about 2.5 mg/kg per body weight. In some embodiments, an indicated daily dosage in the larger subject, including, but not limited to, humans, is in the range from about 0.5 mg to about 100 mg, conveniently administered in divided doses, including, but not limited to, up to four times a day or in extended release form. In some or any embodiments, suitable unit dosage forms for oral administration comprise from about 1 to about 50 mg active ingredient. The foregoing ranges are merely suggestive, as the number of variables in regard to an individual treatment regime is large,

and considerable excursions from these recommended values are not uncommon. In some or any embodiments, the dosages are altered depending on a number of variables, not limited to the activity of the compound used, the disease or condition to be treated, the mode of administration, the requirements of the individual subject, the severity of the disease or condition being treated, and the judgment of the practitioner.

[000175] In some or any embodiments, toxicity and therapeutic efficacy of such therapeutic regimens are determined by standard pharmaceutical procedures in cell cultures or experimental animals, including, but not limited to, the determination of the LD₅₀ (the dose lethal to 50% of the population) and the ED₅₀ (the dose therapeutically effective in 50% of the population). The dose ratio between the toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio between LD₅₀ and ED₅₀. In some or any embodiments, compounds exhibiting high therapeutic indices are preferred. In some embodiments, the data obtained from cell culture assays and animal studies is used in formulating a range of dosage for use in human. In specific embodiments, the dosage of such compounds lies within a range of circulating concentrations that include the ED₅₀ with minimal toxicity. In some or any embodiments, the dosage varies within this range depending upon the dosage form employed and the route of administration utilized.

[000176] Articles of manufacture, comprising packaging material, a compound provided herein that is effective for modulating the activity of the enzyme GCS, or for treatment, prevention or amelioration of one or more symptoms of a GCS-mediated disease or condition, within the packaging material, and a label that indicates that the compound or composition, or pharmaceutically acceptable salt, pharmaceutically acceptable *N*-oxide, pharmaceutically active metabolite, pharmaceutically acceptable prodrug, or pharmaceutically acceptable solvate thereof, is used for modulating the activity of GCS, or for treatment, prevention or amelioration of one or more symptoms of GCS-mediated disease or condition, are provided.

[000177] For use in the therapeutic applications described herein, kits and articles of manufacture are also described herein. In various embodiments, such kits comprise a carrier, package, or container that is compartmentalized to receive one or more containers such as vials, tubes, and the like, each of the container(s) comprising one of the separate elements to be used in a method described herein. Suitable containers include, for example, bottles, vials, syringes, and test tubes. In some embodiments, the containers are formed from a variety of materials such as glass or plastic.

[000178] In some embodiments, the articles of manufacture provided herein contain packaging materials. Packaging materials for use in packaging pharmaceutical products include, but are not limited to, blister packs, bottles, tubes, inhalers, pumps, bags, vials, containers, syringes, bottles, and any packaging material suitable for a selected formulation and intended mode of administration and treatment.

[000179] In some embodiments, the container(s) described herein comprise one or more compounds described herein, optionally in a composition or in combination with another agent as disclosed herein. The container(s) optionally have a sterile access port (for example in some embodiments the container is an intravenous solution bag or a vial having a stopper pierceable by a hypodermic injection needle). Such kits optionally comprise a compound with an identifying description or label or instructions relating to its use in the methods described herein.

[000180] In some embodiments, a kit will comprises one or more additional containers, each with one or more of various materials (such as reagents, optionally in concentrated form, and/or devices) desirable from a commercial and user standpoint for use of a compound described herein. Non-limiting examples of such materials include, but are not limited to, buffers, diluents, filters, needles, syringes; carrier, package, container, vial and/or tube labels listing contents and/or instructions for use, and package inserts with instructions for use. A set of instructions is optionally included.

[000181] In some or any embodiments, a label is on or associated with the container. In some embodiments, a label is on a container when letters, numbers or other characters forming the label are attached, molded or etched into the container itself; a label is associated with a container when it is present within a receptacle or carrier that also holds the container, e.g., as a package insert. In some or any embodiments, a label indicates that the contents are to be used for a specific therapeutic application. In some embodiments, the label indicates directions for use of the contents, such as in the methods described herein.

[000182] In some or any embodiments, the pharmaceutical compositions are presented in a pack or dispenser device which contains one or more unit dosage forms containing a compound provided herein. In some embodiments, the pack contains a metal or plastic foil, such as a blister pack. The pack or dispenser device is optionally accompanied by instructions for administration. In some embodiments, the pack or dispenser is accompanied with a notice associated with the container in form prescribed by a governmental agency regulating the manufacture, use, or sale of pharmaceuticals, which notice is reflective of approval by the agency of the form of the drug for human or veterinary administration. In some or any

embodiments, such notice is, for example, the labeling approved by the U.S. Food and Drug Administration for prescription drugs, or the approved product insert. In some embodiments, compositions containing a compound provided herein are formulated in a compatible pharmaceutical carrier and are placed in an appropriate container labeled for treatment of an indicated condition.

[000183] Any combination of the groups described above for the various variables is contemplated herein.

PREPARATION OF COMPOUNDS

[000184] The following are illustrative examples of how the compounds can be prepared and tested. Although the examples can represent only some embodiments, it should be understood that the following examples are illustrative and not limiting.

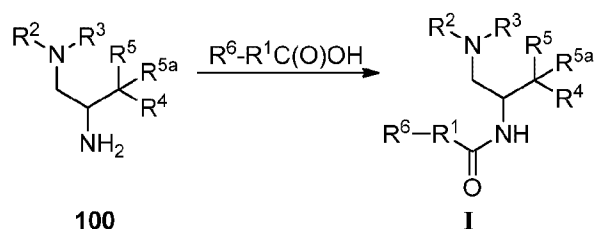
[000185] In a further aspect, it is provided a method of making a compound, comprising synthesizing a compound as any of the various embodiments described above or below. Examples of the method are further described in the Examples.

[000186] Compounds disclosed herein are commercially available or can be readily prepared from commercially available starting materials according to established methodology in the art of organic synthesis. General methods of synthesizing the compound can be found in, e.g., Stuart Warren and Paul Wyatt, Workbook for Organic Synthesis: The Disconnection Approach, second Edition, Wiley, 2010. Synthesis of some of the compounds are exemplified in detail below.

[000187] In some embodiments, individual stereoisomers of compounds are prepared synthetically from commercially available starting materials which contain asymmetric or chiral centers or by preparation of racemic mixtures followed by resolution. These methods of resolution are exemplified by (1) attachment of a mixture of enantiomers to a chiral auxiliary, separation of the resulting mixture of diastereomers by recrystallization or chromatography and liberation of the optically pure product from the auxiliary or (2) direct separation of the mixture of optical enantiomers on chiral chromatographic column.

[000188] Materials were obtained from commercial suppliers and were used without further purification. Air or moisture sensitive reactions were conducted under argon atmosphere using oven-dried glassware and standard syringe/septa techniques. ¹H NMR spectra were measured at 400 MHz unless stated otherwise and data were reported as follows in ppm (δ) from the internal standard (TMS, 0.0 ppm): chemical shift (multiplicity, integration, coupling constant in Hz).

General Scheme 1

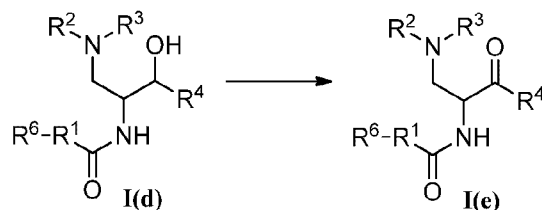


[000189] A Compound of Formula **I** (where all groups are as defined in the Summary of the Invention for a compound of Formula **I** or according to any of the embodiments disclosed herein) can be prepared according to General Scheme 1.

[000190] A Compound of Formula **I** can be prepared using standard amide coupling conditions. More specifically, an intermediate of formula **100**, which can be prepared using procedures disclosed herein or are known to one of ordinary skill in the art, is treated with $\text{R}^6\text{-R}^1\text{-C(O)OH}$ in a solvent such as DMF, DCM or THF, optionally in the presence of a base such as DIPEA or TEA, and in the presence of a coupling agent such as EDCI and/or HOBt to yield a compound of Formula **I**. The mixture can optionally be purified using procedures known to one of ordinary skill in the art. Alternatively, the intermediate of formula $\text{R}^6\text{-R}^1\text{-C(O)OH}$ can be treated with a chlorinating agent such as oxalyl chloride in a solvent such as DMF followed by treatment with the intermediate of formula **100** to yield a compound of Formula **I**. The mixture can optionally be purified (or individual isomers optionally resolved) using procedures known to one of ordinary skill in the art.

[000191] When R^6 is alkoxycarbonyl, the Compound of Formula **I** can be treated with an acid such as TFA in a solvent such as DCM. Reductive akylation on the free amine can done in a solvent such as DCM and/or MeOH in the presence of a reducing agent such as NaBH(OAc)_3 . The mixture can optionally be purified (or individual isomers optionally resolved) using procedures known to one of ordinary skill in the art.

General Scheme 2

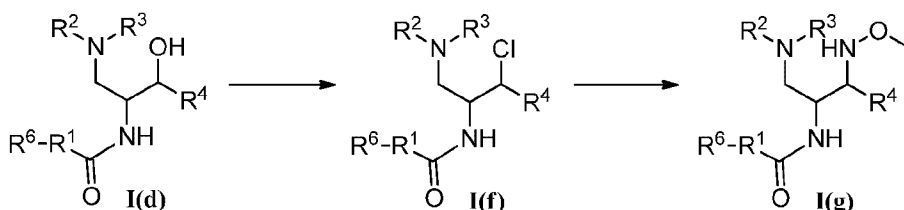


[000192] A Compound of Formula **I(e)** (where all groups are as defined in the Summary of the Invention for a compound of Formula **I** or according to any of the embodiments disclosed herein) can be prepared according to General Scheme 2. A Compound of Formula

I(d) is treated with a base such as NMP, in the presence of NHCO_3 , and in a solvent such as DCM to yield a Compound of Formula **I(e)**. The mixture can optionally be purified (or individual isomers optionally resolved) using procedures known to one of ordinary skill in the art.

[000193]

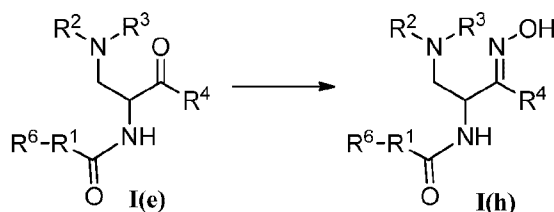
General Scheme 3



[000194] A Compound of Formula **I(f)** or **I(g)** (where all groups are as defined in the Summary of the Invention for a compound of Formula I or according to any of the embodiments disclosed herein) can be prepared according to General Scheme 3. A Compound of Formula **I(d)** is treated with a chlorinating agent such as SOCl_2 in a solvent such as DCM to yield a Compound of Formula **I(f)**. A Compound of Formula **I(g)** is prepared by treating a Compound of Formula **I(f)** with NH_2OCH_3 in a solvent such as MeOH. The mixture can optionally be purified (or individual isomers optionally resolved) using procedures known to one of ordinary skill in the art.

[000195]

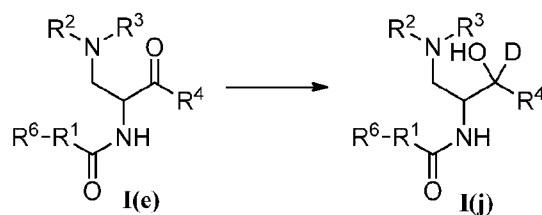
General Scheme 4



[000196] A Compound of Formula **I(h)** (where all groups are as defined in the Summary of the Invention for a compound of Formula I or according to any of the embodiments disclosed herein) can be prepared according to General Scheme 4. A Compound of Formula **I(e)** is treated with hydroxylamine in a solvent such as MeOH to yield a Compound of Formula **I(h)**. The mixture can optionally be purified (or individual isomers optionally resolved) using procedures known to one of ordinary skill in the art.

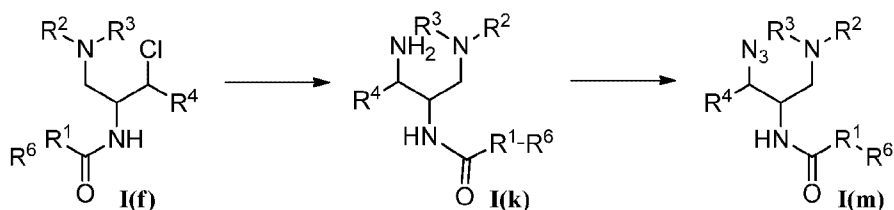
[000197]

General Scheme 5



[000198] A Compound of Formula **I(j)** (where all groups are as defined in the Summary of the Invention for a compound of Formula I or according to any of the embodiments disclosed herein) can be prepared according to General Scheme 5. A Compound of Formula **I(e)** is treated with NaBD₄ in a deuterated solvent such as CD₃OD to yield a Compound of Formula **I(j)**. The mixture can optionally be purified (or individual isomers optionally resolved) using procedures known to one of ordinary skill in the art.

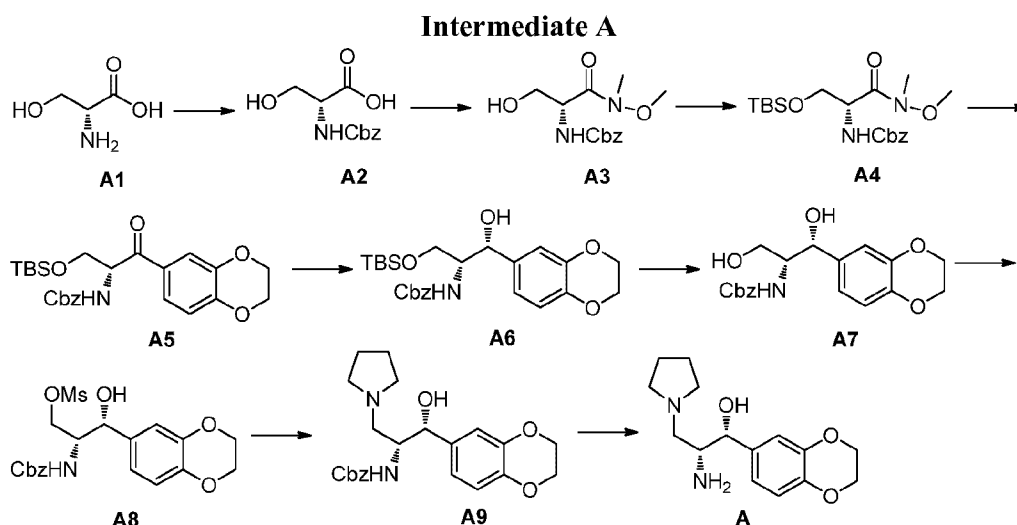
General Scheme 6



[000199] A Compound of Formula **I(k)** or **I(m)** (where all groups are as defined in the Summary of the Invention for a compound of Formula I or according to any of the embodiments disclosed herein) can be prepared according to General Scheme 6. A Compound of Formula **I(f)** is treated with NaN₃ in a solvent such as DMF and heated to about 50 °C to yield a Compound of Formula **I(k)** which can be optionally worked up before proceeding to the next step. The Compound of Formula **I(k)** is then treated with PPh₃ in a solvent such as THF to yield the Compound of Formula **I(m)**. The mixture can optionally be purified (or individual isomers optionally resolved) using procedures known to one of ordinary skill in the art.

[000200] In some or any embodiments of General Schemes 1-6, intermediate of formula **100** or the Compound of Formula **I(d)**, **I(e)**, or **I(f)** is that where R² and R³ together with the nitrogen to which they are attached form a 3-10-membered ring which is optionally substituted with 1, 2, or 3 R⁸ groups.

SYNTHETIC EXAMPLES



[000201] Benzyl chloroformate (50 mL, 50 w.t.% solution in toluene, 148 mmol) was added to a solution of (*R*)-2-amino-3-hydroxypropanoic acid (**A1**, 10.5 g, 100 mmol) in sat. aq NaHCO₃ solution (400 mL). The mixture was stirred vigorously for 4 h at 20 °C, and the aqueous solution was extracted with ether (400 mL x 2). The aqueous phase was acidified with conc. hydrochloric acid to pH = 2 and extracted with ethyl acetate (300 mL x 3). The combined organic phase was dried with Na₂SO₄ and concentrated to afford crude product Compound **A2**. LC-MS (*m/z*): 240 [M+1]⁺; ¹H-NMR (DMSO-*d*₆, 400 MHz) peaks: δ (ppm) 3.653 (m, 2H), 4.051 (m, 1H), 4.884 (m, 1H), 5.038 (s, 2H), 7.303-7.373 (m, 6H), 12.658 (s, 1H).

[000202] To a mixture of EDCI HCl (2.4g, 12.5 mmol), HOBt (1.7 g, 12.5 mmol), DIPEA (2.7 g, 20 mmol) in DCM (50 mL) was added Compound **A2** (1 g, 4 mmol) and *N,O*-dimethylhydroxylamine hydrochloride (1.2 g, 12.5 mmol). The mixture was stirred at room temperature overnight. The mixture was washed with hydrochloric acid solution (1 M, 50 mL x 2), saturated aqueous NaHCO₃ (20 mL), brine (20 mL), and dried over Na₂SO₄. The crude product was purified by silica gel column chromatography (ethyl acetate in petroleum, 30% v/v) to give Compound **A3**. LC-MS (*m/z*): 283 [M+1]⁺; ¹H-NMR (CDCl₃, 400 MHz) peaks: δ (ppm) 3.113 (s, 3H), 3.673 (s, 3H), 3.743 (t, *J* = 4.8 Hz, 2H), 4.766 (m, 1H), 4.959-5.044 (m, 2H), 6.046 (d, *J* = 8.0 Hz, 1H), 7.200-7.254 (m 5H).

[000203] TBDMS-Cl (800 mg, 5.31 mmol) in THF (10 mL) was added dropwise to a solution of Compound **A3** (500 mg, 1.77 mmol) and imidazole (602 mg, 8.86 mmol) in THF

(20 mL) at 0 °C. The mixture was stirred at room temperature for 2 h, and then filtered. The filtrate was washed with 1N HCl (50 mL x 2) and brine (50 mL), and dried over Na₂SO₄. The crude product was purified with silica gel column chromatography (ethyl acetate in petroleum, 13% v/v) to give Compound **A4**. LC-MS (m/z): 396 [M+1]⁺; ¹H-NMR (CDCl₃, 400 MHz) peaks: δ (ppm) 0.012 (s, 3H), 0.085 (s, 6H), 0.852 (s, 9H), 3.211 (s, 3H), 3.756 (s, 3H), 3.794-3.896 (m, 2H), 4.809 (m, 1H), 5.085 (q, *J* = 11.2 Hz, 2H), 5.662 (d, *J* = 8.8 Hz, 1H), 7.286-7.351 (m 5H).

[000204] To a solution of 6-bromo-2,3-dihydrobenzo[b][1,4]dioxine (4.9 g, 23 mmol) in THF (100 mL) was added *n*-BuLi (1.6 M, 15 mL) at -60 °C under N₂ and stirred for 0.5 h, before a solution of Compound **A4** (3 g, 7.6 mmol) in THF (50 mL) was added slowly. The mixture was stirred at -60 °C for 1 h, and followed by addition of a saturated NH₄Cl solution. The mixture was extracted with ethyl acetate (100 mL x 2), brine (100 mL), and then dried over Na₂SO₄. The crude product was purified by column chromatography on silica gel (ethyl acetate in petroleum, 10% v/v) to give Compound **A5**. LC-MS (m/z): 472 [M+1]⁺; ¹H-NMR (CDCl₃, 400 MHz) peaks: δ (ppm) 0.000 (s, 3H), 0.024(s, 3H), 0.892 (s, 9H), 4.024-4.116 (m, 1H), 4.402-4.465 (m, 4H), 5.262(s, 2H), 5.421 (m, 1H), 6.066 (d, *J* = 8.0 Hz, 1H), 7.043 (d, *J* = 8.0 Hz, 1H), 7.444-7.505 (m, 5H), 7.618-7.639 (m, 2H).

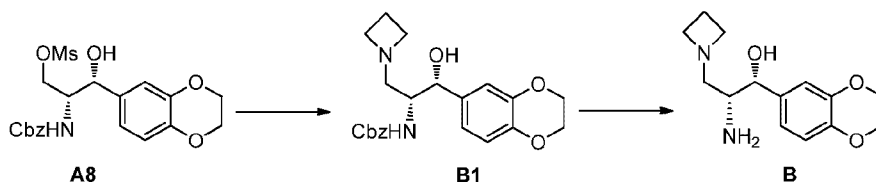
[000205] To a solution of Compound **A5** (5 g, 106 mmol) in THF (25 mL) and water (25 mL) was added acetic acid (75 mL). The resulting mixture was stirred at 35 °C for 16 h, diluted with brine (150 mL), adjusted to pH 8 with saturated aqueous sodium bicarbonate solution (75 mL), extracted with ethyl acetate (100 mL x 2), dried over anhydrous sodium sulfate, concentrated, and purified with flash column chromatography on silica gel (ethyl acetate in petroleum, 20% v/v) to yield Compound **A6**. LC-MS (ESI) (m/z): 358 [M+H]⁺; ¹H-NMR (CDCl₃, 400 MHz): δ (ppm) 2.81 (t, *J* = 6.0 Hz, 1H), 3.83-3.88 (m, 1H), 3.99-4.05 (m, 1H), 4.26-4.33 (m, 4H), 5.13 (s, 2H), 5.30-5.32 (m, 1H), 6.16 (d, *J* = 6.4 Hz, 1H), 6.92 (d, *J* = 8.0 Hz, 1H), 7.31-7.36 (m, 5H), 7.52-7.55 (m, 2H).

[000206] To a solution of Compound **A6** (714 mg, 2 mmol) in dry THF (20 mL) was added dropwise DIBAL-H (1.5 N, 2.7 mL, 4 mmol) under nitrogen at -80 °C. The resultant mixture was stirred at -80 °C for 30 min, and then DIBAL-H (1.5 N, 2.7 mL, 4 mmol) was added dropwise again. The mixture was stirred at -80 °C for 1 h, quenched with aqueous HCl solution (2 N, 12 mL) at -20 °C, extracted with ethyl acetate (50 mL x 2), dried over anhydrous sodium sulfate, and purified with flash column chromatography on silica gel (ethyl acetate in petroleum, 50% v/v) to furnish Compound **A7**. LC-MS (ESI) (m/z): 342 [M-OH]⁺; ¹H-NMR (CDCl₃, 400 MHz): δ (ppm) 2.76 (s, 1H), 3.26 (s, 1H), 3.72-3.83 (m, 3H), 4.21 (s,

4H), 4.86 (s, 1H), 5.02 (s, 2H), 5.51 (d, $J = 8.0$ Hz, 1H), 6.80 (s, 2H), 6.88 (s, 1H), 7.29-7.33 (m, 5H).

[000207] To a solution of the obtained Compound **A7** (3.6 g, 10 mmol) in THF (50 mL) was added Et₃N (3 g, 30 mmol), then the mixture was cooled to -15 °C before adding MsCl (0.8 mL) slowly. The mixture was stirred at -15 °C about half an hour. The reaction mixture was taken up with water (30 mL), extracted with ETHYL ACETATE (30 mL x 3), dried over anhydrous sodium sulfate, and evaporated to get Compound **A8**. To a solution of the resulted mesolate intermediate (**A8**) in THF (50 mL) was added pyrrolidine (5.7 g, 80 mmol), K₂CO₃ (11 g, 80 mmol) and NaI (3 g). The mixture was heated at 50 °C overnight. After filtration and evaporation, the crude product was purified by column chromatography on silica gel (methanol in dichloromethane, 5% v/v) to give Compound **A9**. LC-MS (m/z): 413 [$M+1$]⁺; ¹H-NMR (CDCl₃, 400 MHz): δ (ppm) 1.756 (m, 4H), 2.534 (m, 1H), 2.660 (m, 4H), 2.877 (m, 1H), 4.019 (m, 1H), 4.236 (s, 4H), 4.924 (d, $J = 2.8$ Hz, 1H), 5.043 (s, 2H), 5.079 (m, 1H), 6.7756-6.892 (m, 3H), 7.266-7.361 (m, 5H).

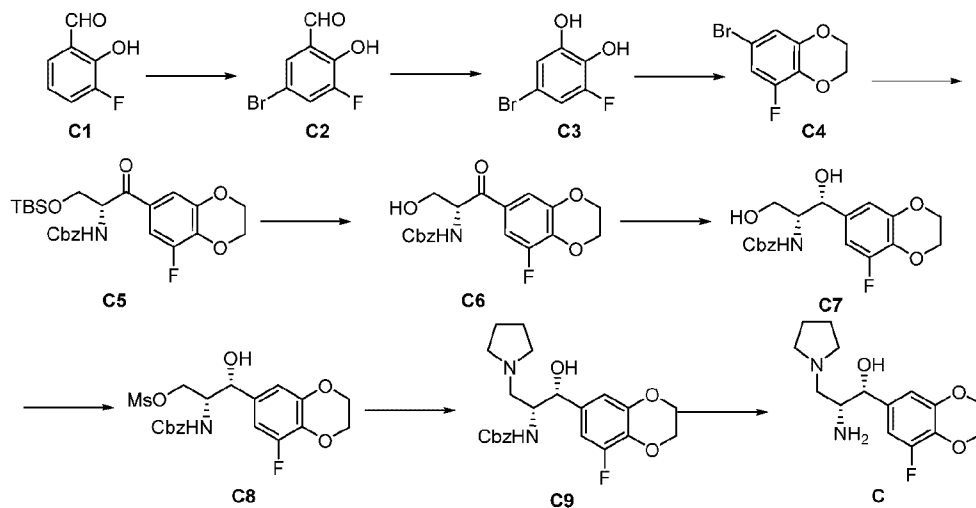
[000208] To a solution of Compound **A9** (2.5 g, 6.1 mmol) in methanol (20 mL) was added Pd(OH)₂ (250 mg), then the mixture was stirred at room temperature under H₂ overnight. The mixture was filtered and the filtrate was evaporated to dryness to give Intermediate **A**. LC-MS (m/z): 279 [$M+1$]⁺; ¹H-NMR (CDCl₃, 400 MHz): δ (ppm) 1.70 (m, 4H), 2.53 (m, 6H), 3.05 (m, 1H), 4.18(s, 4H), 4.47 (d, $J = 3.6$ Hz, 1H), 6.75 (m, 3H).

Intermediate B

[000209] Intermediates **B1** and **B** were synthesized, by employing the procedures described for Intermediates **A9** and **A** using azetidine and Intermediate **B1** in lieu of pyrrolidine and Intermediate **A9**.

[000210] Intermediates **B1**. LC-MS (ESI) m/z : 399 $[M+H]^+$; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ (ppm) 2.09-2.16 (m, 2H), 2.74-2.77 (m, 1H), 2.97-3.00 (m, 1H), 3.35-3.42 (m, 4H), 3.81 (s, 1H), 4.24 (s, 4H), 4.92 (s, 1H), 4.98-5.20 (m, 3H), 6.80-6.82 (m, 3H), 7.26-7.31 (m, 5H).

[000211] Intermediate **B**. LC-MS (ESI) m/z : 265 $[M+H]^+$; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ (ppm) 2.02-2.04 (m, 2H), 2.53-2.57 (m, 2H), 3.22-3.25 (m, 4H), 4.19 (s, 5H), 4.51 (d, J = 3.2 Hz, 1H), 6.72-6.80 (m, 3H).

Intermediate C

[000212] To a solution of Compound **C1** (50 g, 357 mmol) in MeCN (400 mL) was added NBS (60.08 g, 360 mmol) and HCOONH_4 (2.47 mg, 39 mmol) at room temperature and then the mixture was stirred at room temperature for 2 h. After removal of the solvent the mixture was diluted with ethyl acetate (200 mL), then washed with brine, dried over anhydrous Na_2SO_4 , and concentrated to give Compound **C2**. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ (ppm) 7.48-7.23 (m, 2H), 9.87 (s, 1H), 10.89 (s, 1H).

[000213] To a solution of Compound **C2** (40 g, 183 mmol) in THF (260 mL) was added dropwise aq. NaOH solution (0.05 N, 720 mL, 37 mmol) at 0 °C, then 30% H₂O₂ solution (90 mL). The mixture was stirred for 2 h at room temperature and followed by the addition of a second portion of 30% H₂O₂ (90 mL). After stirring for 4 h, it was cooled to 0 °C and aq. NaOH solution (2 N, 112 mL) was added to reach a pH 10~11. The mixture was stirred for 0.5 h and quenched with conc. HCl at 0 °C to pH 2~3. It was extracted with dichloromethane (250 mL x 3) and washed with brine (300 mL x 2), dried over Na₂SO₄, and concentrated to give Compound **C3**. LC-MS (m/z): 205 [M-1]⁻.

[000214] To a mixture of Compound **C3** (30 g, 146 mol), K₂CO₃ (60.3 g, 437 mol) in DMF (450 mL) was added 1, 2-dibromoethane (63 mL, 730 mol). The mixture was stirred at 80 °C for 4 h. After cooling to room temperature, it was filtered and the cake was washed with ethyl acetate (100 mL). The filtrate was diluted with water (900 mL) and extracted with ethyl acetate (400 mL x 3). The organic layer was washed with water (900 mL x 5) and brine (900 mL x 1), dried, concentrated, and purified by column chromatography on silica gel (ethyl acetate in petroleum, 5 % v/v) to afford Compound **C4**. ¹H-NMR (CDCl₃, 400 MHz): δ (ppm) 4.35 (s, 4H), 6.91 (t, *J* = 8 Hz, 1H), 7.33 (s, 1H).

[000215] Intermediates **C5**, **C6**, **C7**, **C8**, **C9**, and **C** were synthesized, by employing the procedures described correspondingly for Intermediates **A5**, **A6**, **A7**, **A8**, **A9**, and **A** using Intermediates **C4**, **C5**, **C6**, **C7**, **C8**, and **C9** in lieu of 6-bromo-2,3-dihydrobenzo[b][1,4]dioxine, Intermediates **A5**, **A6**, **A7**, **A8**, and **A9**.

[000216] Intermediate **C5**. LC-MS (m/z): 490 [M+1]⁺.

[000217] Intermediate **C6**. LC-MS (ESI) m/z: 376 [M+H]⁺; ¹H-NMR (CDCl₃, 400 MHz): δ (ppm) 2.50-2.53 (m, 1H), 3.78-3.83 (m, 1H), 3.91-3.97 (m, 1H), 4.25-4.27 (m, 2H), 4.31-4.33 (m, 2H), 5.07 (s, 2H), 6.00 (d, *J* = 4 Hz, 1H), 7.24-7.31 (m, 7H).

[000218] Intermediate **C7**. LC-MS (ESI) m/z: 360 [M-OH]⁺; ¹H-NMR (CDCl₃, 400 MHz): δ (ppm) 3.45-3.59 (m, 3H), 4.23-4.24 (m, 4H), 4.84 (s, 1H), 5.00 (s, 2H), 5.54 (d, *J* = 8 Hz, 1H), 6.69 (t, *J* = 8 Hz, 2H), 7.27-7.35 (m, 5H).

[000219] Intermediate **C8**. LC-MS (m/z): 438 [M+1-18]⁺.

[000220] Intermediate **C9**. LC-MS (m/z): 431 [M+1]⁺.

[000221] Intermediate **C**. LC-MS (m/z): 297 [M+1]⁺.

mL x 4), dried over anhydrous sodium sulfate, filtered, and concentrated to afford the crude product. The crude product was purified with flash column chromatography on silica gel (petroleum ether) to furnish Compound **E2**. HPLC: Rt: 1.96 minute. ¹H-NMR (CDCl₃, 400 MHz): δ (ppm) 0.80-0.88 (m, 4H), 3.67-3.82 (m, 1H), 7.15 (d, J = 8.8 Hz, 1H), 7.32 (dd, J = 8.8, 2.4 Hz, 1H), 7.47 (d, J = 2.4 Hz, 1H).

[000226] Intermediates **E3**, **E4**, **E5**, **E6**, and **E7**, were synthesized, by employing the procedures described for Intermediates **A5**, **A6**, **A7**, **A8**, and **A9** using Intermediates **E2**, **E3**, **E4**, **E5**, and **E6** in lieu of 6-bromo-2,3-dihydrobenzo[b][1,4]dioxine, Intermediates **A5**, **A6**, **A7**, and **A8**.

[000227] Intermediate **E3**. LC-MS (ESI) m/z : 504 [M+H]⁺; ¹H-NMR (CDCl₃, 400 MHz): δ (ppm) 0.01 (d, J = 6.0 Hz, 6H), 0.87 (s, 9H), 1.02 (d, J = 4.8 Hz, 4H), 1.36-1.40 (m, 1H), 3.99-4.03 (m, 1H), 4.09 (dd, J = 10.0, 3.6 Hz, 1H), 5.26 (s, 2H), 5.42-5.44 (m, 1H), 6.04 (d, J = 8.0 Hz, 1H), 7.44-7.50 (m, 6H), 8.00 (dd, J = 8.8, 1.6 Hz, 1H), 8.11 (s, 1H).

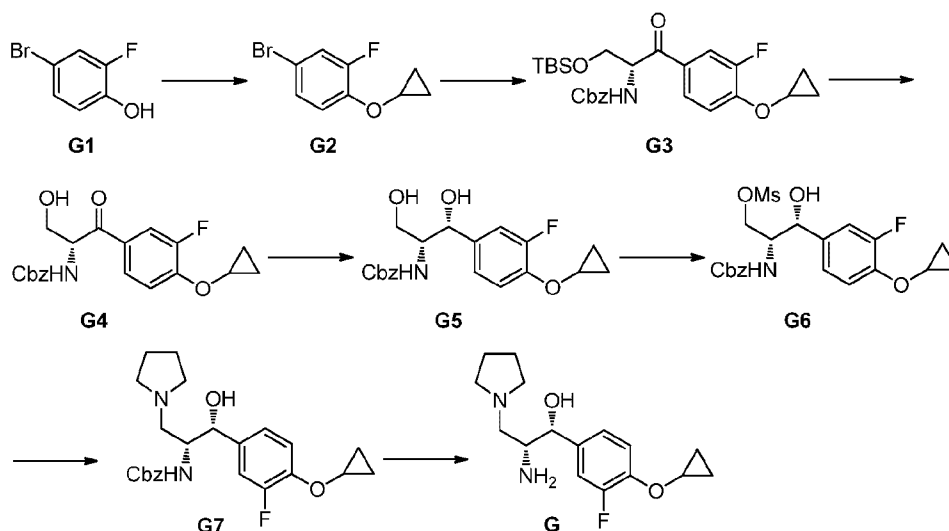
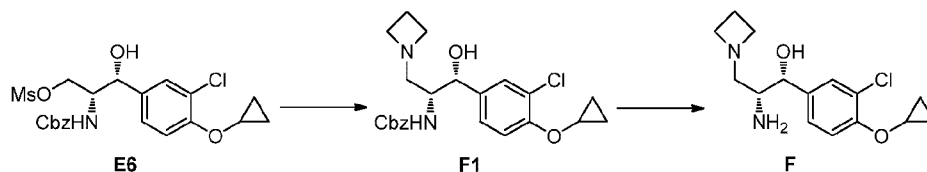
[000228] Intermediate **E4**. LC-MS (ESI) m/z : 390 [M+H]⁺, 412 [M+Na]⁺; ¹H-NMR (CDCl₃, 400 MHz): δ (ppm) 0.89 (d, J = 4.5 Hz, 4H), 2.78 (s, 1H), 3.81-3.92 (m, 2H), 4.01 (d, J = 9.4 Hz, 1H), 5.08-5.17 (m, 2H), 5.26-5.38 (m, 1H), 6.12 (d, J = 6.9 Hz, 1H), 7.25-7.45 (m, 6H), 7.92 (d, J = 8.5 Hz, 1H), 8.02 (s, 1H).

[000229] Intermediate **E5**. LC-MS (ESI) m/z : 374 [M-OH]⁺; ¹H-NMR (CDCl₃, 400 MHz): δ (ppm) 0.80-0.83 (m, 4H), 1.23-1.27 (m, 1H), 2.79 (s, 1H), 3.45 (d, J = 2.0 Hz, 1H), 3.74-3.81 (m, 4H), 4.93-5.08 (m, 2H), 5.52-5.54 (m, 1H), 7.16-7.37 (m, 8H).

[000230] Intermediate **E6**, which was directly used for the next step without further purification. LC-MS (ESI) m/z : 452 [M-OH]⁺.

[000231] Intermediate **E7**, which was directly used for the next step without further purification. LC-MS (ESI) m/z : 311 [M+H]⁺.

[000232] To a solution of Compound **E7** (520 mg, 1.17 mmol) in ethanol (12 mL) and water (2 mL) was added LiOH·H₂O (197 mg, 4.68 mmol). The mixture was heated to 80 °C and stirred for 16 h. The reaction was diluted with water (15 mL) and extracted with dichloromethane (50 mL x 2). The combined organic phases were washed with water (50 mL) and brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to furnish Compound **E**, which was directly used for the next step without further purification. LC-MS (ESI) m/z : 311 [M+H]⁺.



ether, 100% v/v) to furnish Compound **G2**. LC-MS (ESI) m/z: No. ¹H-NMR (CDCl₃, 400 MHz): δ (ppm) 0.79-0.84 (m, 4H), 3.78-3.80 (m, 1H), 7.14-7.23 (m, 3H).

[000237] Intermediates **G3**, **G4**, **G5**, **G6**, **G7**, and **G**, were synthesized, by employing the procedures described for Intermediates **A5**, **A6**, **A7**, **A8**, **A9**, and **A** using Intermediates **G2**, **G3**, **G4**, **G5**, **G6**, and **G7** in lieu of 6-bromo-2,3-dihydrobenzo[b][1,4]dioxine, Intermediates **A5**, **A6**, **A7**, **A8**, and **A9**.

[000238] Intermediate **G3**. LC-MS (ESI) m/z: 488 [M+H]⁺; ¹H-NMR (DMSO-*d*₆, 400 MHz): δ (ppm) -0.08 (s, 6H), 0.82 (m, 1H), 0.84-0.88 (m, 2H), 3.81-3.90 (m, 2H), 4.05-4.09 (m, 1H), 5.03 (s, 2H), 5.13-5.18 (m, 1H), 7.27-7.36 (m, 5H), 7.53 (t, *J* = 8.4 Hz, 1H), 7.64 (d, *J* = 8.4 Hz, 1H), 7.74 (dd, *J* = 12.0, 2.4 Hz, 1H), 7.86 (d, *J* = 8.4 Hz, 1H).

[000239] Intermediate **G4**. LC-MS (ESI) m/z: 374 [M+H]⁺; ¹H-NMR (DMSO-*d*₆, 400 MHz): δ (ppm) 0.75-0.89 (m, 4H), 3.62-3.78 (m, 2H), 4.07-4.09 (m, 1H), 4.91 (t, *J* = 5.6 Hz, 1H), 5.03 (s, 2H), 5.10-5.14 (m, 1H), 7.26-7.38 (m, 5H), 7.55 (t, *J* = 8.8 Hz, 1H), 7.60 (d, *J* = 8.0 Hz, 1H), 7.79 (dd, *J* = 12.0, 1.6 Hz, 1H), 7.90 (d, *J* = 8.4 Hz, 1H).

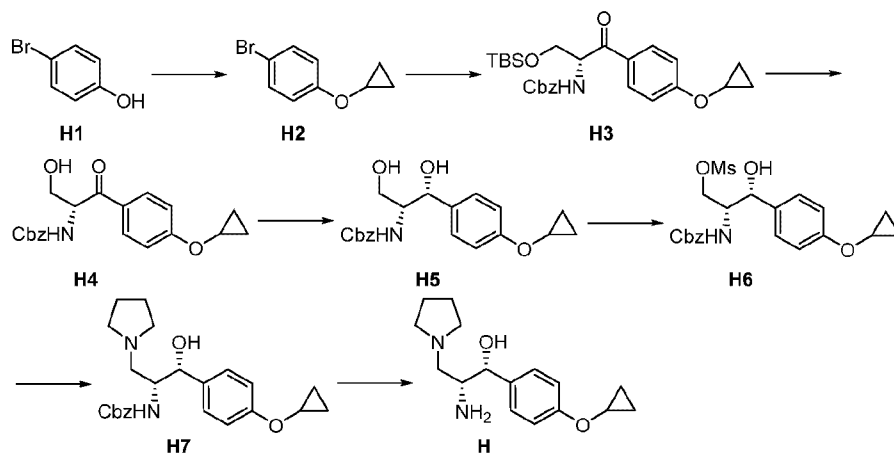
[000240] Intermediate **G5**. LC-MS (ESI) m/z: 376 [M+H]⁺; ¹H-NMR (DMSO-*d*₆, 400 MHz): δ (ppm) 0.38-0.81 (m, 4H), 3.25-3.31 (m, 1H), 3.47-3.53 (m, 1H), 3.64-3.65 (m, 1H), 3.88-3.91 (m, 1H), 4.72-4.77 (m, 2H), 4.87-5.01 (m, 2H), 5.37 (d, *J* = 5.2 Hz, 1H), 6.75 (d, *J* = 10.0 Hz, 1H), 7.05-7.34 (m, 8H).

[000241] Intermediate **G6**, which was used for the next step without further purification. LC-MS (ESI) m/z: 436 [M-OH]⁺.

[000242] Intermediate **G7**. LC-MS (ESI) m/z: 429 [M+H]⁺; ¹H-NMR (DMSO-*d*₆, 400 MHz): δ (ppm) 0.68-0.81 (m, 4H), 1.66 (s, 4H), 2.24-2.50 (m, 5H), 2.59-2.64 (m, 1H), 3.75-3.81 (m, 1H), 3.88-3.91 (m, 1H), 4.72 (s, 1H), 4.87-5.00 (m, 2H), 5.52 (brs, 1H), 6.79 (d, *J* = 9.2 Hz, 1H), 7.05-7.13 (m, 2H), 7.17-7.34 (m, 6H).

[000243] Intermediate **G**. LC-MS (ESI) m/z: 295 [M+H]⁺; ¹H-NMR (DMSO-*d*₆, 400 MHz): δ (ppm) 0.67-0.79 (m, 4H), 1.23 (s, 2H), 1.65 (s, 4H), 2.16-2.20 (m, 1H), 2.29-2.36 (m, 6H), 2.86-2.89 (m, 1H), 3.89-3.93 (m, 1H), 4.38 (d, *J* = 4.8 Hz, 1H), 7.06-7.15 (m, 2H), 7.32 (t, *J* = 8.4 Hz, 1H).

Intermediate H



[000244] To a solution of Compound **H1** (100 g, 0.58 mol) in 1-methyl-2-pyrrolidinone (1.5 L) was added cesium carbonate (377 g, 1.169 mol) and bromocyclopropane (93 mL, 1.16 mol). The mixture was stirred between 140 °C and 150 °C for 24 h. After the reaction mixture was cooled to ambient temperature, the dark solution was diluted with water (1 L) and extracted with a mixture of ethyl acetate (600 mL x 3). The combined organic phases were washed with brine (200 mL x 4), dried over anhydrous sodium sulfate, filtered, and concentrated to afford the crude Compound **H2**. The crude product was purified with flash column chromatography on silica gel (petroleum ether) to furnish Intermediate **H2**. Retention time: 2.19 minutes; ¹H-NMR (CDCl₃, 400 MHz): δ (ppm) 0.66-0.75 (m, 4H), 3.60-3.71 (m, 1H), 6.82-7.02 (m, 2H), 7.28-7.41 (m, 2H).

[000245] Intermediates **H3**, **H4**, **H5**, **H6**, and **H7**, were synthesized, by employing the procedures described for Intermediates **A5**, **A6**, **A7**, **A8**, and **A9** using Intermediates **H2**, **H3**, **H4**, **H5**, and **H6** in lieu of 6-bromo-2,3-dihydrobenzo[b][1,4]dioxine, Intermediates **A5**, **A6**, **A7**, and **A8**.

[000246] Intermediate **H3**. LC-MS (ESI) m/z : 470 [M+H]⁺.

[000247] Intermediate **H4**. LC-MS (ESI) m/z : 356 [M+H]⁺, 378 [M+Na]⁺; ¹H NMR (DMSO-*d*₆, 400 MHz): δ (ppm) 0.65-0.72 (m, 2H), 0.78-0.88 (m, 2H), 3.58-3.71 (m, 1H), 3.75-3.80 (m, 1H), 3.94-3.99 (m, 1H), 4.89 (t, J = 5.8 Hz, 1H), 5.04 (s, 2H), 5.16 (dd, J = 13.0, 5.5 Hz, 1H), 7.17 (d, J = 8.7 Hz, 2H), 7.32-7.38 (m, 4H), 7.51 (d, J = 7.9 Hz, 1H), 8.00 (d, J = 8.7 Hz, 2H).

[000248] Intermediate **H5**. LC-MS (ESI) m/z : 340 [M-OH]⁺. ¹H-NMR (CDCl₃, 400 MHz): δ (ppm) 0.74-0.77 (m, 4H), 1.81 (s, 1H), 2.76 (s, 1H), 3.23 (s, 1H), 3.65-3.90 (m, 4H), 4.92-5.08 (m, 2H), 5.51 (d, J = 7.8 Hz, 1H), 6.99 (d, J = 8.6 Hz, 2H), 7.27-7.38 (m, 7H).

ethyl acetate (100 mL x 3). The combined organic phases were washed water (10 mL) and brine (10 mL x 2), and dried over anhydrous Na₂SO₄. The crude product was purified with column chromatography on silica gel (ethyl acetate in petroleum, 20% v/v) to provide Compound **J4**. LC-MS (m/z): 475 [M+1]⁺; ¹H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 0.06 (s, 3H), 0.08 (s, 3H), 0.92 (s, 9H), 1.34 (d, J = 6.4 Hz, 6H), 3.70-3.81 (m, 3H), 5.01 (s, 1H), 5.05 (d, J = 4.4 Hz, 1H), 5.60 (s, 1H), 5.28 (m, 1H), 5.46 (d, J = 8.0 Hz, 1H), 6.64 (d, J = 8.4 Hz, 1H), 7.32-7.34 (m, 5H), 7.56 (dd, J = 2.4, 8.4 Hz, 1H), 8.11 (s, 1H).

[000257] To a solution of Compound **J4** (7.7 g, 16.24 mmol) in THF (150 mL) was added a solution of TBAF (2.12 g, 8.12 mmol) in THF (10 mL) at 0 °C, then the mixture was stirred at 30 °C overnight. After the reaction was complete as monitored by TLC and LC-MS, it was concentrated by evaporation. Then residue was treated with water (50 mL) and extracted with ethyl acetate (100 mL x 3), washed with brine (10 mL), and dried over anhydrous Na₂SO₄. The crude product was purified with flash column (silica gel, methanol in dichloromethane, 8% v/v) to furnish Compound **J5**. LC-MS (m/z): 361 [M+1]⁺; ¹H-NMR (DMSO-*d*₆, 400 MHz) major characteristic peaks: δ (ppm) 1.27 (d, J = 6.4 Hz, 6H), 3.29 (m, 1H), 3.52-3.59 (m, 2H), 4.46-4.52 (m, 1H), 4.71-4.96 (m, 3H), 5.22 (m, 1H), 5.33 (d, J = 4.8 Hz, 0.6H), 5.39 (d, J = 4.8 Hz, 0.4H), 5.60 (s, 1H), 6.64 (d, J = 8.4 Hz, 1H), 6.79 (d, J = 8.4 Hz, 0.6H), 6.95 (d, J = 8.4 Hz, 0.4H), 7.13-7.28 (m, 5H), 7.59 (m, 1H), 8.03 (s, 1H).

[000258] Intermediates **J6**, **J7**, and **J** were synthesized, by employing the procedures described for Intermediates **A8**, **A9**, and **A** using Intermediates **J5**, **J6**, and **J7** in lieu of Intermediates **A7**, **A8**, and **A9**.

[000259] Intermediate **J6**. LC-MS (m/z): 439 [M+1]⁺.

[000260] Intermediate **J7**. LC-MS (m/z): 414 [M+1]⁺; ¹H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 1.27 (d, J = 6.0 Hz, 6H), 1.71 (m, 4H), 2.59 (m, 4H), 2.72-2.76 (m, 2H), 4.96-5.02 (m, 3H), 5.22 (m, 1H), 6.57 (d, J = 8.4 Hz, 1H), 7.20-7.29 (m, 5H), 7.44 (d, J = 8.4 Hz, 1H), 8.01 (s, 1H).

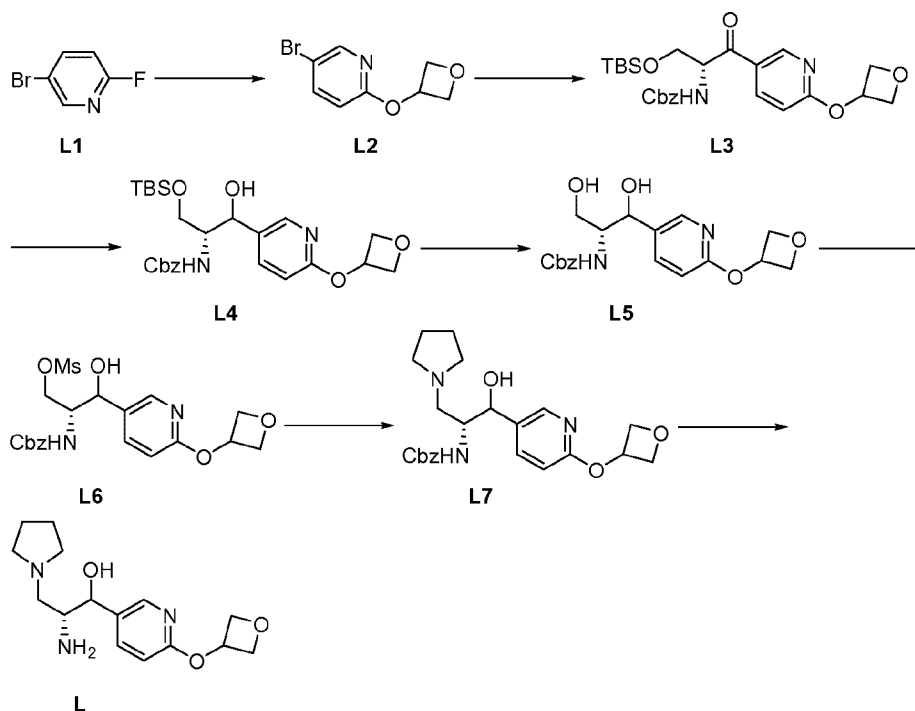
[000261] Intermediate **J**. LC-MS (m/z): 280 [M+1]⁺.

[000267] Intermediate **K6**. LC-MS (ESI) m/z : 438 $[M-OH]^+$; ^1H -NMR ($CDCl_3$, 400 MHz): δ (ppm) 2.98 (s, 3H), 4.22-4.31 (m, 5H), 4.38 (d, $J = 4.4$ Hz, 2H), 5.31 (s, 4H), 5.60 (d, $J = 6.0$ Hz, 1H), 6.68 (d $J = 8.8$ Hz, 1H), 6.79 (t, $J = 7.6$ Hz, 1H), 7.33-7.43 (m, 5H).

[000268] Intermediate **K7**. LC-MS (ESI) m/z : 431 $[M+H]^+$.

[000269] Intermediate **K**. LC-MS (ESI) m/z : 297 $[M+H]^+$; ^1H -NMR (CD_3OD , 400 MHz): δ (ppm) 1.71-1.81 (m, 4H), 2.56-2.68 (m, 4H), 3.08-3.17 (m, 2H), 4.17-4.21 (m, 5H), 4.76 (d, $J = 6.0$ Hz, 1H), 6.59-6.66 (m, 1H), 6.81-6.88 (m, 1H).

Intermediate L



[000270] Compounds 5-bromo-2-fluoropyridine (**L1**, 17.6 g, 0.10 mol) and oxetan-3-ol (11.1 g, 0.15 mol) were dissolved in NMP (100 mL) and treated with potassium *tert*-butoxide (150 mL, 1 M solution in THF, 0.15 mol) at 0 °C. The solution became dark, cloudy, and warmed. After 30 min. the reaction mixture was partitioned between ethyl acetate: petroleum ether (1:1, 400 mL) and water (400 mL). The organic layer was separated, washed with water and 5% aq. LiCl, dried over sodium sulfate, filtered, and concentrated. The residue was purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, 10% v/v) to afford Compound **L2**. LC-MS (ESI) m/z : 232 $[M+H]^+$; ^1H -NMR ($CDCl_3$, 400 MHz) δ (ppm) 4.69-4.72 (m, 2H), 4.97 (t, $J = 6.8$ Hz, 2H), 5.53-5.58 (m, 1H), 6.72 (d, $J = 8.4$ Hz, 1H), 7.68 (dd, $J_1 = 8.4$ Hz, $J_2 = 2.4$ Hz, 1H), 8.11 (d, $J = 2.4$ Hz, 1H).

[000271] Intermediates **L3**, **L4**, **L5**, **L6**, **L7**, and **L**, were synthesized, by employing the procedures described for Intermediates **J3**, **J4**, **J5**, **J6**, **J7**, and **J** using Intermediates **L2**, **L3**, **L4**, **L5**, **L6**, and **L7** in lieu of Intermediates **J2**, **J3**, **J4**, **J5**, **J6**, and **J7**.

[000272] Intermediate **L3**. LC-MS (ESI) m/z : 487 $[M+H]^+$;

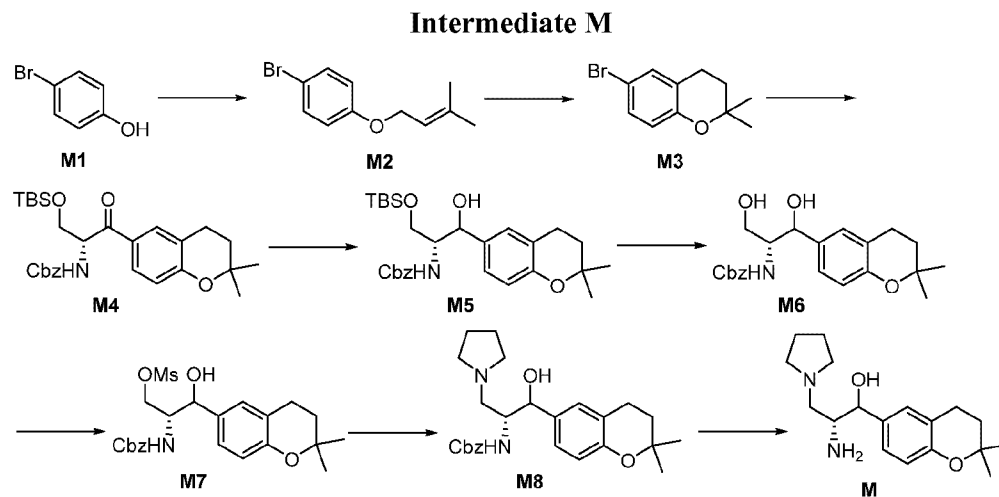
[000273] Intermediate **L4**. LC-MS (ESI) m/z : 489 $[M+H]^+$; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ (ppm) 0.00 (s, 6H), 0.86 (s, 9H), 3.62-3.81 (m, 4H), 4.64-4.67 (m, 2H), 4.89-5.02 (m, 5H), 5.36-5.38 (m, 1H), 5.51-5.54 (m, 1H), 6.66-6.72 (m, 1H), 7.19-7.29 (m, 5H), 7.53-7.56 (m, 1H), 7.79 (s, 1H).

[000274] Intermediate **L5**. LC-MS (ESI) m/z : 375 $[M+H]^+$; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ (ppm) 3.81-3.87 (m, 3H), 4.70-4.73 (m, 2H), 4.96-5.03 (m, 4H), 5.48-5.51 (m, 1H), 5.57-5.61 (m, 1H), 6.73-6.75 (m, 1H), 7.29-7.37 (m, 5H), 7.61-7.64 (m, 1H), 8.05-8.06 (m, 1H).

[000275] Intermediate **L6**. LC-MS (ESI) m/z : 453 $[M+H]^+$.

[000276] Intermediate **L7**. LC-MS (ESI) m/z : 428 $[M+H]^+$.

[000277] Intermediate **L**. LC-MS (ESI) m/z : 293 $[M+H]^+$; $^1\text{H-NMR}$ (MeOD , 400 MHz) δ (ppm) 2.26 (dd, $J_1 = 11.6$ Hz, $J_2 = 4.4$ Hz, 1H), 2.44-2.62 (m, 5H), 3.07-3.12 (m, 1H), 4.08-4.11 (m, 1H), 4.51 (d, $J = 5.6$ Hz, 1H), 4.69-4.72 (m, 2H), 4.97 (t, $J = 6.8$ Hz, 2H), 5.53-5.58 (m, 1H), 6.95 (d, $J = 8.8$ Hz, 1H), 7.75 (dd, $J_1 = 8.8$ Hz, $J_2 = 2.4$ Hz, 1H), 8.11 (d, $J = 2.4$ Hz, 1H).



[000278] A suspension of Compound **M1** (30.00 g, 0.173 mol), 1-bromo-3-methylbut-2-ene (28.42 g, 0.190 mol), K_2CO_3 (35.81 g, 0.360 mol) and KI (500 mg) in acetone (70 mL) was stirred at 65 $^\circ\text{C}$, for 16 h. The mixture was filtrated to remove solid. The filtrate was purified with silica chromatography (ethyl acetate in petroleum ether, from 0% to 2% v/v) to furnish Compound **M2**. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ (ppm) 1.73 (s, 3H), 1.79 (s, 3H), 4.46

(d, $J = 6.8$ Hz, 2H), 5.46 (t, $J = 8.0$ Hz, 1H), 7.78 (d, $J = 9.2$ Hz, 2H), 7.36 (d, $J = 9.2$ Hz, 2H).

[000279] To a solution of Compound **M2** (20.00 g, 0.083 mmol) in DCM (200 mL) was added dropwise trifluoromethanesulfonic acid (7.4 mL) at -78 °C. After addition, the mixture was stirred at 28 °C for 10 min. Then it was quenched with 15% KOH (100 mL), washed with water (50 mL x 3) and brine (50 mL x 2), dried over anhydrous sodium sulfate, concentrated, and purified with silica chromatography (ethyl acetate in petroleum ether, from 0% to 8% v/v) to furnish Compound **M3**. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ (ppm) 1.32 (s, 6H), 1.79 (t, $J = 6.8$ Hz, 3H), 2.74 (d, $J = 6.8$ Hz, 2H), 6.65 (d, $J = 8.0$ Hz, 1H), 7.16 (d, $J = 8.8$ Hz, 2H).

[000280] Intermediates **M4**, **M5**, **M6**, **M7**, and **M8**, were synthesized, by employing the procedures described for Intermediates **J3**, **J4**, **J5**, **J6**, and **J7** using Compound **M3**, **M4**, **M5**, **M6**, and **M7** in lieu of Intermediate **J2**, **J3**, **J4**, **J5**, and **J6**.

[000281] Intermediate **M4**. LC-MS (ESI) m/z : 498 $[\text{M}+\text{H}]^+$; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ (ppm) -0.14 (s, 3H), -0.12 (s, 3H), 0.74 (s, 9H), 1.36 (s, 6H), 2.79-2.85 (m, 2H), 3.75 (t, $J = 6.8$ Hz, 2H), 3.86-3.95 (m, 2H), 5.12 (s, 2H), 5.29-5.34 (m, 1H), 5.93 (d, $J = 7.6$ Hz, 1H), 7.80 (d, $J = 8.4$ Hz, 1H), 7.32-7.38 (m, 6H), 7.70-7.74 (m, 2H).

[000282] Intermediate **M5**. LC-MS (ESI) m/z : 482 $[\text{M-OH}]^+$; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ (ppm) 0.90 (s, 15H), 1.32 (s, 6H), 1.76-1.80 (m, 2H), 2.74 (t, $J = 6.4$ Hz, 2H), 3.67-3.83 (m, 3H), 4.19 (s, 1H), 4.91-5.12 (m, 3H), 5.29-5.46 (m, 1H), 6.73 (d, $J = 8.8$ Hz, 1H), 6.97-7.05 (m, 2H), 7.27-7.38 (m, 5H).

[000283] Intermediate **M6**. LC-MS (ESI) m/z : 368 $[\text{M-OH}]^+$; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ (ppm) 0.95 (s, 6H), 1.79 (t, $J = 6.8$ Hz, 2H), 2.75 (t, $J = 6.8$ Hz, 2H), 3.76-4.26 (m, 4H), 4.62-5.18 (m, 4H), 6.77 (d, $J = 8.4$ Hz, 1H), 6.96-7.06 (m, 2H), 7.30-7.36 (m, 5H).

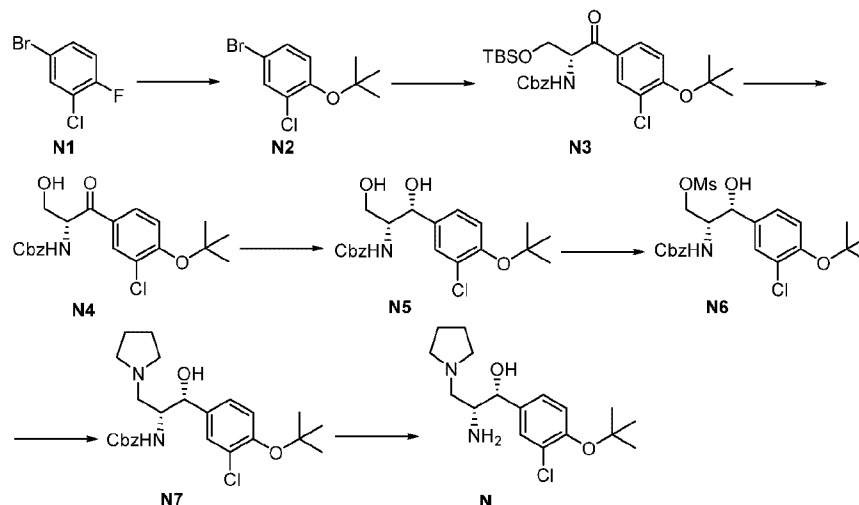
[000284] Intermediate **M7**. LC-MS (ESI) m/z : 446 $[\text{M-OH}]^+$; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ (ppm) 1.02 (s, 6H), 1.82 (t, $J = 6.8$ Hz, 2H), 2.98 (t, $J = 6.8$ Hz, 2H), 3.16 (s, 3H), 3.80-4.20 (m, 4H), 4.80-5.10 (m, 4H), 6.72 (d, $J = 8.4$ Hz, 1H), 6.96-7.06 (m, 2H), 7.30-7.36 (m, 5H).

[000285] Intermediate **M8**. LC-MS (ESI) m/z : 439 $[\text{M-OH}]^+$; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ (ppm) 1.32 (s, 6H), 1.71-1.80 (m, 6H), 2.42-2.56 (m, 2H), 2.66-2.79 (m, 6H), 3.39-3.44 (m, 1H), 3.97-4.06 (m, 1H), 4.70 (s, 1H), 4.93 (s, 1H), 5.04 (s, 2H), 6.73-6.79 (m, 1H), 6.99-7.09 (m, 2H), 7.29-7.38 (m, 5H).

[000286] A solution of Compound **M8** (2.10 g, 4.79 mmol) and KOH (2.68 g, 47.94 mmol) in EtOH/ H_2O (50/5 mL) was stirred at 80 °C for 16 h. And then it was diluted with

ethyl acetate (200 mL), washed with water (200 mL) and brine (200 mL), dried over anhydrous sodium sulfate, and purified with reverse phase chromatography using eluent (methanol in water, from 0% to 100% v/v) to furnish Intermediate **M**. LC-MS (ESI) m/z : 305 $[M-OH]^+$; ^1H -NMR ($CDCl_3$, 400 MHz): δ (ppm) 1.32 (s, 6H), 1.76-1.81 (m, 8H), 2.47-2.68 (m, 6H), 2.78 (t, J = 6.8 Hz, 2H), 3.11-3.16 (m, 1H), 3.49 (s, 1H), 4.55 (s, 1H), 6.75 (d, J = 8.0 Hz, 1H), 7.02-7.12 (m, 2H).

Intermediate N



[000287] To a solution of Compound **N1** (10.00 g, 47.85 mmol) in DMF (100 mL) was added *t*-BuOK (8.04 mL, 71.77 mmol) at room temperature. The mixture was stirred room temperature for 2 h and quenched with water (100 mL). The mixture was diluted with ethyl acetate (300 mL), washed with water (200 mL) and brine (200 mL), dried over anhydrous sodium sulfate, and purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, from 0% to 5% v/v) to afford Compound **N2**. ^1H -NMR ($DMSO-d_6$, 400 MHz): δ (ppm) 1.36 (s, 9H), 7.19 (d, J = 8.8 Hz, 1H), 7.45 (d, J = 8.8 Hz, 1H), 7.71 (s, 1H).

[000288] Intermediates **N3**, **N4**, **N5**, **N6**, and **N7**, were synthesized, by employing the procedures described for Intermediate **A5**, **A6**, **A7**, **A8**, and **A9** using Intermediate **N2**, **N3**, **N4**, **N5**, and **N6** in lieu of 6-bromo-2,3-dihydrobenzo[*b*][1,4]dioxine, Intermediates **A5**, **A6**, **A7**, and **A8**.

[000289] Intermediate **N3**. LC-MS (ESI) m/z : 520 $[M+H]^+$; ^1H -NMR ($CDCl_3$, 400 MHz): δ (ppm) -0.12 (s, 6H), 0.73 (s, 9H), 1.48 (s, 9H), 3.84-3.88 (m, 1H), 3.96-3.99 (m, 1H), 5.12 (s, 2H), 5.29-5.34 (m, 1H), 5.88-5.90 (m, 1H), 7.18 (d, J = 8.4 Hz, 1H), 7.32-7.38 (m, 5H), 7.78 (d, J = 10.8 Hz, 1H), 8.01 (m, 1H).

[000290] Intermediate **N4**. LC-MS (ESI) m/z : 388 $[M-OH]^+$; ^1H -NMR ($CDCl_3$, 400 MHz): δ (ppm) 1.50 (s, 9H), 2.57-2.62 (m, 1H), 3.87-3.92 (m, 1H), 3.97-4.05 (m, 1H), 5.15 (s, 2H), 7.19 (d, $J = 8.4$ Hz, 1H), 7.26-7.38 (m, 6H), 7.83 (d, $J = 7.6$ Hz, 1H), 8.05 (s, 1H).

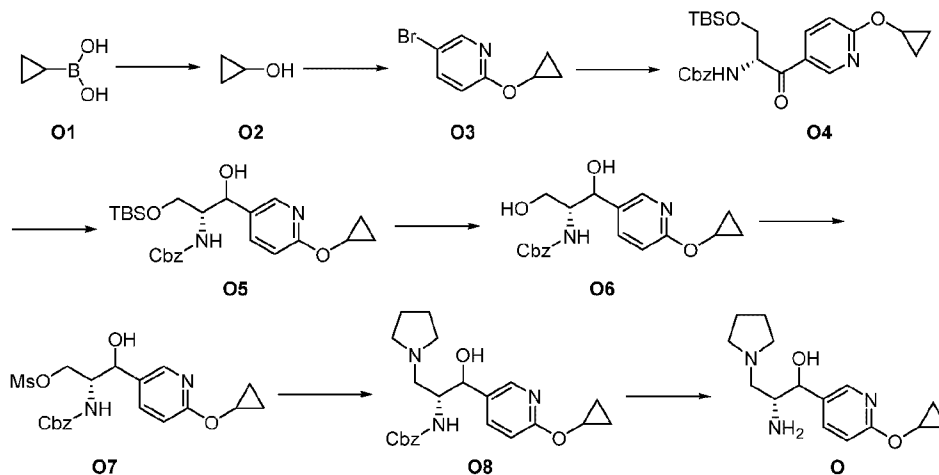
[000291] Intermediate **N5**. LC-MS (ESI) m/z : 390 $[M-OH]^+$; ^1H -NMR ($CDCl_3$, 400 MHz): δ (ppm) 1.40 (s, 9H), 2.43-2.45 (m, 1H), 3.24 (s, 1H), 3.77-3.83 (m, 3H), 4.96-5.10 (m, 3H), 5.47 (s, 1H), 7.06 (d, $J = 8.0$ Hz, 1H), 7.14 (d, $J = 8.8$ Hz, 1H), 7.29-7.37 (m, 5H), 7.41 (s, 1H).

[000292] Intermediate **N6**. The target compound was directly used for the next step without further purification. LC-MS (ESI) m/z : 468 $[M-OH]^+$.

[000293] Intermediate **N7**. LC-MS (ESI) m/z : 461 $[M+H]^+$; ^1H -NMR ($CDCl_3$, 400 MHz): δ (ppm) 1.40 (s, 9H), 1.76-1.81 (m, 4H), 2.65-2.89 (m, 6H), 4.01 (s, 1H), 4.98-5.06 (m, 3H), 7.08 (s, 1H), 7.29-7.41 (m, 6H), 7.41 (s, 1H).

[000294] Intermediate **N** was synthesized, by employing the procedure described for Intermediate **E** using Intermediate **N7** in lieu of Intermediate **E7**. LC-MS (ESI) m/z : 327 $[M+H]^+$; ^1H -NMR ($CDCl_3$, 400 MHz): δ (ppm) 1.41 (s, 9H), 1.76-1.80 (m, 4H), 2.47-2.62 (m, 6H), 3.14 (s, 1H), 4.60 (s, 1H), 5.71 (s, 1H), 7.08-7.14 (m, 2H), 7.38 (s, 1H).

Intermediate O



[000295] A solution of aqueous H_2O_2 (30%, 400 mL, 4.00 mol) was added dropwise with continuous stirring at 0 °C. To a suspension of cyclopropyl boronic acid Compound **O1** (62.0 g, 0.721 mol) in 10% aqueous NaOH (500 mL). The resulting mixture was stirred for 1 h at 0 °C. The reaction mixture was quenched with saturated aqueous $Na_2S_2O_3$ and extracted with Et_2O . The combined organics were dried over anhydrous sodium sulfate, filtered, and concentrated in *vacuo* at 0 °C. The mixture was dissolved in Et_2O (400 mL), 4 Å molecular sieves were added and it was left overnight at room temperature to yield Compound **O2**. ^1H -

NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 0.49-0.57 (m, 4H), 3.48-3.50 (m, 1H).

[000296] Compounds 5-bromo-2-fluoropyridine (25.0 g, 0.12 mol) and cyclopropanol (**O2**, 10.4 g, 0.18 mol) were dissolved in NMP (100 mL) and treated with potassium *tert*-butoxide (180 mL, 1M solution in THF, 0.18 mol) at 0 °C. The solution became dark and cloudy, and warmed. After 30 min, the reaction mixture was partitioned between ethyl acetate and petroleum ether (500 mL, 1/1 v/v) and water (500 mL). The organic layer was separated, washed with water and 5% aq. LiCl, dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified with silica gel column chromatography (ethyl acetate in petroleum ether, 10% v/v) to furnish Compound **O3**. ¹H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 0.74-0.81 (m, 4H), 4.13-4.18 (m, 1H), 6.88 (d, *J* = 8.8 Hz, 1H), 7.66 (dd, *J* = 8.8, 2.4 Hz, 1H), 8.26 (d, *J* = 2.4 Hz, 1H).

[000297] Intermediate **O4**, **O5**, **O6**, **O7**, **O8**, and **O**, were synthesized, by employing the procedures described for Intermediate **J3**, **J4**, **J5**, **J6**, **J7**, and **J** using **O3**, **O4**, **O5**, **O6**, **O7**, and **O8** in lieu of **J2**, **J3**, **J4**, **J5**, **J6**, and **J7**.

[000298] Intermediate **O4**. LC-MS (*m/z*): 471 [M+1]⁺; ¹H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 0.00 (s, 3H), 0.16 (s, 3H), 0.86 (s, 9H), 0.93-0.98 (m, 4H), 4.01-4.03 (m, 1H), 4.11-4.13 (m, 1H), 4.43-4.45 (m, 1H), 5.25 (s, 2H), 5.40-5.42 (m, 1H), 6.03 (d, *J* = 8.0 Hz, 1H), 6.94 (d, *J* = 8.0 Hz, 1H), 7.38-7.49 (m, 5H), 8.25-8.28 (m, 1H), 8.97-8.98 (m, 1H).

[000299] Intermediate **O5**. LC-MS (*m/z*): 473 [M+1]⁺; ¹H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 0.04-0.07 (m, 6H), 0.74-0.80 (m, 4H), 0.91 (s, 9H), 3.78-3.87 (m, 2H), 4.15-4.17 (m, 1H), 5.03-5.08 (m, 3H), 5.45-5.46 (m, 1H), 6.73-6.75 (m, 1H), 7.26-7.35 (m, 5H), 7.59-7.61 (m, 1H), 8.18-8.19 (m, 1H).

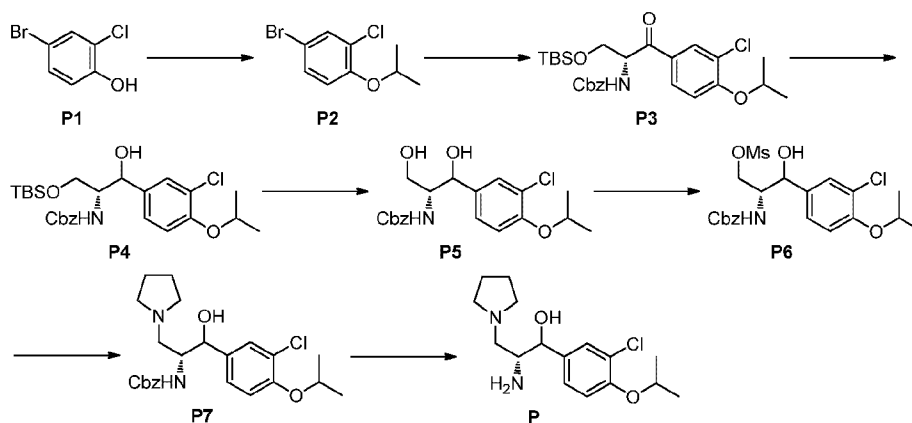
[000300] Intermediate **O6**. LC-MS (*m/z*): 359 [M+1]⁺; ¹H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 0.67-0.71 (m, 4H), 3.68-3.79 (m, 4H), 4.01-4.05 (m, 1H), 4.93-4.98 (m, 2H), 5.53-5.57 (m, 1H), 6.65-6.67 (m, 1H), 7.19-7.26 (m, 5H), 7.52-7.55 (m, 1H), 8.08-8.11 (m, 1H).

[000301] Intermediate **O7**. LC-MS (*m/z*): 437 [M+1]⁺; ¹H-NMR (DMSO-*d*₆, 400 MHz) major characteristic peaks: δ (ppm) 0.63-0.76 (m, 4H), 3.15 (s, 3H), 4.17-4.18 (m, 1H), 4.34-4.36 (m, 1H), 4.78-4.79 (m, 1H), 4.95 (dd, *J* = 30.8, 12.8 Hz, 2H), 5.72 (d, *J* = 4.8 Hz, 1H), 6.78 (d, *J* = 8.4 Hz, 1H), 7.24-7.36 (m, 5H), 7.65 (dd, *J* = 8.4, 2.4 Hz, 1H), 8.11 (d, *J* = 2.4 Hz, 1H).

[000302] Intermediate **O8**. LC-MS (m/z): 412 $[M+1]^+$; $^1\text{H-NMR}$ (MeOD, 400 MHz) major characteristic peaks: δ (ppm) 0.70-0.82 (m, 4H), 1.81-1.83 (m, 4H), 2.60-2.68 (m, 4H), 2.75-2.77 (m, 1H), 3.95-3.98 (m, 1H), 4.04-4.08 (m, 1H), 4.87-4.88 (m, 1H), 4.96-5.04 (m, 2H), 6.87 (d, $J = 8.4$ Hz, 1H), 7.25-7.34 (m, 5H), 7.65 (dd, $J = 8.4, 2.4$ Hz, 1H), 8.11 (d, $J = 2.4$ Hz, 1H).

[000303] Intermediate **O**. LC-MS (m/z): 278 $[M+1]^+$; $^1\text{H-NMR}$ (MeOD, 400 MHz) major characteristic peaks: δ (ppm) 0.70-0.82 (m, 4H), 1.75-1.78 (m, 4H), 2.26 (dd, $J = 11.6, 4.4$ Hz, 1H), 2.44-2.62 (m, 5H), 3.07-3.12 (m, 1H), 4.08-4.11 (m, 1H), 4.51 (d, $J = 5.6$ Hz, 1H), 6.95 (d, $J = 8.8$ Hz, 1H), 7.75 (dd, $J = 8.8, 2.4$ Hz, 1H), 8.11 (d, $J = 2.4$ Hz, 1H).

Intermediate P



[000304] Compound **P1** (31.1g, 150 mmol), K_2CO_3 (31.1g, 225 mmol) and iodopropane (18 mL, 180 mmol) were stirred at 25 °C in DMF (300 mL). After 18 hours, the mixture was diluted with ethyl acetate (600 mL), washed with H_2O (300 mL x 4), and dried over anhydrous sodium sulfate. After evaporation, the crude compound was purified with flash column chromatography on silica gel (petroleum ether, 100% v/v) to yield Compound **P2**. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) major characteristic peaks: δ (ppm) 1.36 (d, $J = 7.0$ Hz, 6H), 4.49-4.52 (m, 1H), 6.81 (d, $J = 8.8$ Hz, 1H), 7.27 (dd, $J = 8.8, 2.4$ Hz, 1H), 7.49 (d, $J = 2.4$ Hz, 1H).

[000305] Intermediates **P3**, **P4**, **P5**, **P6**, and **P7**, were synthesized, by employing the procedures described for Intermediates **J3**, **J4**, **J5**, **J6**, and **J7** using Intermediates **P2**, **P3**, **P4**, **P5**, and **P6** in lieu of Intermediates **J2**, **J3**, **J4**, **J5**, and **J6**.

[000306] Intermediate **P3**. LC-MS (m/z): 506 $[M+1]^+$; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) major characteristic peaks: δ (ppm) -0.11 (s, 3H), 0.01 (s, 3H), 0.87 (s, 9H), 1.54 (s, 3H), 1.55

(s, 3H), 3.98-4.01 (m, 2H), 4.78-4.85 (m, 1H), 5.23 (s, 2H), 5.39-5.42 (m, 1H), 5.60 (d, $J = 7.2$ Hz, 1H), 7.38-7.49 (m, 5H), 7.76 (dd, $J = 8.8, 2.0$ Hz, 1H), 8.13 (d, $J = 2.0$ Hz, 1H).

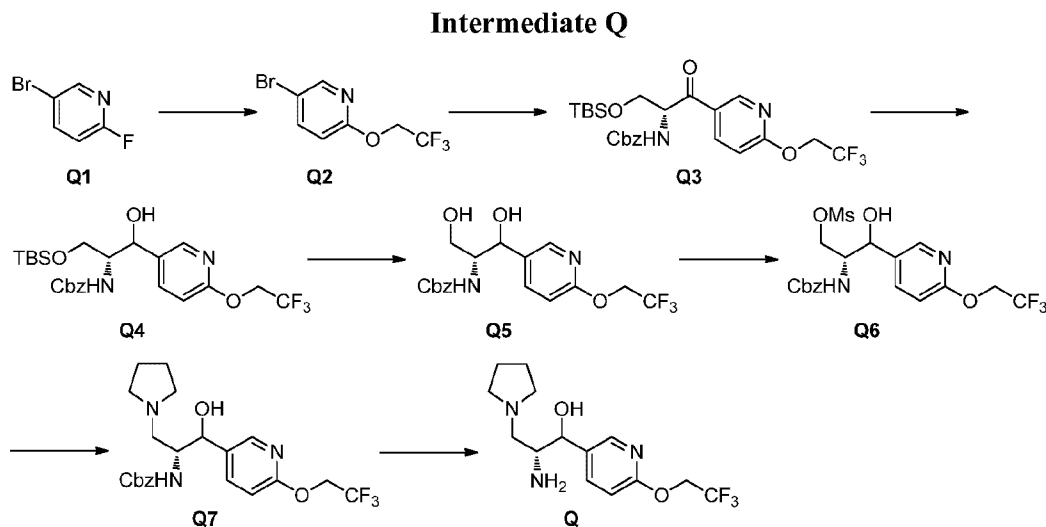
[000307] Intermediate **P4**. LC-MS (m/z): 490 $[M-17]^+$.

[000308] Intermediate **P5**. LC-MS (m/z): 338 $[M-17]^+$; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) major characteristic peaks: δ (ppm) 1.36-1.38 (m, 6H), 2.46-2.56 (m, 1H), 3.17-3.22 (m, 1H), 3.62-3.82 (m, 3H), 4.51-5.11 (m, 3H), 5.46-5.63 (m, 1H), 6.87-6.90 (m, 1H), 7.15-7.17 (m, 1H), 7.30-7.39 (m, 5H).

[000309] Intermediate **P6**, which was used for next step without purification. LC-MS (m/z): 454 $[M-17]^+$.

[000310] Intermediate **P7**. LC-MS (m/z): 447 $[M+1]^+$; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) major characteristic peaks: δ (ppm) 1.35-1.39 (m, 6H), 1.94-2.00 (m, 4H), 2.82-3.32 (m, 5H), 3.49-3.58 (m, 1H), 4.07-4.10 (m, 1H), 4.48-4.59 (m, 1H), 4.99 (s, 2H), 5.08 (m, 1H), 6.84-6.89 (m, 1H), 7.23-7.33 (m, 5H), 7.35-7.45 (m, 1H).

[000311] Intermediate **P** was synthesized, by employing the procedure described for Intermediate **E** using Intermediate **P7** in lieu of Intermediate **E7**. LC-MS (m/z): 313 $[M+1]^+$; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) major characteristic peaks: δ (ppm) 1.37 (s, 3H), 1.38 (s, 3H), 1.77-1.83 (m, 4H), 2.48-2.99 (m, 6H), 3.09-3.14 (m, 1H), 4.35-4.57 (m, 2H), 6.91-6.94 (m, 1H), 7.14-7.21 (m, 1H), 7.28-7.35 (m, 1H).



[000312] Intermediates **Q2**, **Q3**, **Q4**, **Q5**, **Q6**, **Q7**, and **Q**, were synthesized, by employing the procedures described for Intermediates **J2**, **J3**, **J4**, **J5**, **J6**, **J7**, and **J** using Intermediates **Q1**, **Q2**, **Q3**, **Q4**, **Q5**, **Q6**, and **Q7** in lieu of Intermediates **J1**, **J2**, **J3**, **J4**, **J5**, **J6**, and **J7**.

[000313] Intermediate **Q2**. LC-MS (m/z): 257 [M+1]⁺, 259 [M+3]⁺; ¹H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 4.73 (q, J = 8.4 Hz, 2H), 6.79 (d, J = 8.8 Hz, 1H), 7.73 (dd, J = 2.4, 8.8 Hz, 1H), 8.19 (d, J = 2.4 Hz, 1H).

[000314] Intermediate **Q3**. LC-MS (m/z): 413 [M+1]⁺; ¹H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) -0.12 (s, 3H), -0.10 (s, 3H), 0.74 (s, 9H), 3.86-3.90 (m, 1H), 3.98-4.02 (m, 1H), 4.80 (q, J = 8.4 Hz, 2H), 5.13 (s, 2H), 5.29 (t, J = 3.6 Hz, 1H), 5.89 (m, 1H), 6.95 (d, J = 8.4 Hz, 1H), 7.36-7.38 (m, 5H), 8.16 (dd, J = 2.0, 8.4 Hz, 1H), 8.64 (d, J = 2.0 Hz, 1H).

[000315] Intermediate **Q4**. LC-MS (m/z): 515 [M+1]⁺; ¹H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 0.08 (s, 3H), 0.09 (s, 3H), 0.93 (s, 9H), 3.71-3.88 (m, 4H), 4.75 (m, 2H), 5.05-5.10 (m, 2H), 5.44 (d, J = 8.4 Hz, 1H), 6.81 (d, J = 8.8 Hz, 1H), 7.32-7.34 (m, 5H), 7.65 (dd, J = 2.4, 8.4 Hz, 1H), 8.12 (s, 1H).

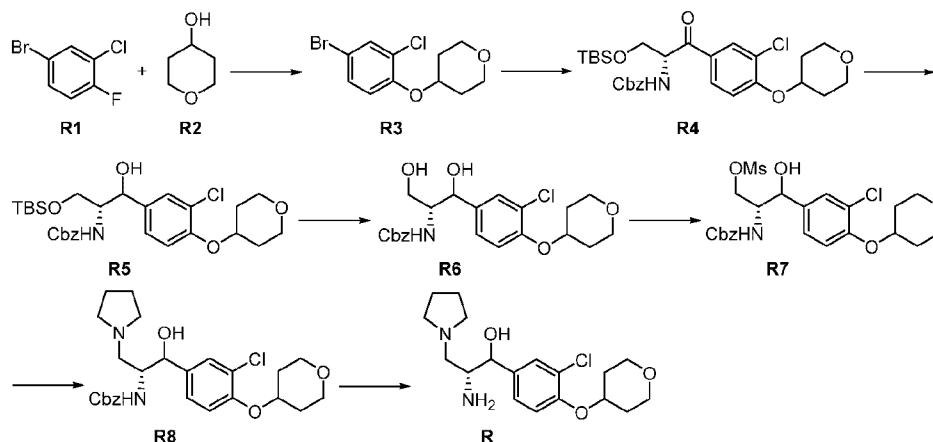
[000316] Intermediate **Q5**. LC-MS (m/z): 401 [M+1]⁺; ¹H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 2.78 (m, 1H), 3.56-3.67 (m, 1H), 3.82 (m, 3H), 4.72-4.74 (m, 2H), 5.01-5.07 (m, 3H), 5.56 (d, J = 8.4 Hz, 0.7H), 5.62 (d, J = 8.0 Hz, 0.3H), 6.79 (d, J = 8.4 Hz, 0.7H), 6.85 (d, J = 8.4 Hz, 0.3H), 7.32-7.34 (m, 5H), 7.65 (d, J = 8.4 Hz, 1H), 8.11 (s, 1H).

[000317] Intermediate **Q6**. LC-MS (m/z): 479 [M+1]⁺; ¹H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 3.02 (s, 3H), 4.25-4.42 (m, 3H), 4.71-4.77 (m, 2H), 5.03 (m, 3H), 5.37 (d, J = 8.4 Hz, 1H), 6.81 (d, J = 8.4 Hz, 1H), 7.32-7.35 (m, 5H), 7.64 (dd, J = 2.4, 8.4 Hz, 1H), 8.13 (d, J = 2.4 Hz, 1H).

[000318] Intermediate **Q7**. LC-MS (m/z): 454 [M+1]⁺; ¹H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 1.80 (m, 4H), 2.67 (m, 4H), 2.86-2.88 (m, 1H), 3.40 (m, 1H), 4.00 (m, 1H), 4.74-4.76 (m, 3H), 5.03-5.07 (m, 3H), 6.82 (d, J = 8.4 Hz, 1H), 7.33-7.36 (m, 5H), 7.60 (dd, J = 2.4, 8.4 Hz, 1H), 8.10 (s, 1H).

[000319] Intermediate **Q**. LC-MS (m/z): 320 [M+1]⁺; ¹H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 1.80 (m, 4H), 2.48-2.53 (m, 4H), 2.61-2.66 (m, 2H), 3.15 (m, 1H), 4.66-4.70 (m, 3H), 4.76 (d, J = 8.8 Hz, 2H), 6.87 (d, J = 8.0 Hz, 1H), 7.66 (dd, J = 2.4, 8.4 Hz, 1H), 8.11 (d, J = 2.4 Hz, 1H).

Intermediate R



[000320] Intermediates **R3**, **R4**, **R5**, **R6**, **R7**, and **R8**, were synthesized, by employing the procedures described for Intermediates **J2**, **J3**, **J4**, **J5**, **J6**, and **J7** using Intermediates **R2**, **R3**, **R4**, **R5**, **R6**, and **R7** in lieu of Intermediates **J1**, **J2**, **J3**, **J4**, **J5**, and **J6**.

[000321] Intermediate **R3**. LC-MS (ESI) m/z : 291 $[M+H]^+$; ^1H -NMR ($CDCl_3$, 400 MHz): δ (ppm) 1.79-1.87 (m, 2H), 1.97-2.04 (m, 2H), 3.56-3.62 (m, 2H), 3.97-4.02 (m, 2H), 4.48-4.53 (m, 1H), 6.82 (d, J = 8.8 Hz, 1H), 7.28-7.31 (dd, J = 8.8, 2.4 Hz, 1H), 7.51 (d, J = 2.8 Hz, 1H).

[000322] Intermediate **R4**. LC-MS (ESI) m/z : 548 $[M+H]^+$; ^1H -NMR ($CDCl_3$, 400 MHz): δ (ppm) -0.12 (s, 3H), -0.10 (s, 3H), 0.75 (s, 9H), 1.84-1.92 (m, 2H), 2.02-2.09 (m, 2H), 3.62-3.68 (m, 2H), 3.86-3.89 (m, 1H), 3.94-4.04 (m, 3H), 4.69-4.72 (m, 1H), 5.13 (s, 2H), 5.28-5.32 (m, 1H), 5.90 (d, J = 8.0 Hz, 1H), 6.97 (d, J = 8.8 Hz, 1H), 7.31-7.38 (m, 5H), 7.84 (dd, J = 8.8, 2.0 Hz, 1H), 8.03 (d, J = 2.0 Hz, 1H).

[000323] Intermediate **R5**. LC-MS (ESI) m/z : 532 $[M-OH]^+$; ^1H -NMR ($CDCl_3$, 400 MHz): δ (ppm) -0.08-0.04 (m, 6H), 0.89-0.91 (m, 9H), 1.80-1.89 (m, 2H), 1.97-2.03 (m, 2H), 3.56-3.62 (m, 2H), 3.66-3.75 (m, 1H), 3.79-3.86 (m, 2H), 3.98-4.04 (m, 2H), 4.49-4.54 (m, 1H), 4.98-5.12 (m, 3H), 5.41-5.54 (m, 1H), 6.89-6.95 (m, 1H), 7.16-7.19 (m, 1H), 7.31-7.42 (m, 6H).

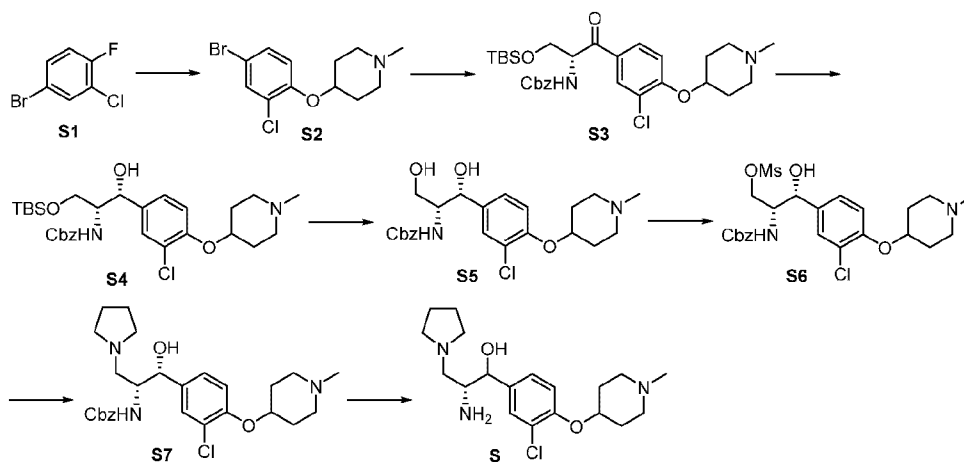
[000324] Intermediate **R6**. LC-MS (ESI) m/z : 418 $[M-OH]^+$; ^1H -NMR ($CDCl_3$, 400 MHz): δ (ppm) 1.80 (m, 2H), 1.97-2.04 (m, 2H), 3.55-3.64 (m, 2H), 3.79-3.84 (m, 3H), 3.98-4.03 (m, 2H), 4.49-4.53 (m, 1H), 4.96-5.11 (m, 3H), 5.46-5.66 (m, 1H), 6.88-6.94 (m, 1H), 7.16-7.22 (m, 1H), 7.31-7.44 (m, 6H).

[000325] Intermediate **R7**. LC-MS (ESI) m/z : 496 $[M-OH]^+$; 1.80-1.88 (m, 2H), 1.98-2.03 (m, 2H), 3.00 (s, 3H), 3.56-3.62 (m, 2H), 3.97-4.00 (m, 2H), 4.07-4.40 (m, 4H), 4.92-5.04 (m, 3H), 5.23-5.32 (m, 1H), 6.89-6.91 (m, 1H), 7.15-7.19 (m, 1H), 7.29-7.41 (m, 6H).

[000326] Intermediate **R8**. LC-MS (ESI) m/z : 489 $[M+H]^+$; ^1H -NMR ($CDCl_3$, 400 MHz): δ (ppm) 1.79-1.89 (m, 6H), 1.97-2.03 (m, 2H), 2.65-2.85 (m, 6H), 3.56-3.62 (m, 2H), 3.98-4.04 (m, 3H), 4.45-4.54 (m, 1H), 5.01-5.11 (m, 4H), 6.89-6.92 (m, 1H), 7.11-7.20 (m, 1H), 7.29-7.42 (m, 6H).

[000327] Intermediate **R** was synthesized, by employing the procedure described for Intermediate **E** using Intermediate **R8** in lieu of Intermediate **E7**. LC-MS (ESI) m/z : 355 $[M+H]^+$.

Intermediate S



[000328] Intermediates **S2**, **S3**, **S4**, **S5**, **S6**, and **S7**, were synthesized, by employing the procedures described for Intermediates **J2**, **J3**, **J4**, **J5**, **J6**, and **J7** using Intermediates **S1**, **S2**, **S3**, **S4**, **S5**, and **S6** in lieu of Intermediates **J1**, **J2**, **J3**, **J4**, **J5**, and **J6**.

[000329] Intermediate **S2**. LC-MS (ESI) m/z : 304 $[M+H]^+$; ^1H -NMR ($CDCl_3$, 400 MHz): δ (ppm) 1.85-2.04 (m, 4H), 2.29 (s, 3H), 2.25-2.34 (m, 2H), 2.64-2.68 (m, 2H), 4.33-4.35 (m, 1H), 6.81 (d, $J = 8.8$ Hz, 1H), 7.28 (dd, $J = 8.8, 2.4$ Hz, 1H), 7.50 (d, $J = 4.8$ Hz, 1H).

[000330] Intermediate **S3**. LC-MS (ESI) m/z : 561 $[M+H]^+$; ^1H -NMR ($CDCl_3$, 400 MHz): δ (ppm) -0.13 (s, 3H), -0.10 (s, 3H), 0.74 (s, 9H), 1.88-2.04 (m, 4H), 2.32 (s, 3H), 2.32-2.38 (m, 2H), 2.67-2.71 (m, 2H), 3.87-3.95 (m, 1H), 4.09-4.15 (m, 1H), 4.37-4.39 (m, 1H), 5.13 (s, 2H), 5.88 (d, $J = 8.0$ Hz, 1H), 6.96 (d, $J = 8.0$ Hz, 1H), 7.35-7.37 (m, 5H), 7.82-7.84 (m, 1H), 8.01 (s, 1H).

[000331] Intermediate **S4**. LC-MS (ESI) m/z : 563 $[M+H]^+$.

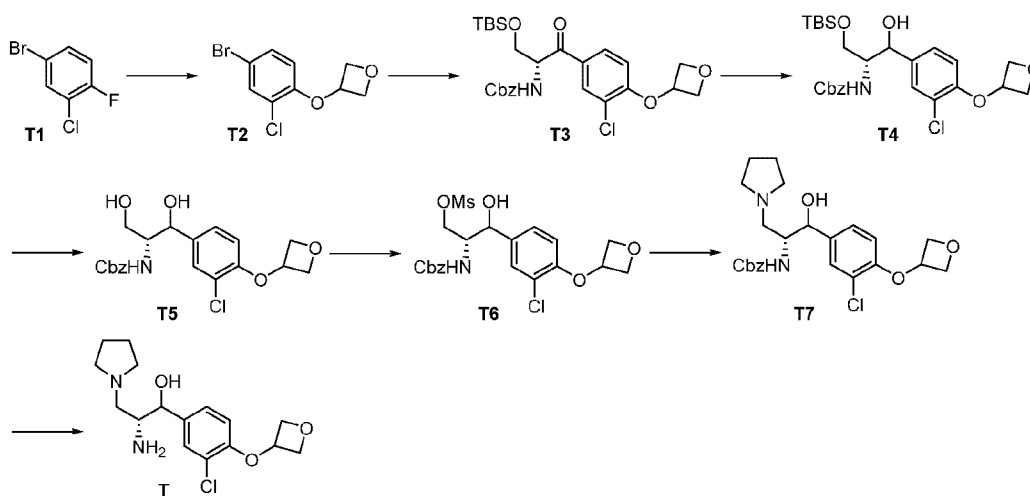
[000332] Intermediate **S5**. LC-MS (ESI) m/z : 449 $[M+H]^+$; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ (ppm) 1.81-1.94 (m, 4H), 2.25 (s, 3H), 2.27-2.29 (m, 2H), 2.55-2.63 (m, 2H), 3.58-3.83 (m, 3H), 4.33 (m, 1H), 4.93 (s, 1H), 5.00-5.09 (m, 2H), 5.55-5.78 (m, 1H), 6.84-6.90 (m, 1H), 7.15-7.45 (m, 7H).

[000333] Intermediate **S6**. LC-MS (ESI) m/z : 527 $[M+H]^+$; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ (ppm) 1.91-2.02 (m, 4H), 2.32 (s, 3H), 2.35-2.37 (m, 2H), 2.68-2.72 (m, 2H), 3.01 (s, 3H), 4.07-4.09 (m, 1H), 4.19-4.22 (m, 1H), 4.37-4.42 (m, 2H), 4.91 (d, $J = 3.6$ Hz, 1H), 5.01-5.05 (m, 2H), 5.27-5.33 (m, 1H), 6.89 (d, $J = 8.8$ Hz, 1H), 7.15-7.17 (m, 1H), 7.26-7.40 (m, 6H).

[000334] Intermediate **S7**. LC-MS (ESI) m/z : 502 $[M+H]^+$.

[000335] Intermediate **S** was synthesized, by employing the procedure described for Intermediate **E** using Intermediate **S7** in lieu of Intermediate **E7**. LC-MS (ESI) m/z : 368 $[M+H]^+$; $^1\text{H-NMR}$ ($\text{DMSO}-d_6$, 400 MHz): δ (ppm) 1.60-1.70 (m, 6H), 1.90 (m, 2H), 2.13-2.22 (m, 6H), 2.25-2.50 (m, 5H), 2.57 (m, 2H), 2.83-2.92 (m, 1H), 4.12 (s, 1H), 4.36 (d, $J = 4.4$ Hz, 1H), 4.42 (m, 1H), 7.12 (d, $J = 8.4$ Hz, 1H), 7.18 (d, $J = 8.8$ Hz, 1H), 7.34 (s, 1H).

Intermediate T



[000336] Intermediates **T2**, **T3**, **T4**, **T5**, **T6**, and **T7**, were synthesized, by employing the procedures described for Intermediates **J2**, **J3**, **J4**, **J5**, **J6**, and **J7** using Intermediates **T1**, **T2**, **T3**, **T4**, **T5**, and **T6** in lieu of Intermediates **J1**, **J2**, **J3**, **J4**, **J5**, and **J6**.

[000337] Intermediate **T2**. LC-MS (ESI) m/z : 263 $[M+H]^+$; ^1H -NMR ($CDCl_3$, 400 MHz): δ (ppm) 4.79-4.82 (m, 2H), 4.97 (t, $J = 6.8$ Hz, 2H), 5.19 (q, $J = 11.6, 5.6$ Hz, 1H), 6.35 (d, $J = 8.8$ Hz, 1H), 7.25-7.29 (m, 1H), 7.52-7.53 (d, $J = 2.4$ Hz, 1H).

[000338] Intermediate **T3**. LC-MS (ESI) m/z : 520 $[M+H]^+$; ^1H -NMR ($CDCl_3$, 400 MHz): δ (ppm) -0.13 (s, 3H), -0.11 (s, 3H), 0.89 (s, 9H), 1.58-1.62 (m, 2H), 2.47-2.52 (m, 2H), 2.80-2.82 (m, 1H), 2.92-3.01 (m, 1H), 4.19-4.24 (m, 2H), 4.95 (d, $J = 2.4$ Hz, 1H), 5.15 (s, 1H), 6.54 (s, 1H), 6.79-6.87 (m, 4H), 7.24-7.25 (m, 1H), 7.35-7.38 (m, 2H), 7.50 (d, $J = 2$ Hz, 1H).

[000339] Intermediate **T4**. LC-MS (ESI) m/z : 504 $[M-OH]^+$.

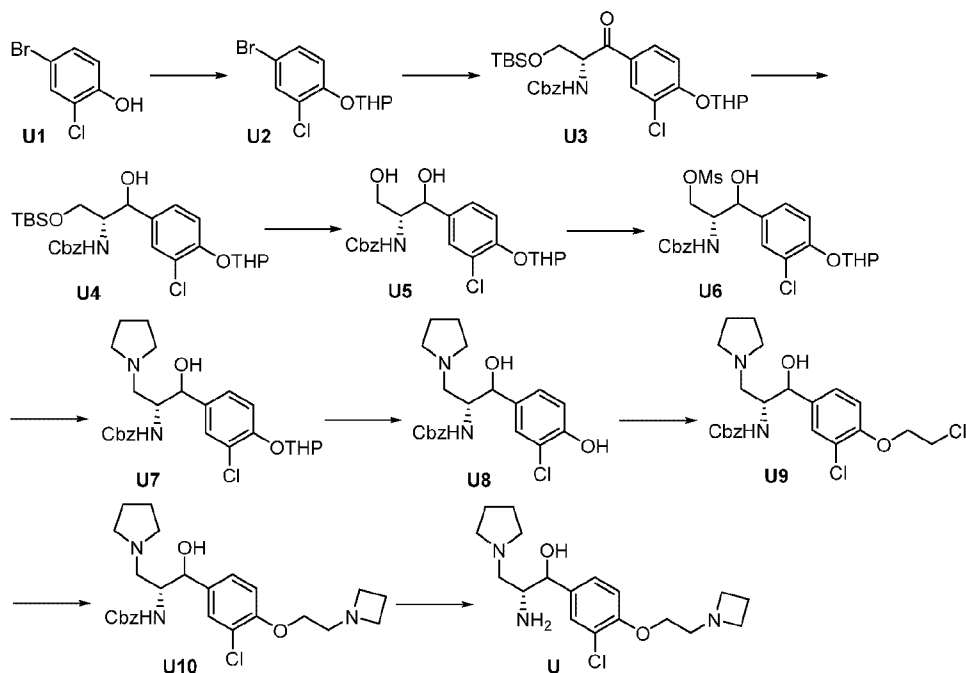
[000340] Intermediate **T5**. LC-MS (ESI) m/z : 390 $[M-OH]^+$; ^1H -NMR ($CDCl_3$, 400 MHz): δ (ppm) 3.70-3.81 (m, 2H), 4.75-4.98 (m, 7H), 5.12-5.18 (m, 1H), 5.56 (d, $J = 8.4$ Hz, 1H), 6.37 (d, $J = 8.4$ Hz, 1H), 7.09-7.12 (m, 1H), 7.29-7.37 (m, 5H), 7.40-7.43 (m, 1H).

[000341] Intermediate **T6**. LC-MS (ESI) m/z : 468 $[M-OH]^+$; ^1H -NMR ($CDCl_3$, 400 MHz): δ (ppm) 2.98 (s, 3H), 3.57-3.67 (m, 2H), 4.79-5.04 (m, 7H), 5.16-5.18 (m, 1H), 5.37-5.38 (m, 1H), 6.42 (d, $J = 8.4$ Hz, 1H), 7.12-7.15 (m, 1H), 7.30-7.44 (m, 6H).

[000342] Intermediate **T7**. LC-MS (ESI) m/z : 461 $[M+H]^+$.

[000343] Intermediate **S** was synthesized, by employing the procedure described for Intermediate **E** using Intermediate **S7** in lieu of Intermediate **E7**. LC-MS (ESI) m/z : 327 $[M+H]^+$; ^1H -NMR (CD_3OD , 400 MHz): δ (ppm) 2.05-2.28 (m, 6H), 2.45-2.65 (m, 5H), 3.09-3.20 (m, 1H), 3.95-4.01 (m, 1H), 4.69-4.71 (m, 1H), 4.95-4.97 (m, 2H), 5.12-5.13 (m, 1H), 6.38-6.43 (d, $J = 8.4$ Hz, 1H), 7.12-7.26 (m, 2H).

Intermediate U



[000344] To a solution of Compound U1 (20 g, 96.2 mmol) in dichloromethane (100 mL) was added 3,4-dihydro-2H-pyran (16.2 g, 192.4 mmol) and a solution of HCl in dioxane (4.0 M, 1 mL) at 0 °C. The mixture was stirred at 25 °C overnight. Saturated sodium bicarbonate solution (20 mL) and dichloromethane (200 mL) were added and the layers were separated. The aqueous layer was extracted with dichloromethane (50 mL x 3). The combined organic layers were washed with water (20 mL x 3) and brine (10 mL x 2), dried over anhydrous sodium sulfate, filtered, and concentrated to give a crude compound. The crude product was purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, 10% v/v) to afford Compound U2. LC-MS (ESI) m/z: No; ¹H-NMR (CDCl₃, 400 MHz): δ (ppm) 1.71-1.88 (m, 3H), 2.05-2.13 (m, 3H), 3.59-3.64 (m, 1H), 3.83-3.90 (m, 1H), 5.47 (t, *J* = 2.8 Hz, 1H), 7.07 (d, *J* = 9.2 Hz, 1H), 7.30 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.51 (d, *J* = 2.4 Hz, 1H).

[000345] Intermediates U3, U4, U5, U6, and U7 were synthesized, by employing the procedures described correspondingly for Intermediates A5, A6, A7, A8, and A9 using Intermediates U2, U3, U4, U5, and U6 in lieu of 6-bromo-2,3-dihydrobenzo[b][1,4]dioxine, Intermediates A5, A6, A7, and A8.

[000346] Intermediates U3. LC-MS (ESI) m/z: 446 [M-101]⁺; ¹H-NMR (CDCl₃, 400 MHz): δ (ppm) -0.12 (s, 3H), -0.10 (s, 3H), 0.75 (s, 9H), 1.62-1.65 (m, 2H), 1.71-1.75 (m,

2H), 1.87-1.90 (m, 1H), 1.98-2.03 (m, 1H), 3.62-3.65 (m, 1H), 3.79-3.84 (m, 1H), 3.87-3.91 (m, 1H), 3.95-3.98 (m, 1H), 5.13 (s, 2H), 5.28-5.33 (m, 1H), 5.62-5.64 (m, 1H), 5.92-5.93 (m, 1H), 7.23-7.25 (m, 1H), 7.31-7.37 (m, 5H), 7.82 (dd, $J = 8.4, 2.0$ Hz, 1H), 8.01 (d, $J = 2.0$ Hz, 1H).

[000347] Intermediates **U4**. LC-MS (ESI) m/z : 448 $[M-101]^+$; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ (ppm) -0.21 (s, 3H), -0.19 (s, 3H), 0.67 (s, 9H), 1.47-1.49 (m, 2H), 1.63-1.68 (m, 2H), 1.79-1.92 (m, 1H), 2.00-2.04 (m, 1H), 3.47-3.57 (m, 2H), 3.71-3.98 (m, 3H), 4.74-4.76 (m, 1H), 5.05 (s, 2H), 5.21-5.25 (m, 1H), 5.55-5.57 (m, 1H), 5.83-5.85 (m, 1H), 7.15-7.17 (m, 1H), 7.30-7.38 (m, 5H), 7.75 (dd, $J = 8.4, 2.0$ Hz, 1H), 7.94 (d, $J = 2.0$ Hz, 1H).

[000348] Intermediates **U5**. LC-MS (ESI) m/z : 334 $[M-101]^+$; $^1\text{H-NMR}$ ($\text{DMSO-}d_6$, 400 MHz): δ (ppm) 1.56-1.66 (m, 3H), 1.81-1.82 (m, 2H), 1.90-1.91 (m, 1H), 3.29-3.31 (m, 1H), 3.55-3.77 (m, 4H), 4.47-4.75 (m, 2H), 4.85-5.00 (m, 2H), 5.38-5.45 (m, 1H), 5.55-5.56 (m, 1H), 6.75 (d, $J = 8.8$ Hz, 1H), 7.17-7.38 (m, 7H).

[000349] Intermediates **U6**. LC-MS (ESI) m/z : 412 $[M-101]^+$; $^1\text{H-NMR}$ ($\text{DMSO-}d_6$, 400 MHz): δ (ppm) 1.57-1.66 (m, 3H), 1.81-1.83 (m, 2H), 1.91-1.93 (m, 1H), 3.15 (s, 3H), 3.53-3.56 (m, 1H), 3.72-3.77 (m, 1H), 4.00-4.09 (m, 2H), 4.33-4.36 (m, 1H), 4.75 (s, 1H), 4.88-5.02 (m, 2H), 5.57 (s, 1H), 5.71 (d, $J = 4.8$ Hz, 1H), 7.16-7.34 (m, 7H), 7.41 (d, $J = 7.6$ Hz, 1H).

[000350] Intermediates **U7**. LC-MS (ESI) m/z : 489 $[M+H]^+$; $^1\text{H-NMR}$ ($\text{DMSO-}d_6$, 400 MHz): δ (ppm) 1.43-1.45 (m, 3H), 1.51-1.53 (m, 2H), 1.64-1.66 (m, 4H), 1.76-1.81 (m, 1H), 1.98-2.01 (m, 2H), 2.42-2.46 (m, 4H), 3.80-3.82 (m, 2H), 4.52-4.66 (m, 2H), 4.89-5.02 (m, 2H), 6.91 (d, $J = 8.4$ Hz, 1H), 7.03 (d, $J = 8.4$ Hz, 1H), 7.20-7.28 (m, 1H), 7.34-7.37 (m, 5H), 10.15 (s, 1H).

[000351] To a solution of Compound **U7** (1.7 g, 3.48 mmol) in methanol (40 mL) was added *p*-TsOH (600 mg, 3.48 mmol). The mixture was stirred at 30 °C overnight. After removal of the solvent, the residue was extracted with ethyl acetate (50 mL x 3), washed with water (10 mL) and brine (10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to furnish a crude compound. The crude product was purified with flash column chromatography on silica gel (methanol in dichloromethane, 5% v/v) to afford Compound **U8**. LC-MS (ESI) m/z : 405 $[M+H]^+$; $^1\text{H-NMR}$ ($\text{DMSO-}d_6$, 400 MHz): δ (ppm) 1.65-1.68 (m, 4H), 2.66-2.67 (m, 4H), 3.65-3.67 (m, 1H), 3.77-3.78 (m, 1H), 4.09-4.12 (m, 1H), 4.64-4.66 (m, 1H), 4.86-5.01 (m, 2H), 6.87-6.89 (m, 1H), 7.14-7.32 (m, 8H), 9.98 (brs, 1H).

[000352] To a solution of Compound **U8** (1.16 g, 2.87 mmol) in DMF (30 mL) was added K_2CO_3 (1.2 g, 8.61 mmol) and 2-chloroethyl 4-methylbenzenesulfonate (1.01 g, 4.31

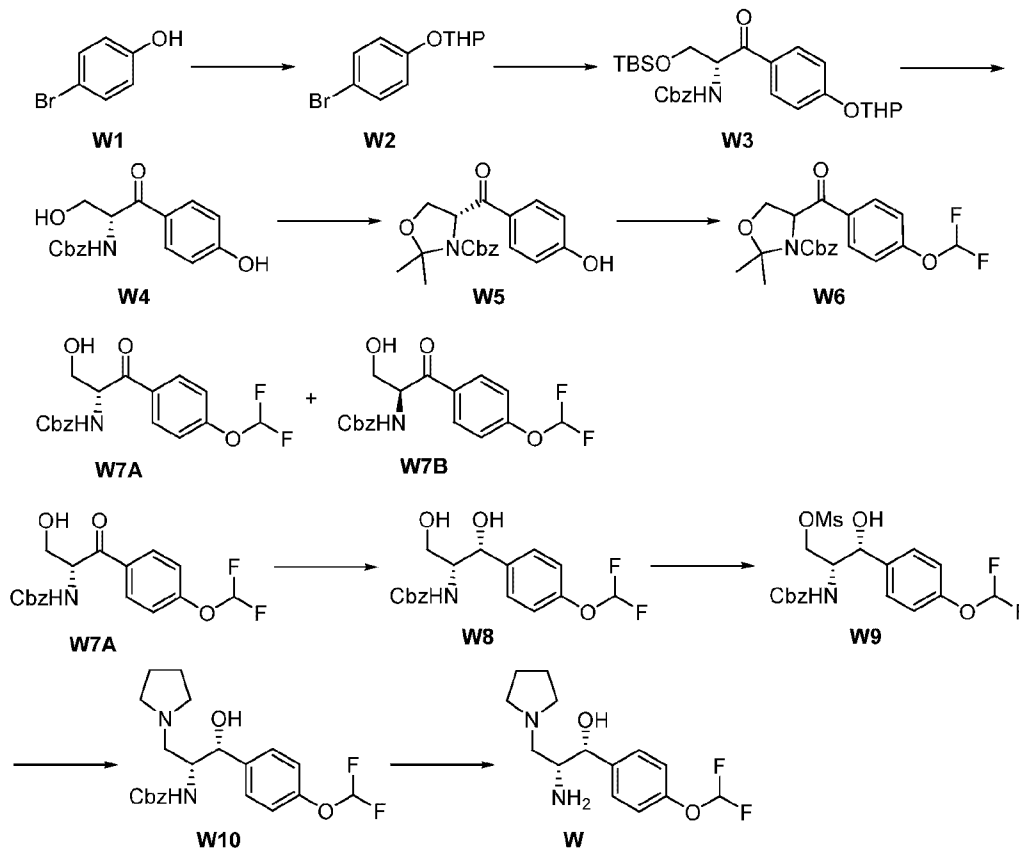
mmol). The mixture was stirred at 60 °C for two hours. After the reaction was monitored with TLC, the mixture was quenched with water (10 mL) and diluted with ethyl acetate (200 mL). The organic phase was washed with water (5 mL x 3) and brine (10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The crude product was purified with flash column chromatography on silica gel (methanol in dichloromethane, 9% v/v) to furnish Compound **U9**. LC-MS (ESI) m/z : 467 $[M+H]^+$; ^1H -NMR (DMSO- d_6 , 400 MHz): δ (ppm) 1.57-1.66 (m, 3H), 1.81-1.83 (m, 2H), 1.91-1.94 (m, 1H), 3.15 (s, 3H), 3.53-3.56 (m, 1H), 3.72-3.77 (m, 1H), 4.01-4.09 (m, 2H), 4.33-4.36 (m, 1H), 4.74-4.75 (m, 1H), 4.88-5.01 (m, 2H), 5.57-5.58 (m, 1H), 5.71-5.72 (m, 1H), 7.16-7.24 (m, 4H), 7.28-7.34 (m, 3H), 7.40-7.42 (m, 1H).

[000353] To a solution of Compound **U9** (1.07 g, 2.30 mmol) in THF (30 mL) was added azetidine (1.31 g, 23 mmol) under nitrogen. The mixture was stirred at 50 °C overnight. After the reaction was monitored with LC-MS, the mixture was quenched with water (10 mL) and extracted with ethyl acetate (50 mL x 3), washed with water (10 mL) and brine (10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to give a crude compound. The crude product was purified with flash column chromatography on silica gel (methanol in dichloromethane, 10% v/v) to give Compound **U10**. LC-MS (ESI) m/z : 488 $[M+H]^+$; ^1H -NMR (CDCl₃, 400 MHz): δ (ppm) 1.77-1.80 (m, 4H), 2.10-2.16 (m, 2H), 2.45-2.60 (m, 2H), 2.64-2.81 (m, 4H), 2.86-2.89 (m, 2H), 3.38 (t, J = 7.2 Hz, 4H), 4.01-4.06 (m, 3H), 4.99 (d, J = 2.0 Hz, 1H), 5.05 (s, 2H), 6.85 (d, J = 8.8 Hz, 1H), 7.13 (dd, J = 8.4, 1.6 Hz, 1H), 7.30-7.40 (m, 6H).

[000354] Intermediate **U** was synthesized, by employing the procedure described for Intermediate **E** using Intermediate **U10** in lieu of Intermediate **E7**. LC-MS (ESI) m/z : 354 $[M+H]^+$; ^1H -NMR (CDCl₃, 400 MHz): δ (ppm) 1.77-1.80 (m, 4H), 2.08-2.15 (m, 2H), 2.46-2.51 (m, 1H), 2.57-2.61 (m, 4H), 2.64-2.69 (m, 1H), 2.87 (t, J = 4.8 Hz, 2H), 3.10-3.14 (m, 1H), 3.38 (t, J = 7.2 Hz, 4H), 4.02 (t, J = 6.0 Hz, 2H), 4.59 (d, J = 4.0 Hz, 1H), 6.87 (d, J = 8.4 Hz, 1H), 7.16 (dd, J = 8.4, 2.0 Hz, 1H), 7.38 (d, J = 2.0 Hz, 1H).

[000357] Intermediate **V** was synthesized, by employing the procedure described for Intermediate **E** using Intermediate **V2** in lieu of Intermediate **E7**. LC-MS (ESI) m/z : 343 $[M+H]^+$.

Intermediate W



[000358] To a stirred solution of Compound **W1** (30.0 g, 173 mmol) and *p*-toluenesulfonic acid (297 mg, 1.73 mmol) in dry dichloromethane (240 mL) was added freshly distilled dihydropyran (60 mL, 657 mmol). The mixture was stirred at room temperature for 1 h. To the reaction mixture was added a 2 M NaOH solution and stirred for another 30 min. The mixture was extracted with ether (200 mL x 2). The combined extracts were dried over anhydrous sodium sulfate, filtered, and concentrated. The crude product was purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, 2% v/v) to give Compound **W2**. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ (ppm) 1.64-1.68 (m, 3H), 1.83-1.87 (m, 2H), 1.95-2.02 (m, 1H), 3.61-3.63 (m, 1H), 3.83-3.86 (m, 1H), 5.36-5.38 (m, 1H), 6.92-6.94 (m, 2H), 7.35-7.37 (m, 2H).

[000359] Compound **W3** was synthesized, by employing the procedure described for Compound **A5** using Compound **W2** in lieu of 6-bromo-2,3-dihydrobenzo[b][1,4]dioxine.

LC-MS (ESI) m/z : 514 $[M+H]^+$; ^1H -NMR ($CDCl_3$, 400 MHz): δ (ppm) -0.15 (s, 3H), -0.13 (s, 3H), 0.74 (s, 9H), 1.66-1.73 (m, 2H), 1.86-1.90 (m, 2H), 2.05-2.10 (m, 1H), 3.60-3.63 (m, 1H), 3.81-3.83 (m, 1H), 3.89-3.95 (m, 2H), 5.12 (s, 2H), 5.32-5.34 (m, 1H), 5.51-5.53 (m, 1H), 5.95-5.97 (m, 1H), 7.08-7.10 (m, 2H), 7.30-7.37 (m, 5H), 7.90-7.92 (m, 2H).

[000360] To a solution of Compound **W3** (4.6 g, 8.97 mmol) in methanol (120 mL) was added TsOH (1.54 g, 8.97 mmol). The reaction mixture was stirred at room temperature overnight. The resulting mixture was concentrated. The residue was purified column chromatography on silica gel (ethyl acetate in petroleum ether, 50% v/v) to give Compound **W4**. LC-MS (ESI) m/z : 316 $[M+H]^+$; ^1H -NMR ($DMSO-d_6$, 400 MHz): δ (ppm) 3.62-3.63 (m, 1H), 3.73-3.74 (m, 1H), 4.86-4.87 (m, 1H), 5.02 (s, 2H), 5.09-5.11 (m, 1H), 6.87 (d, $J = 8.8$ Hz, 2H), 7.30-7.36 (m, 5H), 7.47 (d, $J = 8.0$ Hz, 1H), 7.89 (d, $J = 8.8$ Hz, 2H), 10.44 (s, 1H).

[000361] To a mixture of Compound **W4** (2.35 g, 7.46 mmol) dissolved in acetone (30 mL) and 2, 2-dimethoxy propane (30 mL) was added boron trifluoride etherate (1 mL). The mixture was stirred at room temperature overnight and triethyl amine (1 mL) was added. The solvent was removed to dryness. The crude product was purified with column chromatography on silica gel (ethyl acetate in petroleum ether, 50% v/v) to furnish Compound **W5**. LC-MS (ESI) m/z : 356 $[M+H]^+$; ^1H -NMR ($CDCl_3$, 400 MHz): δ (ppm) 1.60 (d, $J = 11.6$ Hz, 3H), 1.76 (d, $J = 11.6$ Hz, 3H), 3.97-4.01 (m, 1H), 4.31-4.35 (m, 1H), 5.03 (q, $J = 12.4$ Hz, 1H), 5.21 (q, $J = 12.4$ Hz, 1H), 5.36-5.44 (m, 1H), 6.69-6.71 (m, 1H), 6.83-6.85 (m, 1H), 7.11-7.12 (m, 1H), 7.18-7.20 (m, 1H), 7.36-7.39 (m, 3H), 7.63-7.66 (m, 1H), 7.75-7.77 (m, 1H).

[000362] To a solution of Compound **W5** (2.50 g, 7.0 mmol) in DMF (50 mL) and water (7.0 mL) was added sodium chloro(difluoro)acetate (2.66 g, 17.5 mmol) and cesium carbonate (4.56 g, 14.0 mmol). The mixture was stirred for 15 minutes at room temperature and heated to 100 °C under nitrogen for 2 hours. The mixture was partitioned between water (100 mL) and ethyl acetate (100 mL). The organic phase was separated, washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated in *vacuo* to give a crude compound. The crude product was purified with column chromatography on silica gel (ethyl acetate in petroleum ether, 25% v/v) to give Compound **W6**. LC-MS (ESI) m/z : 428 $[M+Na]^+$; ^1H -NMR ($CDCl_3$, 400 MHz): δ (ppm) 1.56-1.79 (m, 6H), 3.96-3.99 (m, 1H), 4.31-4.35 (m, 1H), 4.99-5.19 (m, 2H), 5.36-5.39 (m, 1H), 6.60 (t, $J = 72.8$ Hz, 1H), 7.11-7.20 (m, 5H), 7.36-7.37 (m, 2H), 7.84-7.98 (m, 2H).

[000363] To a solution of Compound **W6** (10.4 g, 25.7 mmol) in MeCN (150 mL) was added TsOH (8.84 g, 51.4 mmol). The reaction mixture was stirred at room temperature for 2 h. The resulting mixture was diluted with ethyl acetate (200 mL), washed with saturated aqueous sodium bicarbonate solution (300 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to furnish a mixture of Compound **W7A** and Compound **W7B**. The mixture was separated with chiral-HPLC (solvent: MeOH (0.5% NH₄OH), column: (R, R)-Whelk-O1, 4.6 * 250 mm, 5 µm) to give Compound **W7A** (Rt: 5.45 min.) and Compound **W7B**. HPLC Rt: 8.1 min. For Compound **W7A**: LC-MS (ESI) m/z: 366 [M+H]⁺; ¹H-NMR (CDCl₃, 400 MHz): δ (ppm) 2.80 (brs, 1H), 3.87-3.90 (m, 1H), 3.99-4.02 (m, 1H), 5.13 (s, 2H), 5.33-5.36 (m, 1H), 6.12 (d, *J* = 6.8 Hz, 1H), 6.61 (t, *J* = 72.8 Hz, 1H), 7.19 (d, *J* = 8.4 Hz, 2H), 7.32-7.35 (m, 5H), 8.03 (d, *J* = 8.4 Hz, 2H). For Compound **W7B**: LC-MS (ESI) m/z: 366 [M+H]⁺; ¹H-NMR (CDCl₃, 400 MHz): δ (ppm) 2.80 (brs, 1H), 3.87-3.90 (m, 1H), 3.99-4.02 (m, 1H), 5.13 (s, 2H), 5.33-5.36 (m, 1H), 6.12 (d, *J* = 6.8 Hz, 1H), 6.61 (t, *J* = 72.8 Hz, 1H), 7.19 (d, *J* = 8.4 Hz, 2H), 7.32-7.35 (m, 5H), 8.03 (d, *J* = 8.4 Hz, 2H).

[000364] Intermediates **W8**, **W9**, **W10**, and **W** were synthesized, by employing the procedures described correspondingly for Intermediates **A7**, **A8**, **A9**, and **A** using Intermediates **W7A**, **W8**, **W9**, and **W10** in lieu of Intermediates **A6**, **A7**, **A8**, and **A9**.

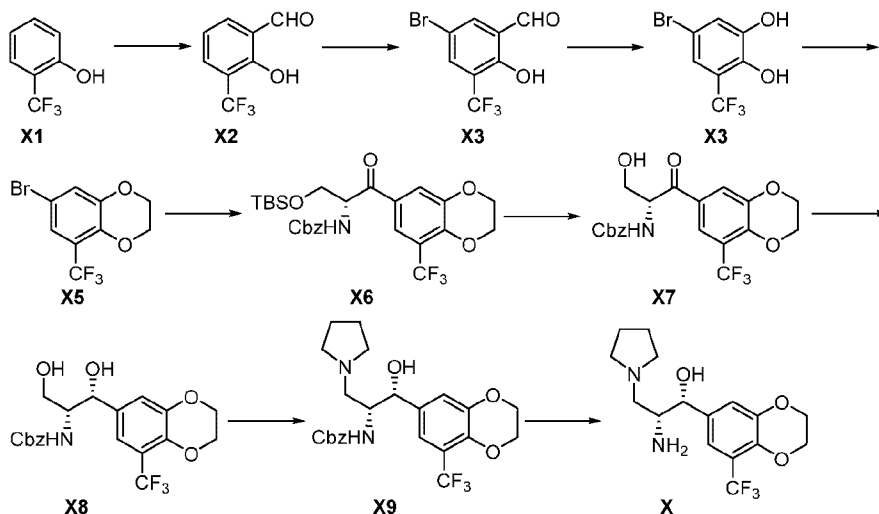
[000365] Intermediate **W8**. LC-MS (ESI) m/z: 350 [M-OH]⁺; ¹H-NMR (CDCl₃, 400 MHz): δ (ppm) 2.54 (s, 1H), 3.31 (s, 1H), 3.77-3.85 (m, 3H), 5.00-5.03 (m, 3H), 5.46-5.48 (m, 1H), 6.48 (t, *J* = 73.6 Hz, 1H), 7.05-7.07 (m, 2H), 7.29-7.35 (m, 7H).

[000366] Intermediate **W9**, which was directly used for the next step without further purification. LC-MS (ESI) m/z: 468 [M+Na]⁺.

[000367] Intermediate **W10**. LC-MS (ESI) m/z: 421 [M+H]⁺; ¹H-NMR (CDCl₃, 400 MHz): δ (ppm) 2.10-2.17 (m, 4H), 2.82-2.92 (m, 2H), 3.38-3.49 (m, 2H), 3.81 (brs, 2H), 4.18-4.20 (m, 1H), 4.91-5.07 (m, 3H), 5.98 (d, *J* = 8.8 Hz, 1H), 6.47 (t, *J* = 74.0 Hz, 1H), 7.03-7.05 (m, 2H), 7.19-7.21 (m, 2H), 7.31-7.33 (m, 5H).

[000368] Intermediate **W**, which was directly used for the next step without further purification. LC-MS (ESI) m/z: 287 [M+H]⁺.

Intermediate X



[000369] To a solution of Compound **X1** (5 g, 31 mmol) in 2,2,2-trifluoroacetic acid (50 mL) was added hexamethylenetriamine (4.7 g, 33.6 mmol). The reaction solution was heated at reflux overnight. After cooling, the mixture was treated with 50% H₂SO₄ (20 mL) at room temperature for 4 h and extracted with ether (50 mL x 3). The combined ether phases were washed with aqueous HCl solution (5 M, 50 mL), water (50 mL) and brine (50 mL), dried over anhydrous sodium sulfate, concentrated, and purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, 10% v/v) to afford Compound **X2**. LC-MS (ESI) m/z: 189 [M-H]⁺; ¹H-NMR (CDCl₃, 400 MHz): δ (ppm) 7.12 (t, *J* = 8 Hz, 1H), 7.78 (d, *J* = 7.6 Hz, 1H), 7.84 (d, *J* = 7.6 Hz, 1H), 9.96 (s, 1H), 11.74 (s, 1H).

[000370] Intermediates **X3**, **X4**, and **X5** were synthesized, by employing the procedures described correspondingly for Intermediates **C2**, **C3**, and **C4** using Intermediates **X2**, **X3**, and **X4** in lieu of Intermediates **C1**, **C2**, and **C3**.

[000371] Intermediate **X3**. LC-MS (ESI) m/z: 267 [M-H]⁺; ¹H-NMR (CDCl₃, 400 MHz): δ (ppm) 7.88-7.92 (m, 1H), 7.92 (s, 1H), 9.90 (s, 1H), 11.63 (s, 1H).

[000372] Intermediate **X4**. LC-MS (ESI) m/z: 255 [M-H]⁺.

[000373] Intermediate **X5**. LC-MS (ESI) m/z: No; ¹H-NMR (CDCl₃, 400 MHz): δ (ppm) 4.30-4.34 (m, 4H), 7.18-7.19 (m, 1H), 7.24-7.25 (m, 1H).

[000374] Intermediates **X6**, **X7**, and **X8** were synthesized, by employing the procedures described correspondingly for Intermediates **A5**, **A6**, and **A7** using Intermediates **X5**, **X6**, and **X7** in lieu of 6-bromo-2,3-dihydrobenzo[b][1,4]dioxine, Intermediates **A5**, **A6**, and **A7**.

[000375] Intermediate **X6**. LC-MS (ESI) m/z: 540 [M+H]⁺; ¹H-NMR (CDCl₃, 400 MHz): δ (ppm) -0.12 (s, 3H), -0.10 (s, 3H), 0.74 (s, 9H), 3.86-3.89 (m, 1H), 3.95-3.97 (m,

1H), 4.34-4.36 (m, 2H), 5.13 (s, 4H), 5.31 (s, 1H), 5.88-5.90 (m, 1H), 7.34-7.38 (m, 5H), 7.67-7.68 (m, 1H), 7.79 (s, 1H).

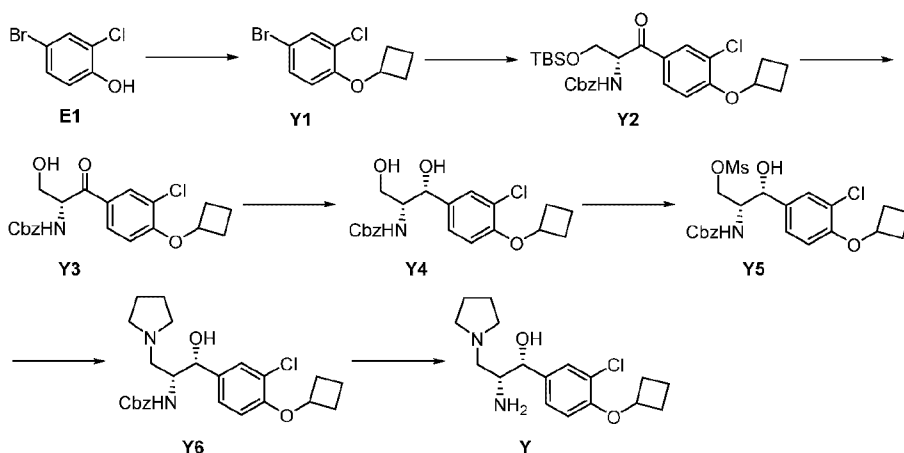
[000376] Intermediate **X7**. LC-MS (ESI) (m/z): 426 [M+H]⁺; ¹H-NMR (CDCl₃, 400 MHz): δ (ppm) 2.61-2.63 (m, 1H), 3.89-3.91 (m, 1H), 3.99-4.01 (m, 1H), 4.33-4.45 (m, 4H), 5.14 (s, 2H), 5.30-5.32 (m, 1H), 6.09 (d, *J* = 6.8 Hz, 1H), 7.32-7.37 (m, 5H), 7.12 (s, 1H), 7.83 (s, 1H).

[000377] Intermediate **X8**. LC-MS (ESI) (m/z): 410 [M-OH]⁺; ¹H-NMR (CDCl₃, 400 MHz): δ (ppm) 2.32 (s, 1H), 3.20 (s, 1H), 3.80-3.85 (m, 3H), 4.29-4.34 (m, 4H), 4.95-4.97 (m, 1H), 5.03-5.04 (m, 2H), 5.48 (d, *J* = 7.2 Hz, 1H), 7.07 (s, 1H), 7.16 (s, 1H), 7.30-7.36 (m, 5H).

[000378] To a solution of Intermediate **X8** (1.5 g, 3.5 mmol) in THF (50 mL) was added triethylamine (1.1 g, 10.5 mmol). The mixture was cooled to -20 °C and MsCl (0.44 g, 3.9 mmol) was added slowly. The mixture was stirred at -20 °C for about half an hour and pyrrolidine (2.1 g, 30 mmol) was added to the mixture. The resulting mixture was stirred at -60 °C for 16 h and cooled to 25 °C. The mixture was diluted with ethyl acetate (200 mL), washed with water (50 mL x 2) and brine (50 mL), dried over anhydrous sodium sulfate, concentrated, and purified with flash column chromatography on silica gel (methanol in dichloromethane, from 5% to 10% v/v) to give Intermediate **X9**. LC-MS (ESI) m/z: 481 [M+H]⁺; ¹H-NMR (CDCl₃, 400 MHz): δ (ppm) 1.76-1.80 (m, 4H), 2.46-2.81 (m, 6H), 3.99 (s, 1H), 4.28-4.35 (m, 5H), 4.97-5.05 (m, 4H), 7.02 (s, 1H), 7.13 (s, 1H), 7.27-7.35 (m, 5H).

[000379] Intermediate **X** was synthesized, by employing the procedure described for Intermediate **A** using Intermediate **X9** in lieu of Intermediate **A9**. LC-MS (ESI) m/z: 347 [M+H]⁺; ¹H-NMR (CDCl₃, 400 MHz): δ (ppm) 1.78-1.81 (m, 4H), 2.51-2.72 (m, 6H), 3.13-3.14 (m, 1H), 4.31-4.36 (m, 4H), 4.60-4.61 (m, 1H), 7.05 (s, 1H), 7.12 (s, 1H).

Intermediate Y



[000380] Compound **Y1** was synthesized, by employing the procedure described for Intermediate **E2** using bromocyclobutane in lieu of bromocyclopropane. LC-MS (ESI) m/z : No. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ (ppm) 1.65-1.73 (m, 1H), 1.84-1.92 (m, 1H), 2.17-2.28 (m, 2H), 2.41-2.49 (m, 2H), 4.60-4.65 (m, 1H), 6.64 (d, $J = 8.8$ Hz, 1H), 7.26 (dd, $J_1 = 8.8$ Hz, $J_2 = 2.4$ Hz, 1H), 7.48 (d, $J = 2.4$ Hz, 1H).

[000381] Intermediates **Y2**, **Y3**, **Y4**, **Y5**, and **Y6** were synthesized, by employing the procedures described correspondingly for Intermediates **A5**, **A6**, **A7**, **A8**, and **A9** using Intermediates **Y1**, **Y2**, **Y3**, **Y4**, and **Y5** in lieu of 6-bromo-2,3-dihydrobenzo[*b*][1,4]dioxine, Intermediates **A5**, **A6**, **A7**, and **A8**.

[000382] Intermediate **Y2**. LC-MS (ESI) m/z : 518 $[\text{M}+\text{H}]^+$; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ (ppm) 0.00 (s, 3H), 0.01 (s, 3H), 0.87 (s, 9H), 1.86-1.91 (m, 1H), 2.05-2.07 (m, 1H), 2.37-2.44 (m, 2H), 2.61-2.68 (m, 2H), 3.99-4.01 (m, 1H), 4.07-4.10 (m, 1H), 4.88-4.92 (m, 1H), 5.25 (s, 2H), 5.42-5.43 (m, 1H), 6.02-6.04 (m, 1H), 6.92-6.94 (m, 1H), 7.45-7.50 (m, 5H), 7.93-7.96 (m, 1H), 8.13-8.14 (m, 1H).

[000383] Intermediate **Y3**. LC-MS (ESI) m/z : 404 $[\text{M}+\text{H}]^+$; $^1\text{H-NMR}$ ($\text{DMSO}-d_6$, 400 MHz): δ (ppm) 1.66-1.68 (m, 1H), 1.81-1.84 (m, 1H), 2.08-2.13 (m, 2H), 3.62-6.64 (m, 1H), 3.72-3.73 (m, 1H), 4.88-4.93 (m, 2H), 5.02 (s, 2H), 5.09-5.11 (m, 1H), 7.09-7.12 (m, 1H), 7.30-7.35 (m, 5H), 7.62-7.63 (m, 1H), 7.93-7.95 (m, 1H), 8.01-8.02 (m, 1H).

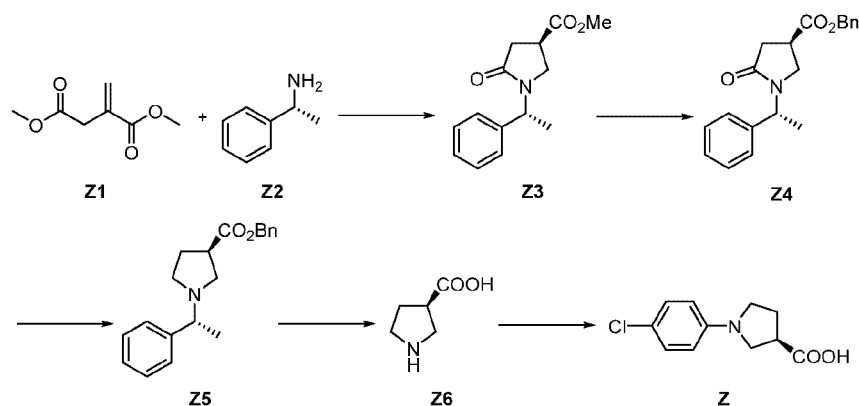
[000384] Intermediate **Y4**. LC-MS (ESI) m/z : 388 $[\text{M}-\text{OH}]^+$; $^1\text{H-NMR}$ ($\text{DMSO}-d_6$, 400 MHz): δ (ppm) 1.62-1.66 (m, 1H), 1.77-1.80 (m, 1H), 1.99-2.08 (m, 2H), 2.40-2.50 (m, 2H), 3.27-3.32 (m, 1H), 3.46-3.51 (m, 1H), 3.61-3.64 (m, 1H), 4.68-4.74 (m, 2H), 4.86-4.99 (m, 2H), 5.36 (brs, 1H), 6.76-6.89 (m, 2H), 7.14-7.35 (m, 6H).

[000385] Intermediate **Y5**, which was directly used for the next step without further purification. LC-MS (ESI) m/z : 466 $[M-OH]^+$.

[000386] Intermediate **Y6**. LC-MS (ESI) m/z : 459 $[M+H]^+$; ^1H -NMR ($CDCl_3$, 400 MHz): δ (ppm) 1.67-1.89 (m, 6H), 2.21-2.27 (m, 2H), 2.44-2.49 (m, 2H), 2.62-2.72 (m, 5H), 4.00 (brs, 1H), 4.63-4.67 (m, 1H), 4.99-5.06 (m, 3H), 6.71-6.73 (m, 1H), 7.08-7.10 (m, 1H), 7.26-7.37 (m, 6H).

[000387] Intermediate **Y** was synthesized, by employing the procedure described for Intermediate **E** using Intermediate **Y6** in lieu of Intermediate **E7**, which was directly used for the next step without further purification. LC-MS (ESI) m/z : 325 $[M+H]^+$; ^1H -NMR ($CDCl_3$, 400 MHz): δ (ppm) 0.62-0.79 (m, 1H), 1.67-1.71 (m, 4H), 1.86-1.89 (m, 1H), 2.22-2.30 (m, 2H), 2.46-2.51 (m, 3H), 2.55-2.368 (m, 5H), 3.11-3.12 (m, 1H), 4.58-4.58 (m, 1H), 4.65-4.69 (m, 2H), 6.75-6.77 (m, 1H), 7.12-7.14 (m, 1H), 7.34-7.37 (m, 3H).

Intermediate **Z**



[000388] A mixture of dimethyl 2-methylenesuccinate (**Z1**, 150 g, 10 mol) and (R)-1-phenylethanamine (**Z2**, 150 g, 15 mol) in methanol (500 mL) was stirred at reflux for 3 days. The reaction mixture was treated with water (500 mL) and extracted with ethyl acetate (500 mL x 3). The extracts were washed with water (500 mL x 3), dried over anhydrous sodium sulfate, and concentrated. The crude product was purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, from 10% to 25% v/v) to afford Compound **Z3**. LC-MS (ESI) m/z : 248 $[M+H]^+$; ^1H -NMR ($CDCl_3$, 400 MHz): δ (ppm) 1.53 (d, $J = 6.4$ Hz, 3H), 2.67-2.79 (m, 2H), 3.09-3.22 (m, 2H), 3.53-3.57 (m, 1H), 3.72 (s, 3H), 5.50 (m, 1H), 7.28-7.37 (m, 5H).

[000389] A mixture of Compound **Z3** (30 g, 12.1 mmol), 4-methylbenzenesulfonic acid (4 g, 2.42 mmol), and phenylmethanol (26 g, 24.2 mmol) in toluene (150 mL) was stirred at

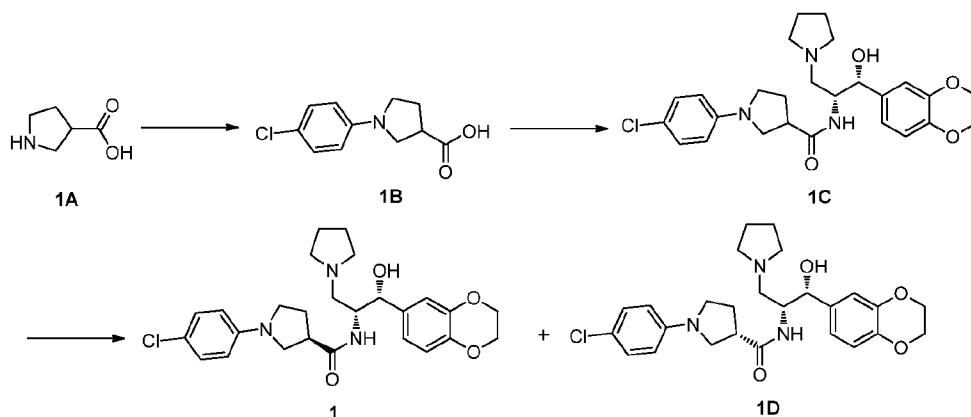
reflux for 2 days. The reaction mixture was treated with ethyl acetate (500 mL), washed with sodium bicarbonate (500 mL x 3) and water (500 mL x 3), dried over anhydrous sodium sulfate, and concentrated. The crude product was purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, from 10% to 33% v/v) to furnish Compound **Z4**. LC-MS (ESI) m/z : 324 $[M+H]^+$; ^1H -NMR ($CDCl_3$, 400 MHz): δ (ppm) 1.44 (d, J = 6.4 Hz, 3H), 1.62-1.69 (m, 2H), 3.09-3.11 (m, 2H), 3.45-3.47 (m, 1H), 5.07 (s, 2H), 5.41-5.43 (m, 1H), 7.14-7.28 (m, 10H).

[000390] To a solution of Compound **Z4** (36 g, 11.1 mmol) in tetrahydrofuran (500 mL) was added borane tetrahydrofuran complex (200 mL, 200 mmol) dropwise at 0 °C. The mixture was stirred at reflux for 0.5 h. The mixture was quenched with methanol (50 mL) and water (50 mL) and stirred at reflux for 1 h and at room temperature for 18 h. The reaction mixture was evaporated in *vacuo*. Ethyl acetate (500 mL) was added. The organic layer was washed with water (500 mL x 3), dried over anhydrous sodium sulfate, and concentrated. The crude product was purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, from 1% to 10% v/v) to give Compound **Z5**. LC-MS (ESI) m/z : 310 $[M+H]^+$; ^1H -NMR ($CDCl_3$, 400 MHz): δ (ppm) 1.28 (d, J = 6.4 Hz, 3H), 1.95-2.02 (m, 2H), 2.37-2.57 (m, 3H), 2.86-2.99 (m, 2H), 3.14-3.15 (m, 1H), 5.19 (s, 2H), 7.14-7.28 (m, 10H).

[000391] To a solution of Compound **Z5** (20 g, 64.7 mmol) in methanol (400 mL) was added 10% palladium on carbon (0.4 g). The mixture was stirred under 1 atm of H_2 atmosphere at 23 °C for 2 days. After the reaction was complete, the mixture was filtered and concentrated in *vacuo* to give Intermediate **Z6**, which was directly used for the next step. LC-MS (ESI) m/z : 116 $[M+H]^+$; ^1H -NMR (CD_3OD , 400 MHz): δ (ppm) 2.07-2.16 (m, 2H), 2.90-2.98 (m, 1H), 3.14-3.23 (m, 1H), 3.24-3.28 (m, 2H), 3.39-3.44 (m, 1H).

[000392] A mixture of 1-chloro-4-iodobenzene (3 g, 13 mmol), Intermediate **Z6** (1 g, 8.7 mmol), CuI (190 mg, 1 mmol), and K_2CO_3 (2.4 g, 17.4 mmol) in DMSO (50 mL) was stirred at 100 °C for 18 h. The reaction mixture was treated with water (50 mL) and extracted with ethyl acetate (150 mL x 3). The extractions were washed with water (100 mL x 2), dried over anhydrous sodium sulfate, concentrated, and purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, from 10% to 33% v/v) to furnish Compound **Z**. LC-MS (ESI) m/z : 226 $[M+H]^+$.

Example 1



[000393] To a solution of Compound **1A** (0.5 g, 4.3 mmol) in DMF (20 mL) was added 1-chloro-4-iodobenzene (1.0 g, 4.3 mmol), CuI (100 mg, 0.5 mmol) and K₂CO₃ (1.2 g, 8.6 mmol). The mixture was stirred for 8 h at 100 °C under N₂. The mixture was diluted with aq NH₄Cl (40 mL), extracted with ethyl acetate (50 mL x 2), washed with brine (100 mL x 2), and evaporated. The crude product was purified by silica gel column chromatography (methanol in dichloromethane, 10% v/v) to give Compound **1B**. LC-MS (m/z): 224 [M-1].

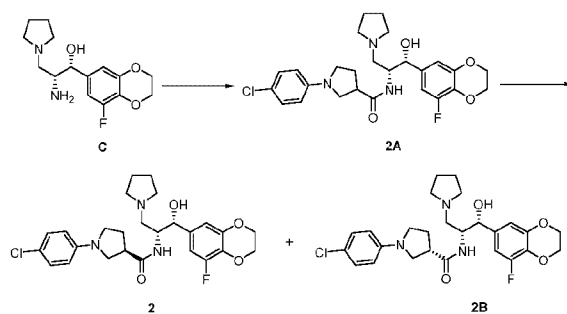
[000394] To a solution of Compound **1B** (0.1 g, 0.44 mmol) in dichloromethane (10 mL) was added Intermediate **A** (124 mg, 0.44 mmol), EDCI (127 mg, 0.66 mmol), HOBt (89 mg, 0.66 mmol). The mixture was stirred at room temperature overnight, quenched with water (20 mL), extracted with dichloromethane (20 mL x 2), washed with brine (50 mL x 2), and evaporated to remove solvents. The crude product was purified by prep-HPLC to give Compound **1C**. Compound **1C** was further subjected to chiral resolution using prep-chiral-HPLC, which gave two isomers Compound **1** and Compound **1D**. For Compound **1**: LC-MS (m/z): 486 [M+1]⁺; ¹H-NMR (DMSO-*d*₆, 400 MHz) major characteristic peaks: δ (ppm) 1.93 (m, 6H), 2.61 (m, 1H), 3.13 (m, 7H), 3.52 (m, 2H), 4.24 (m, 5H), 4.71 (s, 1H), 5.84 (s, 1H), 6.46 (d, *J* = 8.8 Hz, 2H), 6.83 (m, 3H), 7.20 (d, *J* = 8.8 Hz, 2H), 7.96 (d, *J* = 9.6 Hz, 1H), 9.38 (m, 1H). For Compound **1D**: LC-MS (m/z): 486 [M+1]⁺; ¹H-NMR (DMSO-*d*₆, 400 MHz) major characteristic peaks: δ (ppm) 1.83 (m, 6H), 3.19 (m, 8H), 3.52 (s, 2H), 4.20 (m, 5H), 4.71 (s, 1H), 5.84 (s, 1H), 6.46 (d, *J* = 8.8 Hz, 2H), 6.78 (m, 3H), 7.15 (d, *J* = 12 Hz, 2H), 7.92 (d, *J* = 9.6 Hz, 1H), 9.42 (m, 1H).

[000395] Alternatively, Compound **1** can be prepared by employing the following procedures.

[000396] To a solution of (*R*)-pyrrolidine-3-carboxylic acid (0.5 g, 4.3 mmol) in DMSO (20 mL) was added 1-chloro-4-iodobenzene (1.0 g, 4.3 mmol), CuI (100 mg, 0.5 mmol) and K₂CO₃ (1.2 g, 8.6 mmol). The mixture was stirred for 8 hour at 100 °C under N₂. The mixture was diluted with aq. NH₄Cl (40 mL), extracted with ethyl acetate (50 mL x 2), washed with brine (100 mL x 2), and evaporated to remove the solvents. The crude product was purified with column chromatography (on silica gel, methanol in dichloromethane, 10% v/v as the eluents) to furnish (*R*)-1-(4-chlorophenyl) pyrrolidine-3-carboxylic acid. LC-MS (*m/z*): 224 [M-1]⁺.

[000397] To a solution of (*R*)-1-(4-chlorophenyl) pyrrolidine-3-carboxylic acid (0.1 g, 0.44 mmol) in dichloromethane (10 mL) was added Intermediate **A** (124 mg, 0.44 mmol), EDCI.HCl (127 mg, 0.66 mmol), and HOBt (89 mg, 0.66 mmol). The mixture was stirred at room temperature overnight, quenched with water (20 mL), extracted with dichloromethane (20 mL x 2), washed with brine (50 mL x 2), and evaporated to dryness. The crude product was purified with prep-HPLC to give Compound **1**. LC-MS (*m/z*): 486 [M+1]⁺; ¹H-NMR (DMSO-*d*₆, 400 MHz) major characteristic peaks: δ (ppm) 1.87-1.99 (m, 6H), 2.60 (m, 1H), 3.13 (m, 7H), 3.52 (m, 2H), 4.19 (m, 5H), 4.71 (s, 1H), 5.85 (s, 1H), 6.46 (d, *J* = 8.8 Hz, 2H), 6.78 (s, 2H), 6.88 (s, 1H), 7.20 (d, *J* = 12 Hz, 2H), 7.98 (d, *J* = 12 Hz, 1H), 9.31 (m, 1H).

Example 2



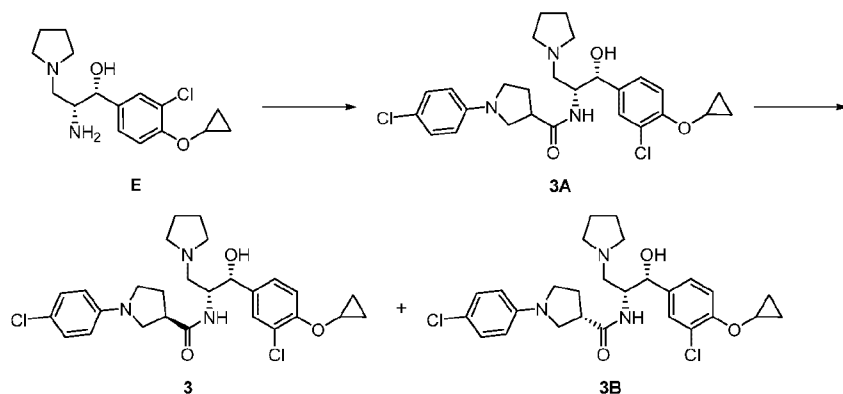
[000398] Compounds **2** and **2B** were synthesized, by employing the procedure described for Compound **1** using Intermediate **C** in lieu of Intermediate **A**.

[000399] Compound **2**. LC-MS (*m/z*): 504 [M+1]⁺; ¹H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 1.75 (s, 4H), 2.12-2.20 (m, 2H), 2.57-2.71 (m, 4H), 2.80-2.98 (m, 3H), 3.18-3.43 (m, 4H), 4.11-4.16 (m, 1H), 4.23-4.27 (m, 4H), 4.92 (s, 1H), 6.15 (d, *J* = 8 Hz, 1H), 6.46 (d, *J* = 8 Hz, 2H), 6.62-6.70 (m, 2H), 7.16 (d, *J* = 12 Hz, 2H). Chiral-HPLC conditions, solvent: MeOH (0.5% DEA), column AD-H 250 * 4.6 mm 5 μ m, Rt: 5.02 min.

[000400] Compound **2B**. LC-MS (*m/z*): 504 [M+1]⁺; ¹H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 1.78 (s, 4H), 2.04-2.18 (m, 2H), 2.61-2.68 (m, 4H), 2.82-

2.99 (m, 3H), 3.19-3.25 (m, 1H), 3.32-3.42 (m, 3H), 4.13-4.18 (m, 1H), 4.25-4.28 (m, 4H), 4.90 (s, 1H), 6.16 (d, $J = 8$ Hz, 1H), 6.45 (d, $J = 8$ Hz, 2H), 6.65(t, $J = 16$ Hz, 2H), 7.15 (d, $J = 8$ Hz, 2H); Chiral-HPLC conditions, solvent: MeOH (0.5% DEA), column AD-H 250 * 4.6 mm 5 μ m, Rt: 8.38 min.

Example 3

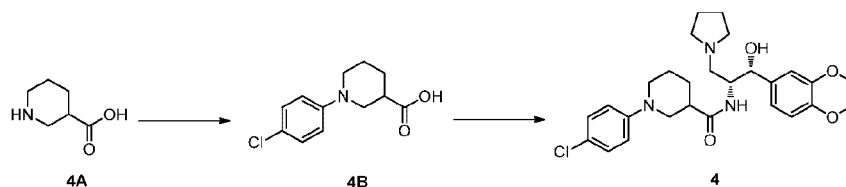


[000401] Compounds **3** and **3B** were synthesized, by employing the procedure described for Compound **1** using Intermediate **E** in lieu of Intermediate **A**.

[000402] Compound **3**. LC-MS (m/z): 518.0 $[M+1]^+$; $^1\text{H-NMR}$ (MeOD, 400 MHz) major characteristic peaks: δ (ppm) 0.62-0.77 (m, 4H), 1.85 (s, 4H), 2.03-2.20 (m, 3H), 2.67-2.83 (m, 7H), 2.98-3.25 (m, 3H), 3.75-3.76 (m, 1H), 4.30 (m, 1H), 4.59 (s, 2H), 6.47 (d, $J = 6.8$ Hz, 2H), 7.10-7.13 (m, 2H), 7.20-7.43 (m, 2H), 7.44 (s, 1H). Chiral-HPLC conditions, solvent: MeOH (0.1% DEA), column: AD-H 250 * 4.6 mm 5 μ m, Rt: 3.51 min.

[000403] Compound **3B**. LC-MS (m/z): 518.0 $[M+1]^+$; $^1\text{H-NMR}$ (MeOD, 400 MHz) major characteristic peaks: δ (ppm) 0.65-0.80 (m, 2H), 1.85 (s, 4H), 1.86-1.98 (m, 1H), 2.13-2.20 (m, 1H), 2.57-2.75 (m, 5H), 3.09-3.37 (m, 5H), 3.83-3.86 (m, 1H), 4.26 (m, 1H), 6.49 (d, $J = 2.4$ Hz, 2H), 7.10-7.12 (m, 2H), 7.23-7.32 (m, 2H), 7.41 (s, 1H). Chiral-HPLC conditions, solvent: MeOH (0.1% DEA), column: AD-H 250 * 4.6 mm 5 μ m, Rt: 5.94 min.

Example 4

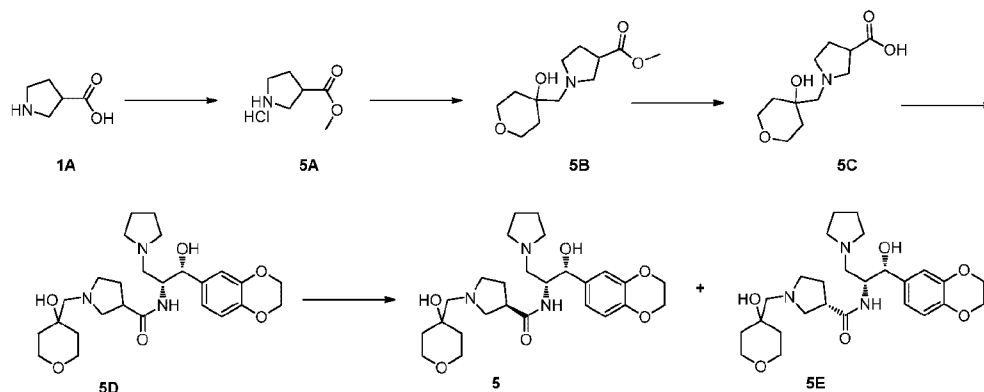


[000404] Compounds **4B** and **4** were synthesized, by employing the procedures described correspondingly for Compounds **1B** and **1** using Compounds **4A** and **4B** in lieu of Compounds **1A** and **1B**.

[000405] Compound **4B**. LC-MS (m/z): 238 $[M-1]^+$.

[000406] Compound **4**. LC-MS (m/z): 500 $[M+H]^+$; ^1H -NMR 5(DMSO- d_6 , 400 MHz) major characteristic peaks: δ (ppm) 1.20 (m, 1H), 1.47 (m, 1H), 1.64 (m, 2H), 1.85 (m, 4H), 2.45 (m, 1H), 2.61 (m, 2H), 3.10 (m, 4H), 3.39 (m, 4H), 4.17 (m, 5H), 4.66 (s, 1H), 6.82 (m, 5H), 7.21 (d, $J = 8.8$ Hz, 2H), 7.78 (d, $J = 9.6$ Hz, 1H), 9.35 (s, 1H).

Example 5



[000407] Thionyl dichloride (3.7 mL, 52.1 mmol) was added dropwise to a solution of Compound **1A** (5 g, 43.4 mmol) in MeOH (80 mL) at 0 °C. The reaction mixture was stirred at room temperature for 18 h. The reaction mixture was concentrated in *vacuo* to furnish Compound **5A**. LC-MS (m/z): 130 $[M+1]^+$; ^1H -NMR ($CDCl_3$, 400 MHz) major characteristic peaks: δ (ppm) 2.14 (m, 1H), 2.27 (m, 1H), 3.25 (m, 3H), 3.45 (m, 2H), 3.65 (s, 3H).

[000408] To a solution of Compound **5A** (0.7 g, 4.2 mmol) and 1,6-dioxaspiro[2.5]octane (0.97 g, 8.48 mmol) in ethanol (30 mL) was added triethylamine (0.856 g, 8.48 mmol). The reaction mixture was stirred at 30 °C under N_2 overnight. The reaction mixture was concentrated and the residue was purified with silica gel chromatography (ethyl acetate in petroleum ether, from 1% to 5% v/v) to furnish Compound **5B**. LC-MS (m/z): 244 $[M+1]^+$; ^1H -NMR ($CDCl_3$, 400 MHz) major characteristic peaks: δ (ppm) 1.40 (d, 2H), 1.53 (m, 2H), 2.02 (m, 2H), 2.43 (dd, 2H), 2.71 (m, 2H), 2.92 (m, 3H), 3.62 (s, 3H), 3.72 (m, 4H).

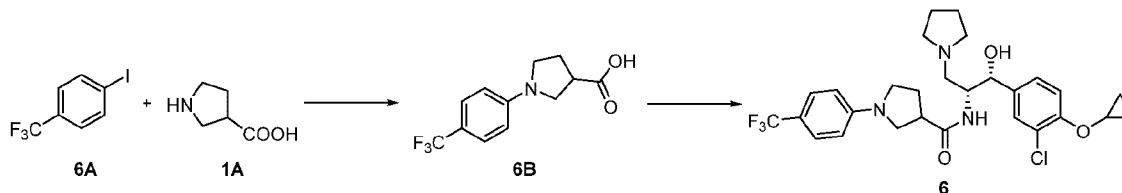
[000409] A solution of 1N lithium hydroxide (5 mL, 5 mmol) was added dropwise to a solution of Compound **5B** (0.6 g, 2.47 mmol) in MeOH (10 mL). The reaction mixture was stirred at room temperature for 2 h. The reaction mixture was treated with 3N HCl (1.7 mL) to adjust pH to 7 and concentrated in *vacuo* to yield Compound **5C**. LC-MS (m/z): 230 $[M+1]^+$.

[000410] Compounds **5** and **5E** were synthesized, by employing the procedures described for Compound **1** using Compound **5C** in lieu of Compound **1B**.

[000411] Compound **5**. LC-MS (m/z): 490 $[M+1]^+$; $^1\text{H-NMR}$ (MeOD, 400 MHz) major characteristic peaks: δ (ppm) 1.36 (m, 2H), 1.55 (m, 3H), 1.70 (m, 4H), 1.90 (m, 1H), 2.40 (m, 3H), 2.49 (m, 6H), 2.71 (m, 4H), 3.65 (m, 4H), 4.07 (m, 1H), 4.10 (s, 4H), 4.70 (d, J = 2.8 Hz, 1H), 6.68 (m, 2H), 6.75 (s, 1H). Chiral-HPLC conditions, solvent: EtOH (0.5% DEA), column: OZ-H 250 * 4.6 mm 5 μm , Rt: 6.39 min.

[000412] Compound **5E**. LC-MS (m/z): 490 $[M+1]^+$; $^1\text{H-NMR}$ (MeOD, 400 MHz) major characteristic peaks: δ (ppm) 1.38 (m, 2H), 1.53 (m, 3H), 1.70 (m, 4H), 1.90 (m, 1H), 2.40 (m, 2H), 2.53 (m, 7H), 2.74 (m, 4H), 3.62 (m, 4H), 4.07 (m, 1H), 4.10 (s, 4H), 4.70 (d, J = 2.8 Hz, 1H), 6.68 (m, 2H), 6.75 (s, 1H). Chiral-HPLC conditions, solvent: EtOH (0.5% DEA), column: OZ-H 250 * 4.6 mm 5 μm , Rt: 10.07 min.

Example 6

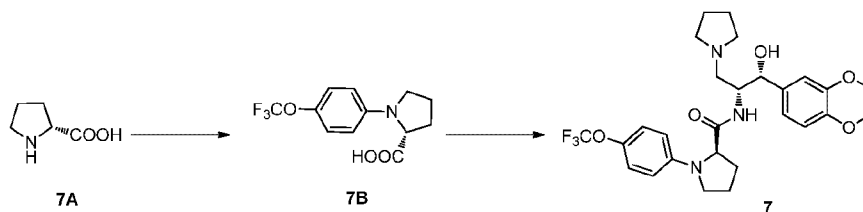


[000413] Compounds **6B** and **6** were synthesized, by employing the procedures described for Compounds **1B** and **1** using Compounds **6A**, **6B**, and Intermediate **E** in lieu of 1-chloro-4-iodobenzene, Compound **1B**, and Intermediate **A**.

[000414] Compound **6B**. LC-MS (ESI) m/z : 258 $[M-H]^+$.

[000415] Compound **6**. LC-MS (m/z): 552.2 $[M+1]^+$. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) major characteristic peaks: δ (ppm) 0.73-0.74 (m, 4H), 1.79 (s, 1H), 2.02-(m, 4H), 2.83-2.91 (m, 5H), 3.01-3.20 (m, 4H), 3.31 (s, 1H), 3.66-3.77 (m, 4H), 4.43 (s, 1H), 4.85 (s, 1H), 6.39-6.41 (d, J = 8.8 Hz, 2H), 7.07-7.09 (m, 1H), 7.14-7.16 (m, 1H), 7.31-7.38 (d, J = 8.4 Hz, 3H), 7.46-7.50 (m, 1H), 11.15 (s, 1H).

Example 7

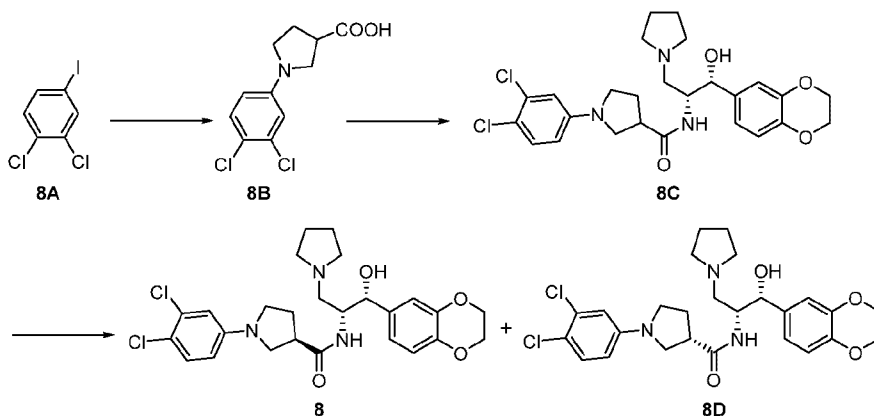


[000416] Compound **7B** was synthesized, by employing the procedure described for Compound **1B** using 1-(4-(trifluoromethyl)phenyl)pyrrolidine-3-carboxylic acid and Compound **7A** in lieu of 1-chloro-4-iodobenzene and Compound **1A**. LC-MS (m/z): 274 $[M-1]^+$; $^1\text{H-NMR}$ ($\text{DMSO}-d_6$, 400 MHz) major characteristic peaks: δ (ppm) 1.978-2.088 (m,

3H), 2.255-2.285 (m, 1H), 3.401-3.438 (m, 2H), 4.156-4.182 (m, 1H), 6.491-6.515 (d, $J = 9.6$ Hz, 2H), 7.140-7.161 (d, $J = 8.4$ Hz, 2H).

[000417] A mixture of Compound **7B** (50 mg, 0.18 mmol), Intermediate **A** (50 mg, 0.18 mmol), HATU (103 mg, 0.27 mmol) and DIPEA (46 mg, 0.36 mmol) in THF (5 mL) was stirred at 25 °C for 16 h. After removal of solvent the residue was purified with prep-HPLC to give Compound **7**. LC-MS (m/z): 536 $[M+1]^+$; $^1\text{H-NMR}$ (MeOD, 400 MHz) major characteristic peaks: δ (ppm) 1.863-2.246 (m, 8H), 3.164-3.325 (m, 4H), 3.404-3.438 (m, 1H), 3.564-3.739 (m, 4H), 4.076-4.099 (m, 1H), 4.234 (s, 4H), 4.458-4.486 (m, 1H), 4.795-4.801 (m, 1H), 6.530-6.552 (m, 2H), 6.897-6.718 (m, 2H), 6.844-6.848 (m, 1H), 7.091-7.114 (d, $J = 9.2$ Hz, 2H).

Example 8



[000418] Compound **8B** was synthesized, by employing the procedure described for Compound **1B** using Compound **8A** in lieu of 1-chloro-4-iodobenzene. LC-MS (m/z): 258 $[M-1]^+$; $^1\text{H-NMR}$ (DMSO- d_6 , 400 MHz) major characteristic peaks: δ (ppm) 2.126-2.234 (m, 2H), 3.183-3.309 (m, 3H), 3.407-3.479 (m, 2H), 6.525-6.554 (dd, $J_1 = 8.8$ Hz, $J_2 = 2.8$ Hz, 1H), 6.712-6.719 (d, $J = 2.8$ Hz, 1H), 7.333-7.355 (d, $J = 8.8$ Hz, 1H), 12.518 (s, 1H).

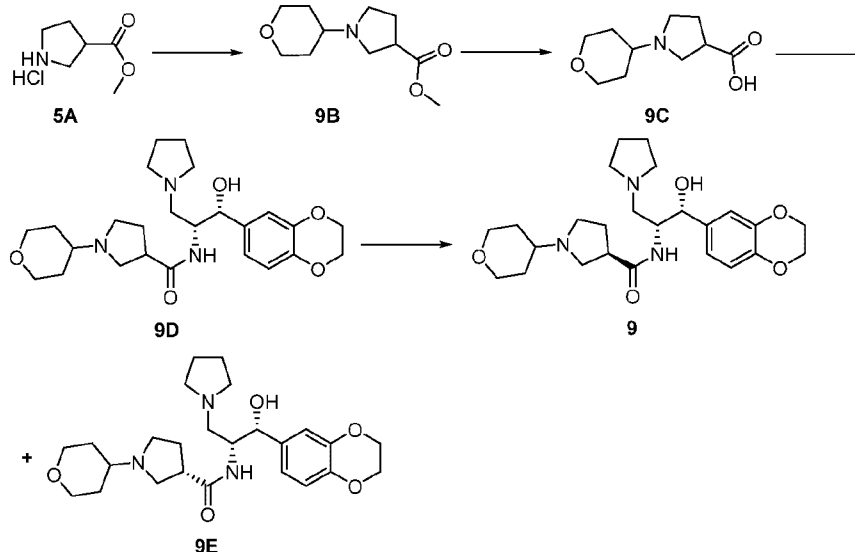
[000419] Compounds **8** and **8D** were synthesized, by employing the procedure described for Compound **7** using Compound **8B** in lieu of Compound **7B**.

[000420] Compound **8**. LC-MS (m/z): 520 $[M+1]^+$; $^1\text{H-NMR}$ (MeOD, 400 MHz) major characteristic peaks: δ (ppm) 1.769-1.818 (m, 1H), 2.010-2.229 (m, 5H), 3.151-3.279 (m, 5H), 3.349-3.412 (m, 2H), 3.473-3.600 (m, 2H), 3.658-3.696 (m, 1H), 3.789-3.830 (m, 1H), 4.249 (s, 4 H), 4.477-4.518 (m, 1H), 4.847-4.858 (m, 1H), 6.459-6.488 (m, 1H), 6.635-6.642 (m, 1H), 6.816-6.968 (m, 3H), 7.244-7.266 (d, $J = 8.8$ Hz, 1H).

[000421] Compound **8D**. LC-MS (m/z): 520 $[M+1]^+$; $^1\text{H-NMR}$ (MeOD, 400 MHz) major characteristic peaks: δ (ppm) 2.046-2.282 (m, 5H), 2.718-2.760 (m, 1H), 3.166-3.336

(m, 4H), 3.353-3.528 (m, 4H), 3.607-3.706 (m, 1H), 3.814-3.823 (m, 1H), 4.207-4.316 (m, 4H), 4.489-4.529 (m, 1H), 4.863-4.874 (m, 1H), 6.467-6.497 (m, 1H), 6.652-6.659 (m, 1H), 6.8832-6.973 (m, 3H), 7.281-7.303 (d, $J = 8.8$ Hz, 1H).

Example 9



[000422] To a solution of Compound **5A** (650 mg, 3.93 mmol) and dihydro-2*H*-pyran-4(3*H*)-one (471 mg, 4.71 mmol) in dichloromethane (30 mL) was added sodium triacetoxyborohydride (1.24 g, 5.09 mmol). The reaction mixture was stirred at 30 °C for 3 h. The reaction mixture was filtered and the filtrate was concentrated and the residue was purified with silica gel column chromatography (methanol in dichloromethane, from 1% to 5% v/v) to yield Compound **9B**. LC-MS (m/z): 214 $[M+1]^+$; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) major characteristic peaks: δ (ppm) 1.94-2.03 (m, 4H), 2.22-2.25 (m, 1H), 2.43-2.48 (m, 1H), 3.02-3.04 (m, 1H), 3.17-3.20 (m, 1H), 3.26-3.85 (m, 3H), 3.48-3.51 (m, 1H), 3.68 (s, 3H), 3.99-4.02 (m, 2H).

[000423] Compound **9C** was synthesized, by employing the procedure described for Compound **5C** using Compound **9B** in lieu of Compound **5B**. LC-MS (m/z): 200 $[M+1]^+$.

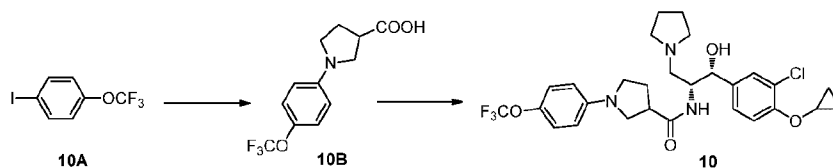
[000424] Compounds **9** and **9E** were synthesized, by employing the procedures described for Compound **7** using Compound **9C** in lieu of Compound **7B**.

[000425] Compound **9**. LC-MS (m/z): 459 $[M+1]^+$; $^1\text{H-NMR}$ (MeOD, 400 MHz) major characteristic peaks: δ (ppm) 1.45-1.51 (m, 2H), 1.71-1.83 (m, 8H), 2.17-2.19 (m, 2H), 2.42-2.61 (m, 6H), 2.65-2.69 (m, 2H), 2.76-2.79 (m, 2H), 3.34-3.35 (m, 2H), 3.84-3.89 (m, 2H), 4.08 (s, 4H), 4.08 (m, 1H), 4.70 (d, $J = 2.8$ Hz, 1H), 6.67 (m, 2H), 6.76 (s, 1H). HPLC

analysis: *n*-hexane (0.1% DEA):EtOH (0.1% DEA), column: AS-H 250 * 4.6 mm 5 μ m, Rt: 9.072 min.

[000426] Compound **9E**. LC-MS (*m/z*): 459 [*M*+1]⁺; ¹H-NMR (MeOD, 400 MHz) major characteristic peaks: δ (ppm) 1.47-1.54 (m, 2H), 1.73-1.85 (m, 8H), 2.00-2.04 (m, 1H), 2.29-2.34 (m, 1H), 2.52-2.69 (m, 7H), 2.73-2.79 (m, 2H), 2.87-2.90 (m, 2H), 3.34-3.44 (m, 2H), 3.92-3.95 (m, 2H), 4.20 (s, 4H), 4.20 (m, 1H), 4.78 (d, *J* = 2.8 Hz, 1H), 6.78 (m, 2H), 6.85 (s, 1H). HPLC analysis: co-solvent *n*-hexane (0.1% DEA): EtOH (0.1% DEA), column: AS-H 250 * 4.6 mm 5 μ m, Rt: 12.706 min.

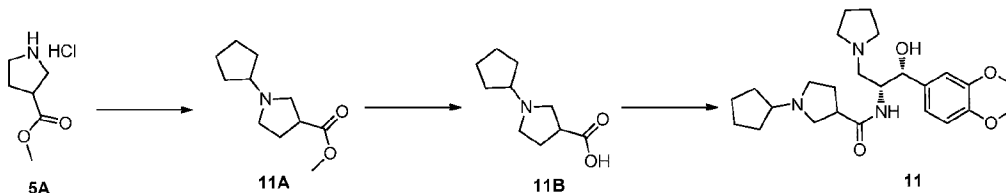
Example 10



[000427] Compound **10B** was synthesized, by employing the procedure described for Compound **1B** using Compound **10A** in lieu of 1-chloro-4-iodobenzene. LC-MS (*m/z*): 274 [*M*-1]⁺; ¹H-NMR (DMSO-*d*₆, 400 MHz) major characteristic peaks: δ (ppm) 2.15-2.25 (m, 2H), 3.21-3.48 (m, 5H), 6.57-6.59 (d, *J* = 8.8 Hz, 2H), 7.15-7.17 (d, *J* = 8.8 Hz, 2H), 12.52 (s, 1H).

[000428] Compound **10** was synthesized, by employing the procedure described for Compound **7** using Compound **10B** and Intermediate **E** in lieu of Compound **7B** and Intermediate **A**. LC-MS (*m/z*): 568 [*M*+1]⁺; ¹H-NMR (MeOD, 400 MHz) major characteristic peaks: δ (ppm) 0.64-0.82 (m, 4H), 2.04-2.24 (m, 6H), 2.53-2.57 (m, 1H), 3.13-3.30 (m, 6H), 3.49-3.60 (m, 5H), 4.56-4.58 (m, 1H), 4.94-4.95 (m, 1H), 6.49-6.51 (m, 2H), 7.07-7.09 (d, *J* = 8.4 Hz, 2H), 7.30-7.32 (m, 2H), 7.54-7.55 (m, 1H).

Example 11

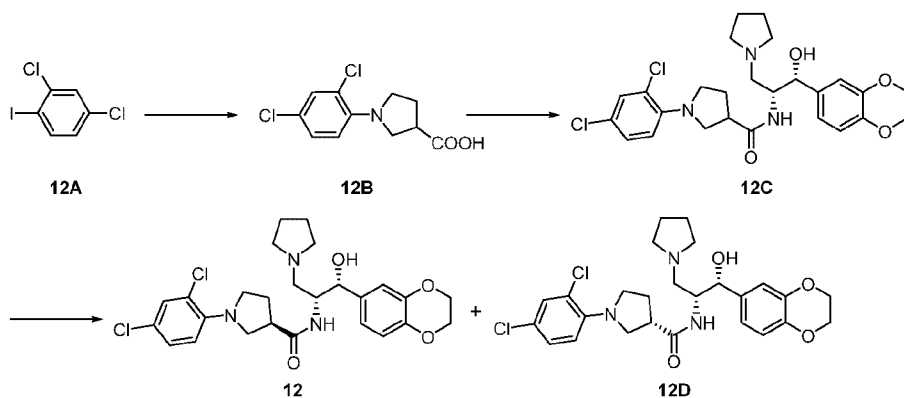


[000429] Compound **11A** was synthesized, by employing the procedure described for Compound **9B** using cyclopentanone in lieu of dihydro-2*H*-pyran-4(3*H*)-one. LC-MS (*m/z*): 198 [*M*+1]⁺; ¹H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 1.41-1.84 (m, 8H), 2.06-2.11 (m, 2H), 2.43-2.49 (m, 2H), 2.56-2.60 (m, 1H), 2.74-2.79 (m, 1H), 2.97-3.07 (m, 2H), 3.68 (s, 3H).

[000430] Compound **11B** was synthesized, by employing the procedure described for Compound **5C** using Compound **11A** in lieu of Compound **5B**. LC-MS (m/z): 184 $[M+1]^+$; $^1\text{H-NMR}$ ($\text{DMSO-}d_6$, 400 MHz) major characteristic peaks: δ (ppm) 1.48-1.51 (m, 4H), 1.62-1.63 (m, 2H), 1.77-1.79 (m, 2H), 1.92-1.98 (m, 2H), 2.63-2.91 (m, 6H).

[000431] A solution of Compound **11B** (110 mg, 0.6 mmol) in SOCl_2 (1 mL) was stirred at 30 °C for 18 h. The mixture was concentrated and DCM (5 mL) was added, followed by the addition of Intermediate **A** (167 mg, 0.6 mmol) and Et_3N (0.3 mL, 1.8 mmol). It was stirred at 30 °C for 18 h. The solvent was evaporated and the residue was purified with prep-HPLC to furnish Compound **11**. LC-MS (m/z): 444 $[M+1]^+$. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) major characteristic peaks: δ (ppm) 1.58-2.06 (m, 14H), 2.90-3.87 (m, 12H), 4.19-4.22 (m, 4H), 4.45-4.50 (m, 1H), 4.75-4.86 (m, 1H), 6.81 (s, 2H), 6.88-6.92 (m, 1H), 11.46 (s, 1H), 11.65 (s, 1H).

Example 12



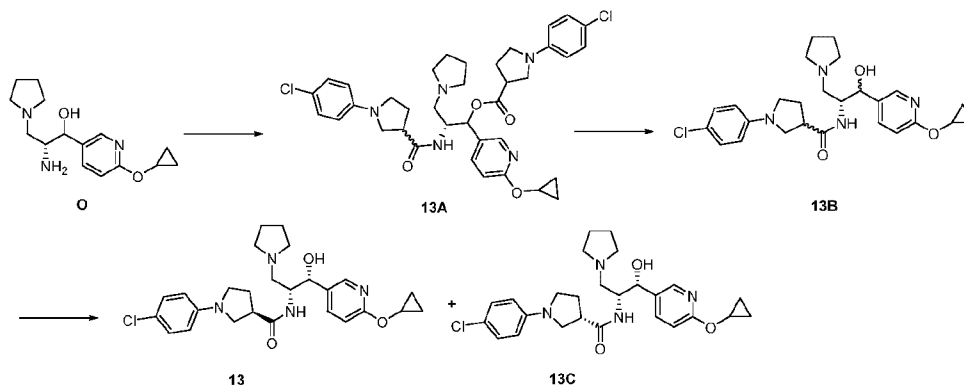
[000432] Compound **12B** was synthesized, by employing the procedure described for Compound **1B** using Compound **12A** in lieu of 1-chloro-4-iodobenzene. LC-MS m/z : 258 $[M-1]^+$; $^1\text{H-NMR}$ ($\text{DMSO-}d_6$, 400 MHz) major characteristic peaks: δ (ppm) 2.22-2.28 (m, 2H), 3.15-3.22 (m, 1H), 3.34-3.43 (m, 2H), 3.54-3.66 (m, 2H), 6.96-6.99 (m, 1H), 7.18-7.20 (m, 1H), 7.32-7.33 (m, 1H).

[000433] Compounds **12** and **12D** were synthesized, by employing the procedures described for Compound **7** using Compound **12B** in lieu of Compound **7B**.

[000434] Compound **12**. LC-MS (m/z): 520 $[M+1]^+$; $^1\text{H-NMR}$ (MeOD , 400 MHz) major characteristic peaks: δ (ppm) 1.67-1.78 (m, 1H), 2.00-2.05 (m, 2H), 2.16-2.18 (m, 3H), 3.08-3.16 (m, 4H), 3.20-3.25 (m, 1H), 3.34-3.36 (m, 4H), 3.54 (m, 1H), 3.65 (m, 1H), 4.22 (s, 4H), 4.45-4.50 (m, 1H), 4.84 (m, 1H), 6.77-6.70 (m, 1H), 6.85-6.87 (m, 1H), 6.94 (m, 2H), 7.17-7.20 (m, 1H), 7.33 (m, 1H). HPLC analysis: solvent: MeOH (0.1% DEA), column: AS-H (4.6 * 250mm, 5 μm), R.t.: 9.45 min.

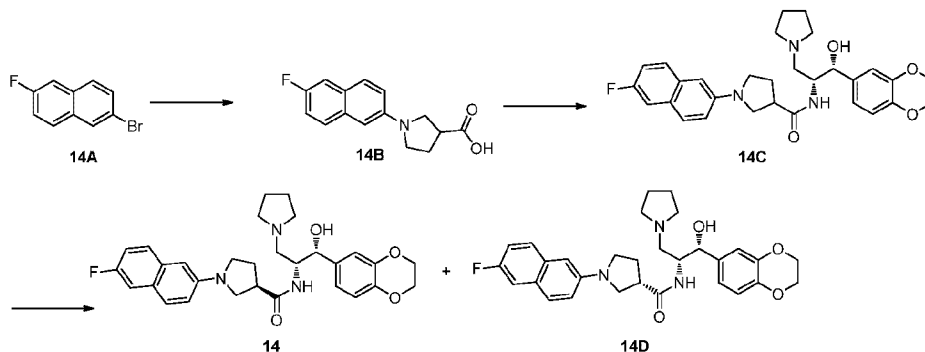
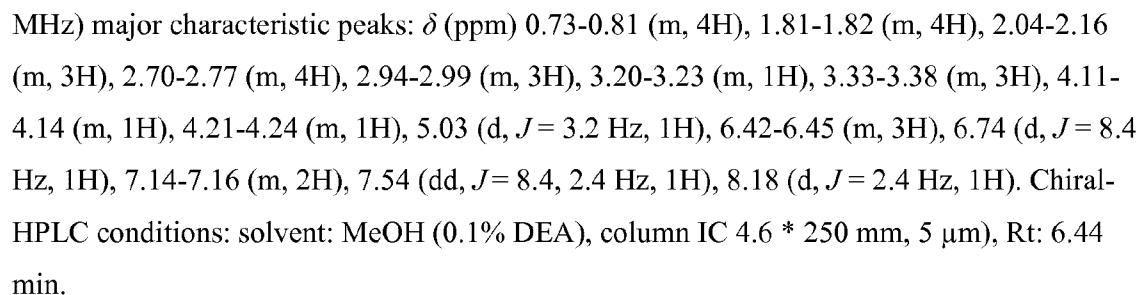
[000435] Compound **12D**. LC-MS (m/z): 520 $[M+1]^+$; $^1\text{H-NMR}$ (MeOD, 400 MHz) major characteristic peaks: δ (ppm) 1.92-1.96 (m, 4H), 1.99-2.07 (m, 2H), 2.75-2.79 (m, 1H), 2.94-2.96 (m, 1H), 2.98-3.13 (m, 3H), 3.27-3.47 (m, 4H), 3.58-3.59 (m, 1H), 3.70 (m, 1H), 4.01 (s, 4H), 4.36-4.39 (m, 1H), 4.72 (m, 1H), 6.63 (m, 1H), 6.75 (m, 1H), 6.80-6.82 (m, 2H), 7.09 (m, 1H), 7.23 (m, 1H). HPLC analysis: solvent: MeOH (0.1% DEA), column: AS-H (4.6 * 250 mm 5 μm , R.t.: 4.95 min.

Example 13



[000436] To a solution of Intermediate **O** (175 mg, 0.63 mmol) in DMF (5 mL) was added HATU (478 mg, 1.26 mmol) DIPEA (162 mg, 1.26 mmol) and Compound **1B** (283 mg, 1.26 mmol) at 0 °C, and then the reaction mixture was allowed to warm to room temperature and stirred at 30 °C for 10 h. The mixture was purified with prep-HPLC to give Compound **13A**. LC-MS (m/z): 692 $[M+1]^+$.

[000437] To a solution of Compound **13A** (150 mg, 0.22 mmol) in THF (5 mL) was added LiOH (1M solution, 0.44 mL, 0.44 mmol). The reaction mixture was stirred overnight at 30 °C before being neutralized with 1N hydrochloride. After the mixture was diluted with water (4 mL) and extracted with ethyl acetate (20 mL x 3), the combined organic layers were dried over anhydrous sodium sulfate, filtered, and evaporated to give a crude product mixture **13B**, which was separated by chiral-prep-HPLC (co-solvent MeOH (0.1% DEA), column IC 4.6 * 250 mm, 5 μm) to yield Compound **13** and Compound **13C**. For Compound **13**: LC-MS (m/z): 485 $[M+1]^+$; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) major characteristic peaks: δ (ppm) 0.76-0.81 (m, 4H), 1.73-1.76 (m, 4H), 2.11-2.21 (m, 3H), 2.59-2.67 (m, 4H), 2.80 (dd, $J = 12.8, 4.8$ Hz, 1H), 2.91-2.96 (m, 2H), 3.19-3.25 (m, 1H), 2.27-3.29 (m, 2H), 3.35-3.38 (m, 1H), 4.16-4.18 (m, 1H), 5.04 (d, $J = 2.8$ Hz, 1H), 6.28 (d, $J = 8.0$ Hz, 1H), 6.45-6.47 (m, 2H), 6.75 (d, $J = 8.4$ Hz, 1H), 7.15-7.17 (m, 2H), 7.53 (dd, $J = 8.8, 2.4$ Hz, 1H), 8.20 (d, $J = 2.4$ Hz, 1H). Chiral-HPLC conditions: solvent: MeOH (0.1% DEA), column IC 4.6 * 250 mm, 5 μm , Rt: 5.52 min. For Compound **13C**: LC-MS (m/z): 485 $[M+1]^+$; $^1\text{H-NMR}$ (CDCl_3 , 400

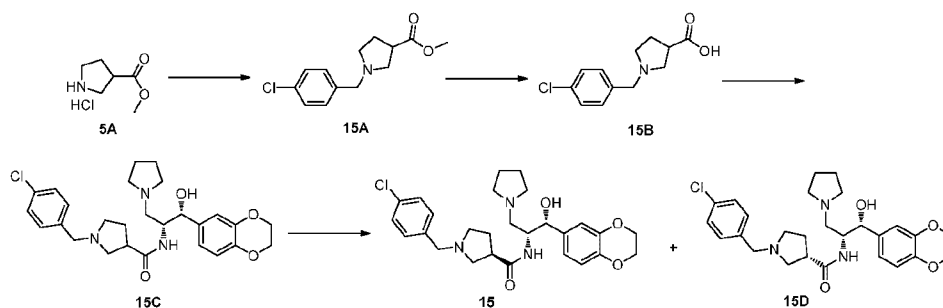


[000438] Compounds **14B**, **14**, and **14D** were synthesized, by employing the procedures described correspondingly for Compounds **1B** and **1** using Compounds **14A** and **14B** in lieu of 1-chloro-4-iodobenzene and Compound **1B**.

[000439] Compound **14B**. LC-MS (m/z): 260 [M+1]⁺; ¹H-NMR (DMSO-*d*₆, 400 MHz) major characteristic peaks: 2.17 (br s, 2H), 3.29-3.38 (m, 5H), 6.76 (s, 1H), 7.03 (d, *J* = 8.0 Hz, 1H), 7.21 (t, *J* = 7.6 Hz, 1H), 7.73 (d, *J* = 9.2 Hz, 1H), 7.60-7.69 (m, 2H).

[000440] Compound **14**. LC-MS (m/z): 520 [M+1]⁺; ¹H-NMR (MeOD, 400 MHz) major characteristic peaks: 1.29 (br s, 4H), 1.99-2.07 (m, 1H), 2.18-2.26 (m, 1H), 2.56-2.73 (m, 6H), 3.12-3.16 (m, 1H), 3.34-4.49 (m, 4H), 4.20 (s, 4H), 4.23-4.28 (m, 1H), 4.78 (s, 1H), 6.76-6.82 (m, 3H), 6.88 (s, 1H), 7.00-7.04 (m, 1H), 7.09-7.14 (m, 1H), 7.31 (d, *J* = 6.0 Hz, 1H), 7.60-7.64 (m, 2H). Chiral-HPLC conditions: solvent MeOH (0.5% DEA), column AS-H 250 * 4.6 mm 5 μm, Rt: 4.46 min.

[000441] Compound **14D**. LC-MS (m/z): 520 [M+1]⁺; ¹H-NMR (MeOD, 400 MHz) major characteristic peaks: 1.81 (br s, 4H), 1.12-2.24 (m, 2H), 2.60-3.00 (m, 6H), 3.01-3.05 (m, 1H), 3.11-3.15 (m, 1H), 3.34-3.53 (m, 3H), 4.14-4.27 (m, 5H), 4.80 (s, 1H), 6.76-6.81 (m, 3H), 6.89 (s, 1H), 7.00-7.03 (m, 1H), 7.10-7.16 (m, 1H), 7.30 (d, *J* = 10.0 Hz, 1H), 7.61-7.66 (2H). Chiral-HPLC conditions: solvent MeOH (0.5% DEA), column AS-H 250 * 4.6 mm 5 μm, Rt: 6.11 min.

Example 15

[000442] Compound **15A** was synthesized, by employing the procedure described for Compound **9B** using 4-chlorobenzaldehyde in lieu of tetrahydro-4H-pyran-4-one. LC-MS (m/z): 254 $[M+1]^+$; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) major characteristic peaks: δ (ppm) 1.94-2.03 (m, 4H), 2.22-2.25 (m, 1H), 2.43-2.48 (m, 1H), 3.02-3.04 (m, 1H), 3.17-3.20 (m, 1H), 3.26-3.85 (m, 3H), 3.48-3.51 (m, 1H), 3.68 (s, 3H), 3.99-4.02 (m, 2H).

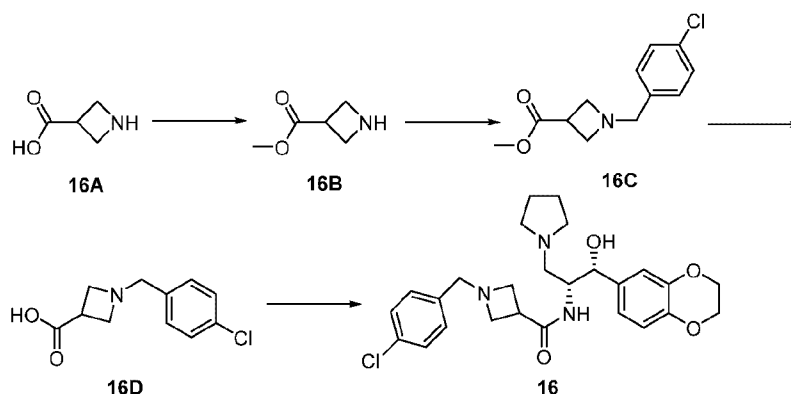
[000443] Compound **15B** was synthesized, by employing the procedure described for Compound **5C** using Compound **15A** in lieu of Compound **5B**. LC-MS (m/z): 240 $[M+1]^+$.

[000444] Compounds **15** and **15D** were synthesized, by employing the procedures described for Compound **7** using Compound **15B** in lieu of Compound **7B**.

[000445] Compound **15**. LC-MS (m/z): 499 $[M+1]^+$; $^1\text{H-NMR}$ (MeOD , 400 MHz) major characteristic peaks: δ (ppm) 1.60-1.71 (m, 2H), 1.85-1.95 (m, 8H), 2.35-2.52 (m, 8H), 2.62-2.76 (m, 3H), 3.46-3.51 (m, 2H), 4.04-4.08 (m, 5H), 4.71 (d, $J = 2.8$ Hz, 1H), 6.61-6.66 (m, 2H), 6.74 (s, 1H), 7.21-7.26 (m, 4H). Chiral-HPLC conditions: solvent: solvent: *n*-hexane (0.1% DEA):EtOH (0.1% DEA) 85:15, column: AS-H 250 * 4.6 mm 5 μm , Rt: 7.523 min.

[000446] Compound **15D**. LC-MS (m/z): 499 $[M+1]^+$; $^1\text{H-NMR}$ (MeOD , 400 MHz) major characteristic peaks: δ (ppm) 1.60-1.73 (m, 2H), 1.91-1.99 (m, 8H), 2.40-2.59 (m, 9H), 2.65-2.76 (m, 2H), 3.41-3.61 (m, 2H), 4.074-4.08 (m, 5H), 4.70 (d, $J = 2.8$ Hz, 1H), 6.63-6.69 (m, 2H), 6.75 (s, 1H), 7.19-7.26 (m, 4H). Chiral-HPLC conditions: solvent: *n*-hexane (0.1% DEA):EtOH (0.1% DEA) 85:15, column: AS-H 250 * 4.6 mm 5 μm , R.t.: 11.747 min.

Example 16



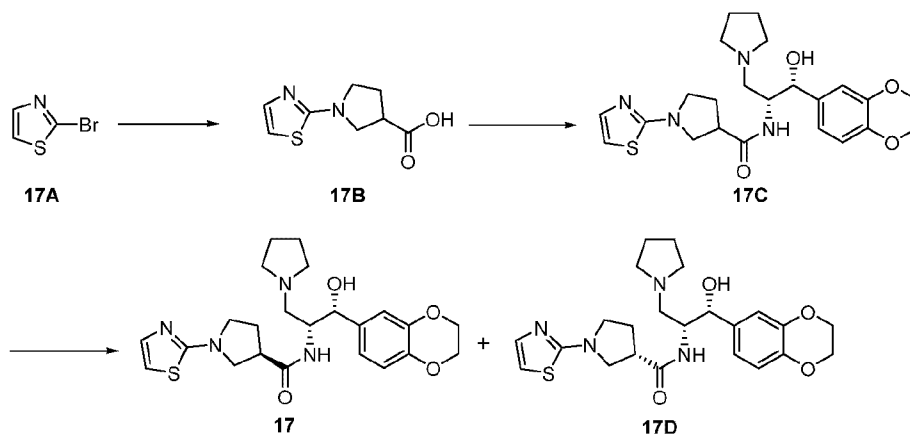
[000447] Compound **16B** was synthesized, by employing the procedure described for Compound **5A** using Compound **16A** in lieu of Compound **1A**. LC-MS (m/z): 115 $[M+1]^+$; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) major characteristic peaks: δ (ppm) 3.79 (s, 3H), 3.78-3.82 (m, 1H), 4.27-4.34 (m, 4H).

[000448] Compound **16C** was synthesized, by employing the procedure described for Compound **9B** using 4-chlorobenzaldehyde and Compound **16B** in lieu of tetrahydro-4H-pyran-4-one and Compound **5A**. LC-MS (m/z): 240 $[M+1]^+$; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) major characteristic peaks: δ (ppm) 3.30-3.34 (m, 3H), 3.61-3.58 (m, 4H), 3.63 (s, 3H), 7.14-7.23 (m, 4H).

[000449] Compound **16D** was synthesized, by employing the procedure described for Compound **5C** using Compound **16C** in lieu of Compound **5B**. LC-MS (m/z): 226 $[M+1]^+$.

[000450] Compound **16** was synthesized, by employing the procedure described for Compound **7** using Compound **16D** in lieu of Compound **7B**. LC-MS (m/z): 486 $[M+1]^+$; $^1\text{H-NMR}$ (MeOD , 400 MHz) major characteristic peaks: δ (ppm) 1.80-1.81 (m, 4H), 2.52-2.57 (m, 1H), 2.63-2.70 (m, 4H), 2.87-2.90 (m, 2H), 3.11-3.18 (m, 2H), 3.34-3.35 (m, 2H), 3.48-3.52 (m, 2H), 4.00-4.16 (m, 5H), 4.73 (d, $J = 2.8$ Hz, 1H), 6.73-6.74 (m, 2H), 6.80 (s, 1H), 7.24-7.32 (m, 4H).

Example 17



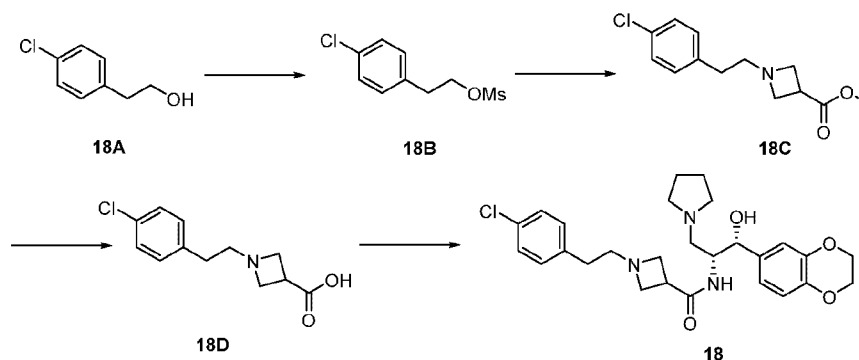
[000451] Compound **17B** was synthesized, by employing the procedure described for Compound **1B** using Compound **17A** in lieu of 1-chloro-4-iodobenzene. LC-MS (m/z): 197 $[M-1]^+$; $^1\text{H-NMR}$ ($\text{DMSO-}d_6$, 400 MHz) major characteristic peaks: δ (ppm) 2.20 (m, 2H), 3.23 (m, 1H), 3.40 (m, 2H), 3.56 (m, 2H), 6.72 (d, $J = 3.6$ Hz, 1H), 7.14 (d, $J = 3.2$ Hz, 1H), 12.57 (s, 1H).

[000452] Compounds **17** and **17D** were synthesized, by employing the procedures described for Compound **1** using **17B** in lieu of Compound **1B**.

[000453] Compound **17**. LC-MS (m/z): 459 $[M+1]^+$; $^1\text{H-NMR}$ (MeOD, 400 MHz) major characteristic peaks: δ (ppm) 2.04-2.15 (m, 6H), 3.17 (m, 3H), 3.31 (m, 3H), 3.43 (m, 1H), 3.70 (m, 6H), 4.20 (s, 4H), 4.47 (d, $J = 10.8$ Hz, 1H), 4.80 (s, 1H), 6.79 (d, $J = 8.0$ Hz, 1H), 6.89 (s, 2H), 6.98 (d, $J = 4.8$ Hz, 1H), 7.36 (d, $J = 4.0$ Hz, 1H).

[000454] Compound **17D**. LC-MS (m/z): 459 $[M+1]^+$; $^1\text{H-NMR}$ (MeOD, 400 MHz) major characteristic peaks: δ (ppm) 1.86 (m, 1H), 2.03 (m, 4H), 2.34 (m, 1H), 3.18 (m, 2H), 3.32-3.43 (m, 5H), 3.57-3.77 (m, 6H), 4.23 (s, 4H), 4.51 (d, $J = 10.8$ Hz, 1H), 4.83 (s, 1H), 6.79 (d, $J = 8.4$ Hz, 1H), 6.89 (s, 2H), 6.98 (d, $J = 4.8$ Hz, 1H), 7.34 (d, $J = 4.4$ Hz, 1H).

Example 18



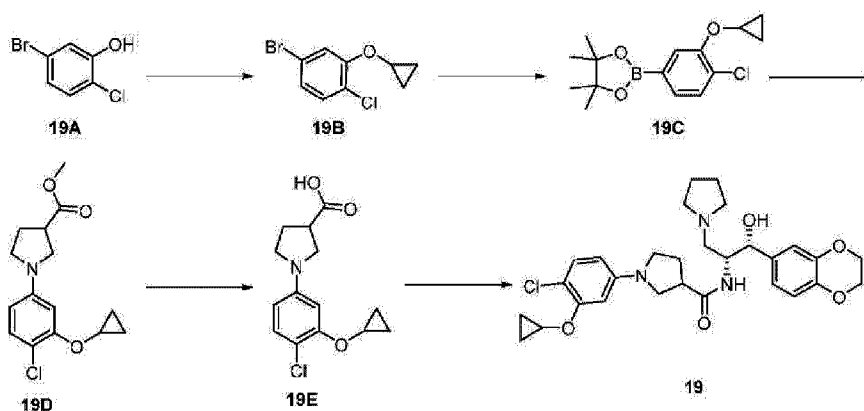
[000455] To a solution of Compound **18A** (10.0 g, 64 mmol) in THF (100 mL) was added Et₃N (19.4 g, 192 mmol). The mixture was cooled to 0 °C and MsCl (8.1 g, 70.5 mmol) was added slowly. The mixture was stirred about half an hour at 25 °C. The mixture was diluted with ethyl acetate (500 mL), washed with water (100 mL x 2) and brine (100 mL), dried over sodium sulfate, and concentrated. The crude product was purified with column chromatography on silica gel (eluted with ethyl acetate in petroleum ether, from 10% to 20% v/v) to give Compound **18B**. LC-MS (m/z): 235 [M+1]⁺; ¹H-NMR (DMSO-*d*₆, 400 MHz): major characteristic peaks δ (ppm) 2.99 (t, *J* = 6.8 Hz, 2H), 3.11 (s, 3H), 4.41 (t, *J* = 7.2 Hz, 2H), 7.32-7.39 (m, 4H).

[000456] A mixture of Compound **18B** (2.0 g, 8.5 mmol), Et₃N (2.6 g, 25.6 mmol) and methyl azetidine-3-carboxylate hydrochloride (1.3 g, 8.5 mmol) in THF (20 mL) was stirred under N₂ at 60 °C overnight. The mixture was diluted with ethyl acetate (300 mL), washed with water (100 mL x 2) and brine (100 mL), dried over sodium sulfate, and concentrated. The crude product was purified with column chromatography on silica gel (methanol in dichloromethane, from 5% to 10% v/v) to give Compound **18C**. LC-MS (m/z): 254 [M+1]⁺; ¹H-NMR (CDCl₃, 400 MHz): major characteristic peaks δ (ppm) 2.62-2.66 (m, 4H), 3.25-3.26 (m, 3H), 3.48-3.51 (m, 2H), 3.70 (s, 3H), 7.09-7.12 (m, 2H), 7.23-7.25 (m, 2H).

[000457] Compound **18D** was synthesized, by employing the procedure described for Compound **5C** using Compound **18C** in lieu of Compound **5B**. LC-MS (m/z): 240 [M+1]⁺; ¹H-NMR (DMSO-*d*₆, 400 MHz) major characteristic peaks: δ (ppm) 2.72-2.75 (m, 2H), 2.99-3.03 (m, 2H), 3.20-3.24 (m, 1H), 3.58-3.63 (m, 2H), 3.76-3.78 (m, 2H), 7.29-7.31 (m, 2H), 7.35-7.37 (m, 2H).

[000458] Compound **18** was synthesized, by employing the procedure described for Compound **1** using Compound **18D** in lieu of Compound **1B**. LC-MS (m/z): 500 [M+1]⁺; ¹H-NMR (MeOD, 400 MHz) major characteristic peaks: δ (ppm) 2.01-2.13 (m, 4H), 2.84-2.87 (m, 2H), 3.13-3.15 (m, 2H), 3.36-3.41 (m, 3H), 3.54-3.56 (m, 2H), 3.66-3.75 (m, 3H), 4.11-4.13 (m, 1H), 4.20 (s, 5H), 4.34-4.39 (m, 1H), 4.46-4.48 (m, 1H), 4.76 (d, *J* = 3.2 Hz, 1H), 6.78-6.90 (m, 3H), 7.27 (d, *J* = 8.4 Hz, 2H), 7.36 (d, *J* = 8.4 Hz, 2H).

Example 19



[000459] A mixture of Compound **19A** (2.0 g, 10 mmol), bromocyclopropane (2.4 g, 20 mmol), Cs_2CO_3 (9.8 g, 30 mmol) in DMSO (40 mL) was stirred at 170 °C for 2 days under high pressure. The mixture was cooled to room temperature and filtered through celiteTM. The filtrate was diluted with ethyl acetate (100 mL), washed with brine (100 mL x 2), dried over sodium sulfate, and concentrated. The crude was purified with column chromatography on silica gel (petroleum ether, 100% v/v) to render Compound **19B**. LC-MS (m/z): 247 $[\text{M}+1]^+$; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) major characteristic peaks: δ (ppm) 0.78-0.82 (m, 4H), 3.71-3.73 (m, 1H), 6.95-6.95 (m, 1H), 7.13-7.18 (m, 1H), 7.34-7.36 (m, 1H).

[000460] A mixture of Compound **19B** (1.0 g, 4.1 mmol), AcOK (1.2 g, 12.2 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (1.5 g, 6.1 mmol), and $\text{Pd}(\text{dppf})\text{Cl}_2$ (250 mg, 0.36 mmol) in 1,4-dioxane (50 mL) under N_2 protection was stirred at 100 °C for 18 h. The reaction mixture was cooled to room temperature and filtered through celite. The filtrate was diluted with ethyl acetate (100 mL), washed with brine (100 mL x 2), dried over sodium sulfate, and concentrated. The crude was purified with column chromatography on silica gel (ethyl acetate in petroleum ether, from 1% to 10% v/v) to yield Compound **19C**. LC-MS (m/z): 295 $[\text{M}+1]^+$; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) major characteristic peaks: δ (ppm) 0.78-0.82 (m, 4H), 1.27 (s, 12H), 3.82-3.85 (m, 1H), 7.27 (s, 2H), 7.57 (s, 1H).

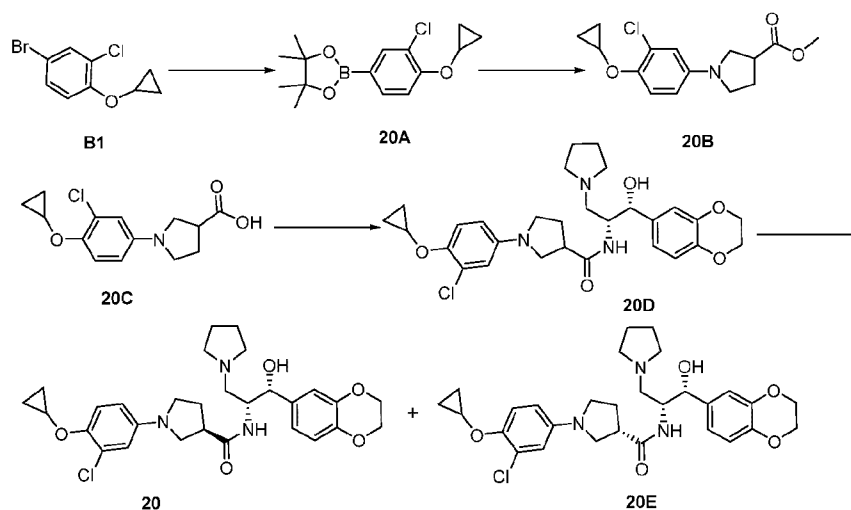
[000461] To a solution of Compound **19C** (500 mg, 1.7 mmol), methyl pyrrolidine-3-carboxylate (220 mg, 1.7 mmol), 4A molecular sieves (200 mg) and $\text{Cu}(\text{OAc})_2$ (305 mg, 1.7 mmol) in DCM (10 mL) was added triethylamine (0.5 mL, 3.4 mmol). The reaction mixture was stirred at 30 °C equipped with a drying tube for 2 days. The reaction mixture was filtered, the filtrate was concentrated, and the residue was purified with column chromatography on silica gel (ethyl acetate in petroleum ether, from 1% to 5% v/v) to afford Compound **19D**. LC-MS (m/z): 296 $[\text{M}+1]^+$; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) major

characteristic peaks: δ (ppm) 0.73-0.76 (m, 4H), 2.28-2.30 (m, 2H), 3.24-3.35 (m, 3H), 3.49-3.52 (m, 2H), 3.78 (s, 3H), 3.82-3.85 (m, 1H), 6.82-6.85 (m, 2H), 7.18 (s, 1H).

[000462] Compound **19E** was synthesized, by employing the procedure described for Compound **5C** using Compound **19D** in lieu of Compound **5B**. LC-MS (m/z): 262 $[M+1]^+$.

[000463] Compound **19** was synthesized, by employing the procedure described for Compound **1** using Compound **19E** in lieu of Compound **1B**. LC-MS (m/z): 542 $[M+1]^+$; ^1H -NMR (CDCl_3 , 400 MHz) major characteristic peaks: δ (ppm) 0.76-0.80 (m, 4H), 1.68-1.70 (m, 4H), 2.08-2.10 (m, 3H), 2.56-2.89 (m, 7H), 3.19-3.34 (m, 4H), 3.70 (m, 1H), 4.15 (m, 5H), 4.65-4.89 (m, 1H), 5.99-6.10 (m, 2H), 6.40-6.41 (m, 1H), 6.73-6.75 (m, 3H), 7.06-7.07 (m, 1H).

Example 20



[000464] Compound **20A** was synthesized, by employing the procedure described for Compound **19C** using 4-bromo-2-chloro-1-cyclopropoxybenzene in lieu of Compound **19B**. LC-MS (m/z): 295 $[M+1]^+$; ^1H -NMR (CDCl_3 , 400 MHz) major characteristic peaks: δ (ppm) 0.84-0.88 (m, 4H), 1.33 (s, 12H), 3.80-3.84 (m, 1H), 7.27 (d, $J = 8.4$ Hz, 1H), 7.67 (dd, $J = 8, 1.6$ Hz, 1H), 7.78 (d, $J = 8.6$ Hz, 1H).

[000465] Compound **20B** was synthesized, by employing the procedure described for Compound **19D** using Compound **20A** in lieu of Compound **19C**. LC-MS (m/z): 296 $[M+1]^+$; ^1H -NMR (CDCl_3 , 400 MHz) major characteristic peaks: δ (ppm) 0.70-0.85 (m, 4H), 2.26-2.32 (m, 2H), 3.19-3.37 (m, 3H), 3.47-3.49 (m, 2H), 3.73 (s, 3H), 3.47-3.77 (m, 1H), 6.43 (dd, $J = 9.2, 3.2$ Hz, 1H), 6.59 (d, $J = 3.2$ Hz, 1H), 7.16 (d, $J = 8.4$ Hz, 1H).

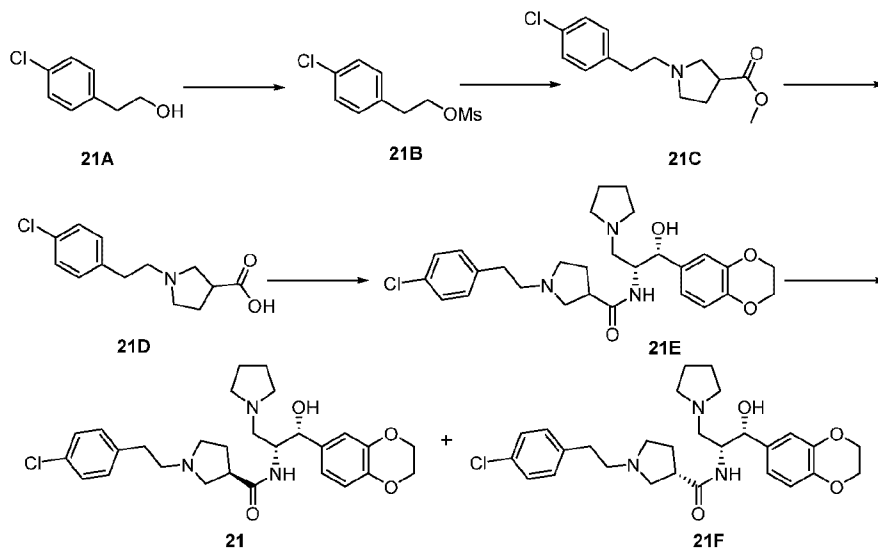
[000466] Compound **20C** was synthesized, by employing the procedure described for Compound **5C** using Compound **20B** in lieu of Compound **5B**. LC-MS (m/z): 262 $[M+1]^+$.

[000467] Compound **20** and **20E** were synthesized, by employing the procedure described for Compound **1** using Compound **20C** in lieu of Compound **1B**.

[000468] Compound **20**. LC-MS (m/z): 542 [M+1]⁺; ¹H-NMR (MeOD, 400 MHz) major characteristic peaks: δ (ppm) 0.62-0.64 (m, 4H), 1.68-1.72 (m, 4H), 1.92-2.11 (m, 2H), 2.49-2.83 (m, 7H), 2.95-3.03 (m, 1H), 3.07-3.13 (m, 1H), 3.16-3.19 (m, 1H), 3.25-3.29 (m, 1H), 3.67-3.72 (m, 1H), 4.07-4.20 (m, 5H), 4.69 (d, $J = 3.2$ Hz, 1H), 6.38 (dd, $J_1 = 9.2$ Hz, $J_2 = 3.2$ Hz, 1H), 6.49 (d, $J = 2.8$ Hz, 1H), 6.65-6.70 (m, 2H), 6.78 (d, $J = 2$ Hz, 1H), 7.09 (d, $J = 8.8$ Hz, 1H). Chiral-HPLC conditions: solvent: MeOH (0.1% DEA), column: OJ-H 250 * 4.6 mm 5 μ m, Rt: 3.7 min.

[000469] Compound **20E**. LC-MS (m/z): 542 [M+1]⁺; ¹H-NMR (MeOD, 400 MHz) major characteristic peaks: δ (ppm) 0.60-0.62 (m, 4H), 1.71 (m, 4H), 1.79-2.09 (m, 3H), 2.47-2.65 (m, 6H), 2.97-3.01 (m, 1H), 3.07-3.17 (m, 2H), 3.23-3.25 (m, 1H), 3.65-3.69 (m, 1H), 4.09-4.16 (m, 5H), 4.67 (d, $J = 3.2$ Hz, 1H), 6.37 (dd, $J_1 = 9.2$ Hz, $J_2 = 2.8$ Hz, 1H), 6.45 (d, $J = 2.8$ Hz, 1H), 6.64-6.70 (m, 2H), 6.76 (d, $J = 2$ Hz, 1H), 7.07 (d, $J = 8.8$ Hz, 1H). Chiral-HPLC conditions: solvent: MeOH (0.1% DEA), column: OJ-H 250 * 4.6 mm 5 μ m, Rt: 5.9 min.

Example 21



[000470] Compound **21B** was synthesized, by employing the procedure described for Compound **18B** using Compound **21A** in lieu of Compound **18A**. LC-MS (m/z): 235 [M+1]⁺; ¹H-NMR (DMSO-*d*₆, 400 MHz) major characteristic peaks: δ (ppm) 2.99 (t, $J = 6.8$ Hz, 2H), 3.11 (s, 3H), 4.41 (t, $J = 7.2$ Hz, 2H), 7.32-7.39 (m, 4H).

[000471] Compound **21C** was synthesized, by employing the procedure described for Compound **18C** using Compound **21B** in lieu of Compound **18B**. LC-MS (m/z): 268 [M+1]⁺;

$^1\text{H-NMR}$ (CDCl_3 , 400 MHz) major characteristic peaks: δ (ppm) 2.10-2.13 (m, 2H), 2.56-2.78 (m, 7H), 2.90-2.94 (m, 1H), 3.03-3.06 (m, 1H), 3.70 (s, 3H), 7.12-7.14 (m, 2H), 7.23-7.25 (m, 2H).

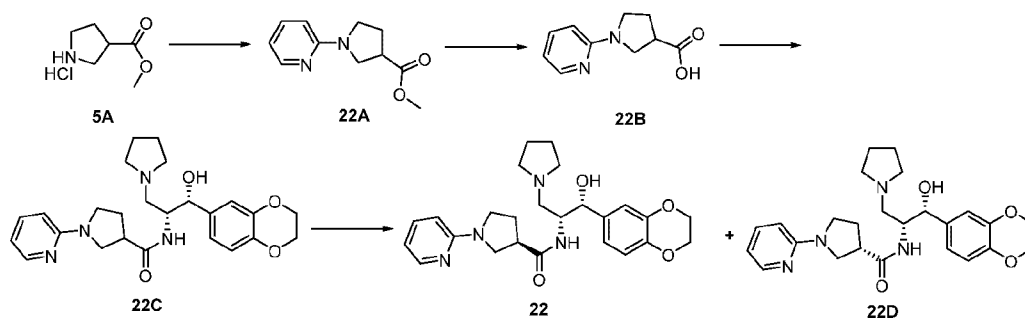
[000472] Compound **21D** was synthesized, by employing the procedure described for Compound **5C** using Compound **21C** in lieu of Compound **5B**. LC-MS (m/z): 254 $[\text{M}+1]^+$; $^1\text{H-NMR}$ ($\text{DMSO}-d_6$, 400 MHz): δ (ppm) 1.95-2.00 (m, 2H), 2.67-2.69 (m, 1H), 2.77-2.85 (m, 6H), 2.90-2.97 (m, 2H), 7.26-7.27 (m, 2H), 7.33-7.35 (m, 2H).

[000473] Compound **21** and **21F** were synthesized, by employing the procedure described for Compound **1** using Compound **21D** in lieu of Compound **1B**.

[000474] Compound **21**. LC-MS (m/z): 514 $[\text{M}+1]^+$; $^1\text{H-NMR}$ (MeOD , 400 MHz) major characteristic peaks: δ (ppm) 1.79 (m, 4H), 1.88 (m, 2H), 2.33 (m, 1H), 2.56-2.77 (m, 14H), 4.17 (s, 5H), 4.78 (d, $J = 2.8$ Hz, 1H), 6.78 (m, 2H), 6.85 (s, 1H), 7.21 (m, 2H), 7.27 (m, 2H). Chiral-HPLC conditions, solvent: EtOH (0.1% DEA), column: OZ-H 250 * 4.6 mm 5 μm , Rt: 11.44 min.

[000475] Compound **21F**. LC-MS (m/z): 514 $[\text{M}+1]^+$; $^1\text{H-NMR}$ (MeOD , 400 MHz) major characteristic peaks: δ (ppm) 1.78 (m, 5H), 2.03 (m, 1H), 2.55-2.87 (m, 15H), 4.18 (s, 5H), 4.75 (d, $J = 3.6$ Hz, 1H), 6.77 (m, 2H), 6.85 (s, 1H), 7.19 (m, 2H), 7.25 (m, 2H). Chiral-HPLC conditions, solvent: EtOH (0.1% DEA), column: OZ-H 250 * 4.6 mm 5 μm , Rt: 11.64 min.

Example 22



[000476] A mixture of Compound **5A** (990 mg, 6 mmol) 2-fluoropyridine (600 mg, 6 mmol) and *N,N*-diethylpropan-2-amine (2.3 g, 18 mmol) in *N*-methylpyrrolidone (20 mL) was stirred at 150 °C for 2 h. The reaction mixture was diluted with water, and extracted with ethyl acetate (150 mL x 3). The extraction was washed with water, dried with sodium sulfate, and concentrated. The crude was purified with column chromatography on silica gel (ethyl acetate in petroleum ether, from 1% to 10% v/v) to afford Compound **22A**. LC-MS (m/z): 207 $[\text{M}+1]^+$; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) major characteristic peaks: δ (ppm) 2.19-2.25 (m,

2H), 3.12-3.16 (m, 1H), 3.39-3.43 (m, 1H), 3.52-3.54 (m, 1H), 3.59-3.70 (m, 5H), 6.28 (d, $J = 8.8$ Hz, 1H), 6.46-6.49 (m, 1H), 7.34-7.39 (m, 1H), 8.07-8.08 (d, $J = 4.8$ Hz, 1H).

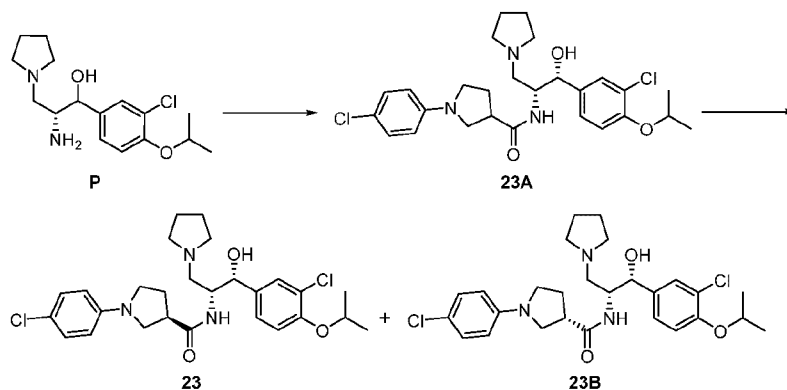
[000477] Compound **22B** was synthesized, by employing the procedure described for Compound **5C** using Compound **22A** in lieu of Compound **5B**. LC-MS (m/z): 193 $[M+1]^+$.

[000478] Compound **22** and **22D** were synthesized, by employing the procedure described for Compound **7** using Compound **22B** in lieu of Compound **7B**.

[000479] Compound **22**. LC-MS (m/z): 453 $[M+1]^+$; $^1\text{H-NMR}$ (MeOD, 400 MHz) major characteristic peaks: δ (ppm) 1.72-1.73 (m, 4H), 2.06-2.07 (m, 2H), 2.54-2.70 (m, 6H), 3.07-3.10 (m, 2H), 3.30-3.32 (m, 1H), 3.48-3.50 (m, 2H), 4.08-4.15 (m, 5H), 4.68 (d, $J = 2.8$ Hz, 1H), 6.36-6.38 (m, 1H), 6.47-6.48 (m, 1H), 6.64-6.77 (m, 2H), 6.77 (s, 1H), 7.41-7.43 (m, 1H), 7.89-8.00 (m, 1H). Chiral-HPLC conditions: solvent: IPA (0.1% DEA), column: OJ-H 250 * 4.6 mm 5 μm , Rt: 3.64 min.

[000480] Compound **22D**. LC-MS (m/z): 453 $[M+1]^+$; $^1\text{H-NMR}$ (MeOD, 400 MHz) major characteristic peaks: δ (ppm) 1.72-1.73 (m, 4H), 1.83-1.86 (m, 1H), 2.07-2.08 (m, 1H), 2.56-2.71 (m, 6H), 3.00-3.04 (m, 1H), 3.25-3.46 (m, 4H), 4.11-4.18 (m, 5H), 4.68 (d, $J = 2.8$ Hz, 1H), 6.35-6.37 (m, 1H), 6.44-6.47 (m, 1H), 6.65-6.72 (m, 2H), 6.78 (s, 1H), 7.38-7.42 (m, 1H), 7.86-7.88 (m, 1H). Chiral-HPLC conditions: solvent: IPA (0.1% DEA), column: OJ-H 250 * 4.6 mm 5 μm , Rt: 6.18 min.

Example 23



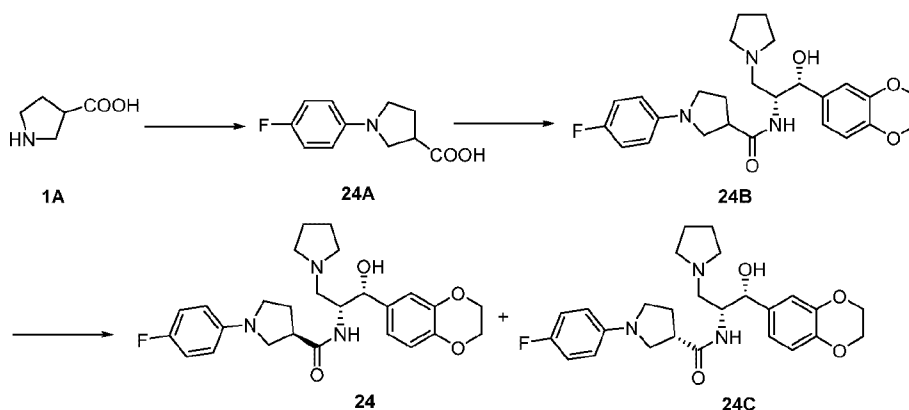
[000481] Compound **23** and **23B** were synthesized, by employing the procedure described for Compound **1** using Intermediate **P** in lieu of Compound **1B**.

[000482] Compound **23**. LC-MS (m/z): 520 $[M+1]^+$; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) major characteristic peaks: δ (ppm) 1.32-1.35 (m, 6H), 2.10 (m, 6H), 2.89-2.99 (m, 4H), 3.17-3.30 (m, 4H), 3.64-3.75 (m, 3H), 4.44-4.48 (m, 2H), 4.91 (s, 1H), 6.41 (d, $J = 8.8$ Hz, 2H), 6.82 (d, $J = 8.4$ Hz, 1H), 7.08 (d, $J = 8.4$ Hz, 1H), 7.13 (d, $J = 8.8$ Hz, 2H), 7.38 (s, 1H), 7.52 (s, 1H),

11.33 (s, 1H); Chiral-HPLC conditions: solvent: MeOH (0.5% DEA), column: OJ-H 250 * 4.6 mm 5 μ m, Rt: 3.36 min.

[000483] Compound **23B**. LC-MS (m/z): 520 $[M+1]^+$; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) major characteristic peaks: δ (ppm) 1.36-1.37 (m, 6H), 1.79 (m, 4H), 1.98-2.06 (m, 1H), 2.10-2.13 (m, 1H), 2.64-2.70 (m, 4H), 2.85-2.87 (m, 2H), 2.91-2.96 (m, 1H), 3.18-3.24 (m, 1H), 3.31-3.42 (m, 3H), 4.18-4.23 (m, 1H), 4.47-4.53 (m, 1H), 4.98 (d, $J = 2.4$ Hz, 1H), 6.20 (d, $J = 7.6$ Hz, 1H), 6.45 (d, $J = 9.2$ Hz, 2H), 6.83 (d, $J = 8.4$ Hz, 1H), 7.06 (dd, $J = 8.4$, 2.0 Hz, 1H), 7.15 (d, $J = 8.8$ Hz, 1H), 7.36 (d, $J = 2.0$ Hz, 1H); Chiral-HPLC conditions: solvent: MeOH (0.5% DEA), column: OJ-H 250 * 4.6 mm 5 μ m, Rt: 5.14 min.

Example 24



[000484] Compound **24A** was synthesized, by employing the procedure described for Compound **1B** using 1-fluoro-4-iodobenzene in lieu of 1-chloro-4-iodobenzene. LC-MS m/z: 208 $[M-1]^+$; $^1\text{H-NMR}$ ($\text{DMSO}-d_6$, 400 MHz) major characteristic peaks: δ (ppm) 2.12-2.22 (m, 2H), 3.18-3.48 (m, 5H), 6.51-6.55 (m, 2H), 6.99-7.03 (m, 2H), 12.45 (s, 1H)

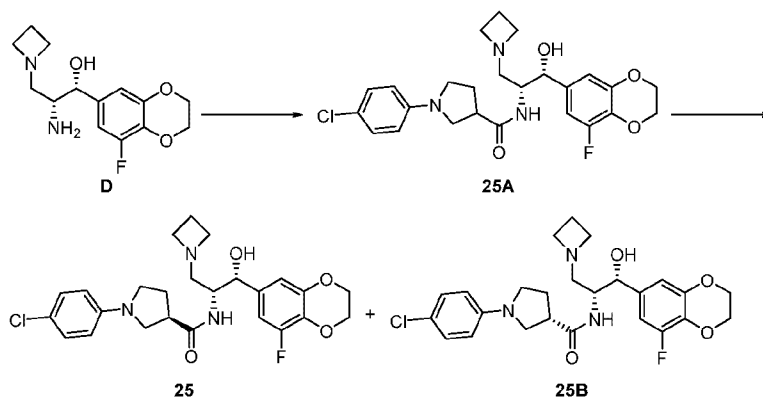
[000485] Compound **24** and **24C** were synthesized, by employing the procedures described for Compound **7** using Compound **24A** in lieu of Compound **7B**.

[000486] Compound **24**. LC-MS (m/z): 470 $[M+1]^+$; $^1\text{H-NMR}$ (MeOD, 400 MHz) major characteristic peaks: δ (ppm) 1.84 (m, 4H), 2.05-2.17 (m, 2H), 2.76-2.84 (m, 5H), 2.87-2.97 (m, 2H), 3.17-3.36 (m, 4H), 4.15 (m, 4H), 4.26-4.29 (m, 1H), 4.77-4.78 (d, $J = 3.2$ Hz, 1H), 6.47-6.51 (m, 2H), 6.73-6.77 (m, 2H), 6.86-6.92 (m, 3H). Chiral-HPLC conditions, solvent: EtOH (0.1% DEA), column: OJ-H (250 * 4.6 mm 5 μ m), Rt: 2.62 min.

[000487] Compound **24C**. LC-MS (m/z): 470 $[M+1]^+$; $^1\text{H-NMR}$ (MeOD, 400 MHz) major characteristic peaks: δ (ppm) 1.73 (m, 1H), 2.03 (m, 4H), 2.10-2.18 (m, 1H), 3.09-3.11 (m, 4H), 3.16-3.39 (m, 7H), 4.20 (s, 4H), 4.40-4.25 (m, 1H), 4.79-4.80 (d, $J = 2.4$ Hz, 1H),

6.48-6.51 (m, 2H), 6.76-6.91 (m, 5H). Chiral-HPLC conditions, solvent: EtOH (0.1% DEA), column: OJ-H (250 * 4.6 mm 5 μ m), Rt: 3.9 min.

Example 25

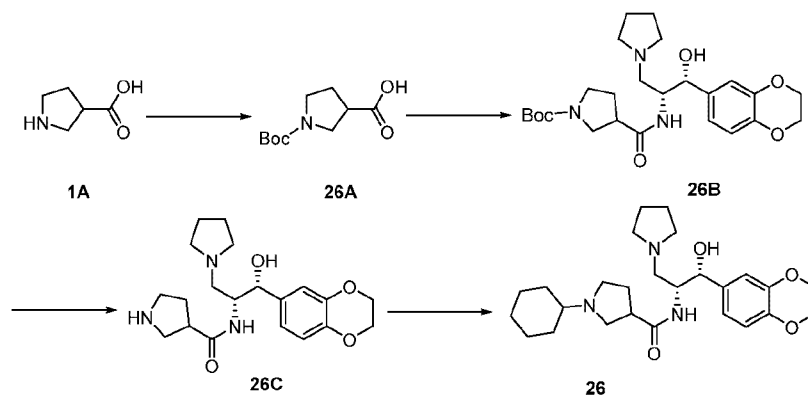


[000488] Compound **25** and **25B** were synthesized, by employing the procedure described for Compound **1** using Intermediate **D** in lieu of Intermediate **A**.

[000489] Compound **25**. LC-MS (m/z): 500 $[M+1]^+$; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) major characteristic peaks: δ (ppm) 2.07-2.20 (m, 4H), 2.62-2.67 (m, 1H), 2.71-2.75 (m, 1H), 2.84-2.88 (m, 1H), 3.05-3.13 (m, 1H), 3.20-3.29 (m, 2H), 3.31-3.43 (m, 4H), 4.00-4.04 (m, 1H), 4.20-4.26 (m, 4H), 4.71 (s, 1H), 6.49 (d, $J = 8$ Hz, 2H), 6.71 (t, $J = 12$ Hz, 2H), 7.12 (d, $J = 8$ Hz, 2H). Chiral-HPLC conditions, solvent: MeOH (0.5% DEA), column AS-H 250 * 4.6 mm 5 μ m, Rt: 7.05 min.

[000490] Compound **25B**. LC-MS (m/z): 500 $[M+1]^+$; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) major characteristic peaks: δ (ppm) 1.71-1.91 (m, 4H), 2.01-2.19 (m, 2H), 2.38-2.46 (m, 1H), 2.56-2.63 (m, 1H), 3.06-3.24 (m, 3H), 3.35-3.56 (m, 4H), 4.20-4.27 (m, 5H), 4.79 (s, 1H), 6.50 (d, $J = 8$ Hz, 2H), 6.77 (d, $J = 8$ Hz, 2H), 7.12 (d, $J = 8$ Hz, 2H); Chiral-HPLC conditions, solvent: MeOH (0.5% DEA), column AS-H 250 * 4.6 mm 5 μ m, Rt: 5.52 min.

Example 26



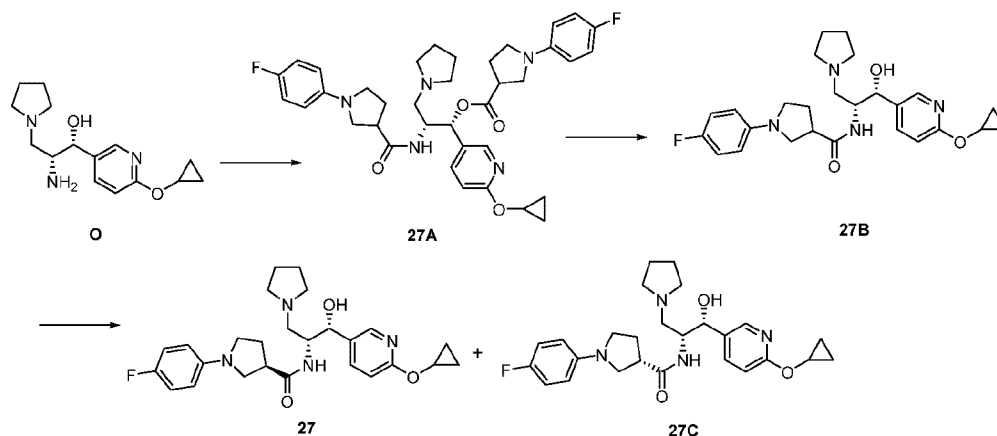
[000491] To a solution of Compound **1A** (575 mg, 5 mmol) in acetone (5 mL) and water (10 mL) was added Na_2CO_3 (636 mg, 6 mmol), Boc_2O (1.1 g, 5 mmol) at 0 °C. The mixture was stirred at 25 °C for 3 h. After evaporation to remove the volatiles, the aqueous layer was extracted with DCM (20 mL x 2), acidified with 1M HCl, extracted with DCM (20 mL x 3). The combined organic layers were dried over anhydrous sodium sulfate, and concentrated to furnish Compound **26A**. LC-MS (m/z): 214 $[\text{M}-1]^+$; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) major characteristic peaks: δ (ppm) 1.39 (s, 9H), 1.96-1.98 (m, 2H), 3.00-3.02 (m, 1H), 3.25 -3.28 (m, 4H), 12.48 (s, 1H).

[000492] To a solution of Compound **26A** (430 mg, 2 mmol), Intermediate **A** (556 mg, 2 mmol), EDCl.HCl (576 mg, 3 mmol) and HOBt (405 mg, 3 mmol) in DMF (10 mL) was added DIPEA (774 mg, 6 mmol). The mixture was stirred at 25 °C for 16 h. The mixture was added ethyl acetate (50 mL), washed with water (50 mL x 3) and brine (50 mL x 1), and dried over anhydrous sodium sulfate. The crude compound was purified with flash column chromatography on silica gel (MeOH in DCM, 7% v/v) to afford Compound **26B**. LC-MS (m/z): 476 $[\text{M}+1]^+$; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) major characteristic peaks: δ (ppm) 1.44 (m, 9H), 1.80 (s, 4H), 2.01 (m, 2H), 2.69 (m, 6H), 3.30 (m, 5H), 4.19 (s, 1H), 4.24 (m, 4H), 4.94 (s, 1H), 6.01 (m, 1H), 6.78 (m, 3H).

[000493] To a solution of Compound **26B** (400 mg, 0.84 mmol) in DCM (5 mL) was added TFA (0.8 mL) stirred at 25 °C for 3 h, basified by NEt_3 , and concentrated to obtain Compound **26C**. LC-MS (m/z): 376 $[\text{M}+1]^+$.

[000494] To a solution of Compound **26C** (380 mg, 1 mmol) and cyclohexanone (200 mg, 2 mmol) in DCM (5 mL) and MeOH (1 mL) was added NaBH(OAc)_3 (640 mg, 3 mmol). The mixture was stirred at 25 °C for 1 h, added NH_4OH (2 mL) and water (5 mL), extracted with DCM (20 mL x 3). To the mixture was added ethyl acetate (100 mL), washed with water (20 mL x 3), brine (20 mL x 1), and dried over anhydrous sodium sulfate. The crude product was purified with prep-HPLC to give Compound **26**. LC-MS (m/z): 458 $[\text{M}+1]^+$; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) major characteristic peaks: δ (ppm) 1.15 (m, 6H), 1.33 (m, 2H), 1.95 (m, 9H), 3.11 (m, 12H), 4.12 (s, 4H), 4.67 (m, 1H), 6.70 (m, 3H), 7.74 (m, 1H), 10.19 (m, 2H).

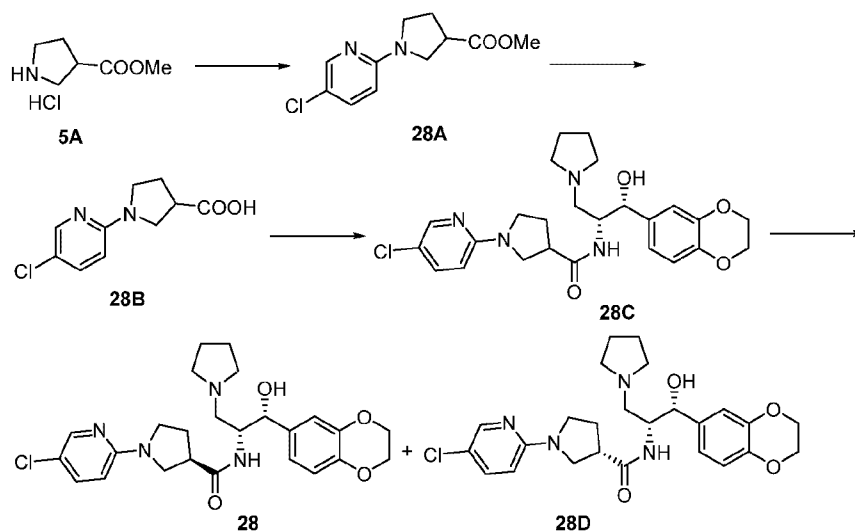
Example 27



[000495] To a solution of Intermediate **O** (200 mg, 0.72 mmol) in CH_2Cl_2 (20 mL) was added Compound **24A** (300 mg, 1.44 mmol), EDCI.HCl (275 mg, 1.44 mmol) and HOBt (194 mg, 1.44 mmol) at 30 °C. The reaction mixture was stirred for 5 h at the same temperature. It was washed with sat aq NaHCO_3 (10 mL), dried over anhydrous sodium sulfate, and filtered. The filtrate was evaporated and the resulting residue was purified with prep-TLC (MeOH in CH_2Cl_2 , 10% v/v) to yield Compound **27A**. LC-MS (m/z): 660 $[\text{M}+1]^+$.

[000496] To a solution of Compound **27A** (150 mg, 0.23 mmol) in THF (5 mL) was added LiOH (1M solution, 0.46 mL, 0.46 mmol). The reaction mixture was stirred overnight at 30 °C, and then neutralized with 1N hydrochloride, diluted with water (4 mL), and extracted with ethyl acetate (20 mL $\times$ 3). The combined organic layers were dried over anhydrous sodium sulfate and filtered. The filtrate was evaporated to dryness and the crude product was separated with chiral-prep-HPLC (solvent MeOH (0.1% DEA), column IC 4.6 * 150 mm, 5 μm) to furnish Compound **27** and Compound **27C**. For Compound **27**, LC-MS (m/z): 469 $[\text{M}+1]^+$; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) major characteristic peaks: δ (ppm) 0.76-0.81 (m, 4H), 1.72-1.75 (m, 4H), 2.01-2.10 (m, 1H), 2.17-2.22 (m, 1H), 2.59-2.67 (m, 4H), 2.80 (dd, $J = 13.2, 4.4$ Hz, 1H), 2.93 (dd, $J = 13.2, 4.4$ Hz, 1H), 2.95-2.96 (m, 1H), 3.18-3.20 (m, 1H), 2.25-3.28 (m, 2H), 3.35-3.38 (m, 1H), 4.15-4.20 (m, 2H), 5.04 (d, $J = 2.8$ Hz, 1H), 6.40 (d, $J = 8.0$ Hz, 1H), 6.47-6.51 (m, 2H), 6.75 (d, $J = 8.8$ Hz, 1H), 6.92-6.96 (m, 2H), 7.53 (dd, $J = 8.4, 2.4$ Hz, 1H), 8.20 (d, $J = 2.4$ Hz, 1H). For Compound **27C**: LC-MS (m/z): 469 $[\text{M}+1]^+$; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) major characteristic peaks: δ (ppm) 0.73-0.81 (m, 4H), 1.78-2.00 (m, 4H), 2.01-2.19 (m, 2H), 2.64-2.69 (m, 4H), 2.79-2.92 (m, 2H), 2.93-2.98 (m, 1H), 3.18-3.24 (m, 1H), 3.31-3.38 (m, 3H), 4.13-4.21 (m, 2H), 5.03 (d, $J = 3.2$ Hz, 1H), 6.37 (d, $J = 7.6$ Hz, 1H), 6.46-6.49 (m, 2H), 6.71 (d, $J = 8.8$ Hz, 1H), 6.91-6.96 (m, 2H), 7.52 (dd, $J = 8.8, 2.4$ Hz, 1H), 8.17 (d, $J = 2.4$ Hz, 1H).

Example 28



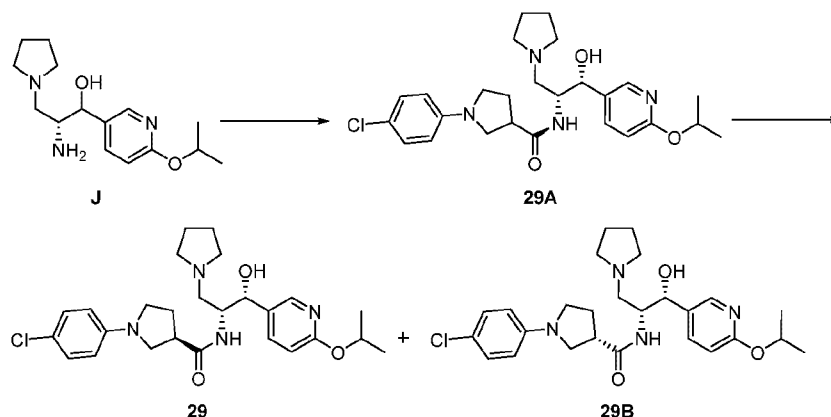
[000497] To a mixture of 2,5-dichloropyridine (1.5 g, 10 mmol) and Compound **5A** (2 g, 12 mmol) in DMF (20 mL) was added K_2CO_3 (4.2 g, 30 mmol). The mixture was stirred at 90 °C overnight. The mixture was purified with column chromatography on silica gel (ethyl acetate in petroleum ether, from 10% to 50% v/v) to give Compound **28A**. LC-MS (m/z): 241 $[M+1]^+$; ^1H -NMR ($CDCl_3$, 400 MHz) major characteristic peaks: δ (ppm) 2.24 (m, 2H), 3.14 (m, 1H), 3.37 (m, 1H), 3.61 (m, 2H), 3.65 (s, 3H), 6.21 (d, $J = 9.2$ Hz, 1H), 7.33 (d, $J = 8.8$ Hz, 1H), 8.01 (s, 1H).

[000498] Compound **28B** was synthesized, by employing the procedure described for Compound **5C** using Compound **28A** in lieu of Compound **5B**, which was used for the next step without further purification. LC-MS (m/z): 227 $[M+1]^+$.

[000499] Compounds **28** and **28D** were synthesized, by employing the procedure described for Compound **1** using Compound **28B** in lieu of Compound **1B**.

[000500] Compound **28**. LC-MS (m/z): 487 $[M+1]^+$; ^1H -NMR ($CDCl_3$, 400 MHz) major characteristic peaks: δ (ppm) 1.78 (m, 4H), 2.18 (m, 2H), 2.66 (m, 4H), 2.84 (m, 2H), 2.96 (m, 1H), 3.58 (m, 4H), 4.24 (m, 5H), 4.95 (s, 1H), 6.10 (m, 1H), 6.29 (s, 1H), 6.85 (m, 3H), 7.39 (m, 1H), 8.07 (s, 1H); Chiral-HPLC conditions, solvent: EtOH (0.5% DEA), column: OZ-H 250 * 4.6 mm 5 μ m, Rt.: 3.13 min.

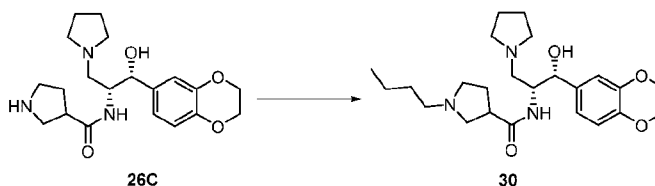
[000501] Compound **28D**. LC-MS (m/z): 487 $[M+1]^+$; ^1H -NMR ($CDCl_3$, 400 MHz) major characteristic peaks: δ (ppm) 1.83 (m, 4H), 2.08 (m, 2H), 2.78 (m, 4H), 2.91 (m, 2H), 2.98 (m, 1H), 3.58 (m, 4H), 4.24 (m, 5H), 4.95 (s, 1H), 6.10 (m, 1H), 6.29 (s, 1H), 6.85 (m, 3H), 7.39 (m, 1H), 8.07 (s, 1H). Chiral-HPLC conditions, solvent: EtOH (0.5% DEA), column: OZ-H 250 * 4.6 mm 5 μ m, Rt.: 4.48 min.

Example 29

[000502] Compounds **29** and **29B** were synthesized, by employing the procedure described for Compound **1** using Intermediate **J** in lieu of Intermediat **A**.

[000503] Compound **29**. LC-MS (m/z): 487 $[M+1]^+$; $^1\text{H-NMR}$ (MeOD, 400 MHz) major characteristic peaks: δ (ppm) 1.30 (d, $J = 5.6$ Hz, 6H), 1.81-1.83 (m, 4H), 2.11-2.18 (m, 2H), 2.60-2.66 (m, 4H), 2.68-2.72 (m, 2H), 2.83-2.94 (m, 1H), 3.07-3.14 (m, 1H), 3.19-3.25 (m, 1H), 3.33-3.37 (m, 2H), 4.26-4.30 (m, 1H), 4.90 (d, $J = 2.8$ Hz, 1H), 5.12-5.18 (m, 1H), 6.48 (d, $J = 9.2$ Hz, 2H), 6.66 (d, $J = 8.4$ Hz, 1H), 7.11 (d, $J = 8.8$ Hz, 2H), 7.64 (dd, $J = 8.8, 2.4$ Hz, 1H), 8.10 (d, $J = 2.4$ Hz, 1H). Chiral-HPLC conditions, solvent: MeOH (0.5% DEA), column: AD-H 250 * 4.6 mm 5 μm , Rt: 3.18 min.

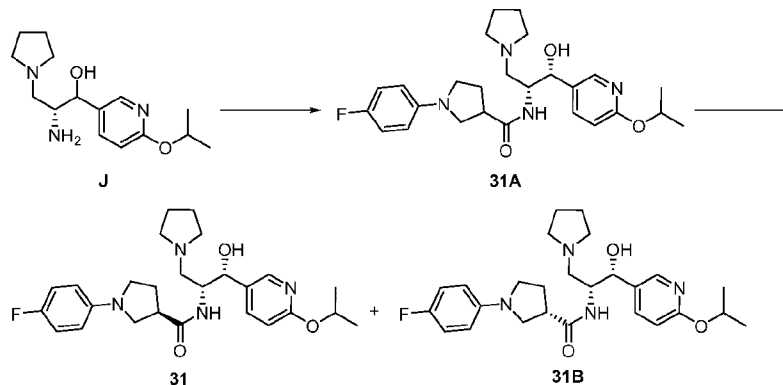
[000504] Compound **29B**. LC-MS (m/z): 487 $[M+1]^+$; $^1\text{H-NMR}$ (MeOD, 400 MHz) major characteristic peaks: δ (ppm) 1.31 (d, $J = 6.0$ Hz, 6H), 1.81-1.83 (m, 4H), 1.87-1.93 (m, 1H), 2.11-2.19 (m, 1H), 2.60-2.68 (m, 4H), 2.72-2.81 (m, 2H), 3.08-3.15 (m, 1H), 3.21-3.26 (m, 2H), 3.33-3.40 (m, 2H), 4.26-4.30 (m, 1H), 4.90 (d, $J = 2.8$ Hz, 1H), 5.14-5.20 (m, 1H), 6.48 (d, $J = 9.2$ Hz, 2H), 6.68 (d, $J = 8.4$ Hz, 1H), 7.11 (d, $J = 9.2$ Hz, 2H), 7.66 (dd, $J = 8.8, 2.4$ Hz, 1H), 8.10 (d, $J = 2.0$ Hz, 1H). Chiral-HPLC conditions, solvent: MeOH (0.5% DEA), column: AD-H 250 * 4.6 mm 5 μm , Rt: 6.16 min.

Example 30

[000505] Compound **30** was synthesized, by employing the procedure described for Compound **9B** using butyraldehyde and Compound **26C** in lieu of tetrahydro-4H-pyran-4-one and Compound **5A**. LC-MS (m/z): 432 $[M+1]^+$; $^1\text{H-NMR}$ (MeOD, 400 MHz) major

characteristic peaks: δ (ppm) 0.89-0.955 (m, 3H), 1.32-1.38 (m, 2H), 1.57-1.63 (m, 2H), 1.87-2.35 (m, 6H), 3.03-3.14 (m, 6H), 3.24-3.82 (m, 7H), 4.15 (d, $J = 8.1$ Hz, 4H), 4.36-4.46 (m, 1H), 4.73 (d, $J = 2.8$ Hz, 1H), 6.74-6.87 (m, 3H).

Example 31

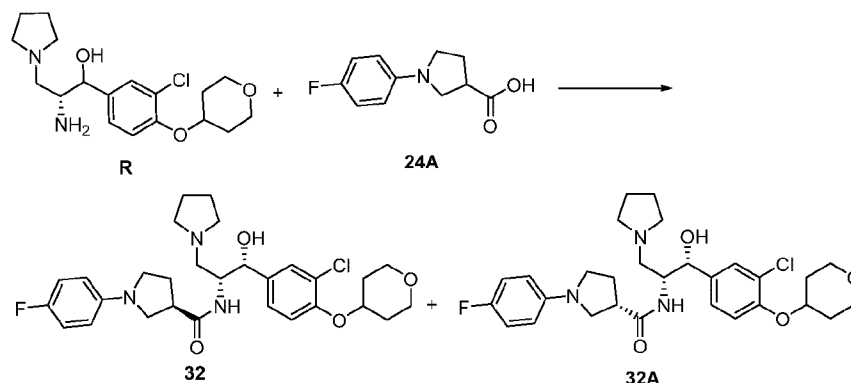


[000506] Compounds **31** and **31B** were synthesized, by employing the procedure described for Compound **1** using Intermediate **J** and Compound **24A** in lieu of Intermediate **A** and Compound **1B**.

[000507] Compound **31**. LC-MS (m/z): 471 $[M+1]^+$; $^1\text{H-NMR}$ (MeOD, 400 MHz) major characteristic peaks δ (ppm) 1.30 (d, $J = 6.4$ Hz, 6H), 1.81-1.83 (m, 4H), 2.11-2.17 (m, 2H), 2.62-2.70 (m, 4H), 2.75-2.85 (m, 2H), 2.90-2.94 (m, 1H), 3.07-3.14 (m, 1H), 3.20-3.29 (m, 2H), 3.34-3.36 (m, 1H), 4.27-4.31 (m, 1H), 4.91 (d, $J = 2.8$ Hz, 1H), 5.13-5.20 (m, 1H), 6.49-6.52 (m, 2H), 6.67 (d, $J = 8.4$ Hz, 1H), 6.89-6.93 (m, 2H), 7.65 (dd, $J = 8.4, 2.4$ Hz, 1H), 8.11 (d, $J = 2.4$ Hz, 1H). Chiral-HPLC conditions, solvent: MeOH (0.1% DEA), column: IC 250 * 4.6 mm 5 μm , Rt: 2.44 min.

[000508] Compound **31B**. LC-MS (m/z): 471 $[M+1]^+$; $^1\text{H-NMR}$ (MeOD, 400 MHz) major characteristic peaks δ (ppm) 1.32 (d, $J = 6.0$ Hz, 6H), 1.82-1.84 (m, 4H), 1.86-1.91 (m, 1H), 2.12-2.20 (m, 2H), 2.63-2.71 (m, 4H), 2.77-2.83 (m, 2H), 3.08-3.15 (m, 1H), 3.21-3.25 (m, 2H), 3.35-3.37 (m, 1H), 4.27-4.31 (m, 1H), 4.90 (d, $J = 2.8$ Hz, 1H), 5.15-5.21 (m, 1H), 6.48-6.52 (m, 2H), 6.68 (d, $J = 8.8$ Hz, 1H), 6.88-6.92 (m, 2H), 7.66 (dd, $J = 8.4, 2.4$ Hz, 1H), 8.10 (d, $J = 2.4$ Hz, 1H). Chiral-HPLC conditions, solvent: MeOH (0.1% DEA), column: OJ-H 250 * 4.6 mm 5 μm , Rt: 6.51 min.

Example 32

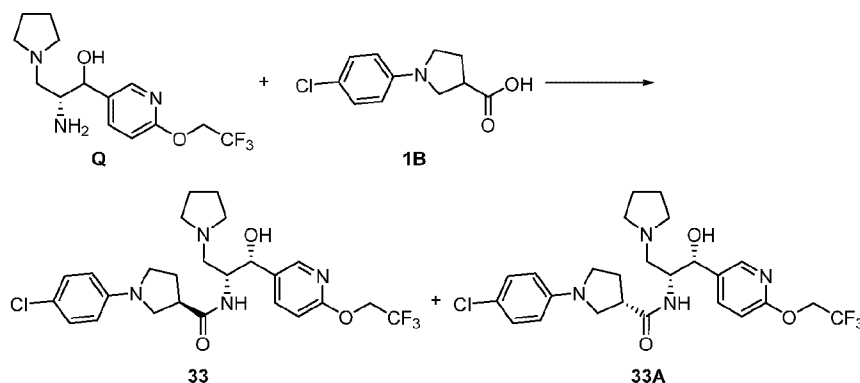


[000509] Compounds **32** and **32A** were synthesized, by employing the procedure described for Compound **1** using Intermediate **R** and Compound **24A** in lieu of Intermediate **A** and Compound **1B**.

[000510] Compound **32**. LC-MS (m/z): 545 $[M+1]^+$; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) major characteristic peaks: δ (ppm) 1.72 (m, 4H), 1.79-1.87 (m, 2H), 1.97-2.19 (m, 4H), 2.60-2.67 (m, 4H), 2.79-2.84 (m, 1H), 2.90-2.97 (m, 2H), 3.15-3.24 (m, 3H), 3.34-3.39 (m, 1H), 3.55-3.60 (m, 2H), 3.97-4.03 (m, 2H), 4.17-4.22 (m, 1H), 4.45-4.51 (m, 1H), 5.00 (d, $J = 2.4$ Hz, 1H), 6.35 (d, $J = 7.6$ Hz, 1H), 6.48 (dd, $J = 8.8, 4.4$ Hz, 2H), 6.86 (d, $J = 8.4$ Hz, 1H), 6.92-6.97 (m, 2H), 7.08 (dd, $J = 8.4, 2.0$ Hz, 1H), 7.41 (d, $J = 2.0$ Hz, 1H). Chiral-HPLC conditions, solvent: MeOH (0.5% DEA), column: OJ-H 250 * 4.6 mm 5 μm , Rt: 3.17 min.

[000511] Compound **32A**. LC-MS (m/z): 545 $[M+1]^+$; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) major characteristic peaks: δ (ppm) 1.70 (m, 4H), 1.87-1.97 (m, 6H), 2.21 (m, 1H), 2.88 (m, 2H), 3.22 (m, 2H), 3.41-3.47 (m, 4H), 3.69 (m, 4H), 3.87 (m, 2H), 4.41-4.49 (m, 2H), 4.82 (s, 1H), 6.82 (m, 1H), 6.98 (m, 3H), 7.15 (m, 3H), 7.33 (m, 1H), 7.80 (s, 1H), 10.31 (s, 1H). Chiral-HPLC conditions, solvent: MeOH (0.5% DEA), column: OJ-H 250 * 4.6 mm 5 μm , Rt: 5.29 min.

Example 33



[100514] Compound **33A**. LC-MS (m/z): 527 [M+1]⁺; ¹H-NMR (MeOD, 400 MHz) major characteristic peaks: δ (ppm) 1.82-1.90 (m, 5H), 2.11-2.15 (m, 1H), 2.63-2.70 (m, 4H), 2.77-2.81 (m, 2H), 3.07-3.15 (m, 1H), 3.21-3.25 (m, 1H), 3.35-3.38 (m, 2H), 4.28-4.32 (m, 1H), 4.80-4.84 (m, 2H), 4.94 (d, $J = 3.2$ Hz, 1H), 6.48 (d, $J = 8.8$ Hz, 2H), 6.85 (d, $J = 8.8$ Hz, 1H), 7.11 (d, $J = 8.8$ Hz, 2H), 7.76 (dd, $J = 8.8, 2.4$ Hz, 1H), 8.16 (d, $J = 2.0$ Hz, 1H). Chiral-HPLC conditions, solvent: MeOH (0.1% DEA), column: OJ-H 250 * 4.6 mm 5 μ m, Rt: 10.05 min.

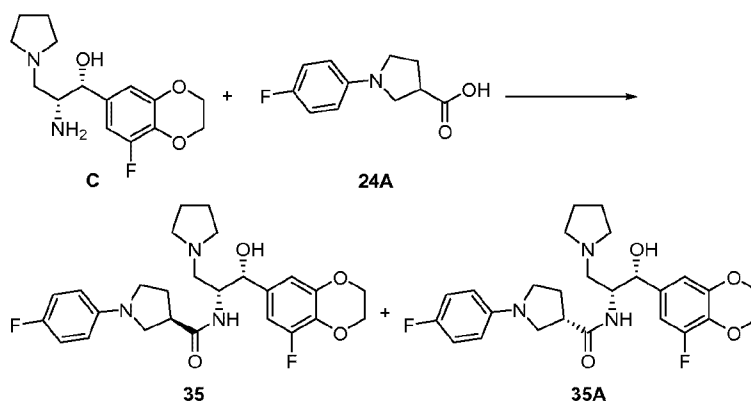
[illegible]

- 159 -

1H). Chiral-HPLC conditions, solvent: MeOH (0.5% DEA), column: OJ-H 250 * 4.6 mm 5 μ m, Rt: 2.96 min.

[000517] Compound **34A**. LC-MS (m/z): 511 [M+1]⁺; ¹H-NMR (MeOD, 400 MHz) major characteristic peaks: δ (ppm) 1.80-1.83 (m, 4H), 1.84-1.89 (m, 1H), 2.09-2.14 (m, 1H), 2.62-2.66 (m, 4H), 2.74-2.79 (m, 2H), 3.06-3.14 (m, 1H), 3.20-3.24 (m, 2H), 3.33-3.38 (m, 2H), 4.27-4.31 (m, 1H), 4.81-4.86 (m, 2H), 4.94 (d, J = 2.8 Hz, 1H), 6.48-6.51 (m, 2H), 6.85 (d, J = 8.4 Hz, 1H), 6.87-6.92 (m, 2H), 7.75 (dd, J = 8.4, 2.4 Hz, 1H), 8.16 (d, J = 2.0 Hz, 1H). Chiral-HPLC conditions, solvent: MeOH (0.5% DEA), column: OJ-H 250 * 4.6 mm 5 μ m, Rt: 5.73 min.

Example 35

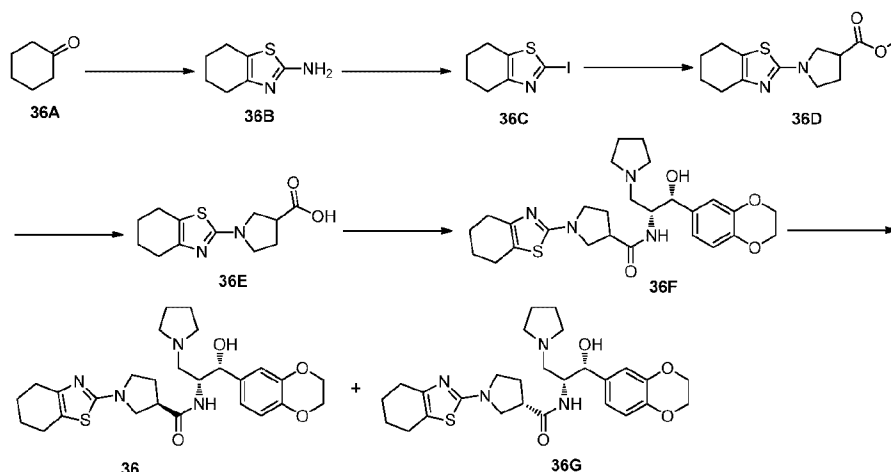


[000518] Compounds **35** and **35A** were synthesized, by employing the procedure described for Compound **7** using Intermediate **C** and Compound **24A** in lieu of Intermediate **A** and Compound **7B**.

[000519] Compound **35**. LC-MS (m/z): 488 [M+1]⁺; ¹H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 1.92-1.96 (m, 1H), 2.07 (m, 4H), 2.17-2.20 (m, 1H), 3.07-3.54 (m, 12H), 4.25-4.29 (m, 5H), 4.84-4.87 (m, 1H), 6.46-6.49 (m, 2H), 6.63-6.70 (m, 3H), 6.91-6.96 (m, 2H). Chiral-HPLC conditions, solvent: MeOH (0.1% DEA), column: OJ-H (250 * 4.6 mm 5 μ m), R.t.: 2.42 min.

[000520] Compound **35A**. LC-MS (m/z): 488 [M+1]⁺; ¹H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 1.60 (m, 1H), 2.09 (m, 5H), 3.09-3.62 (m, 12H) 4.23 (s, 4H), 4.33 (m, 1H), 4.83-4.85 (m, 1H), 6.43-6.47 (m, 2H), 6.62-6.67 (m, 2H), 6.87-6.94 (m, 3H). Chiral-HPLC conditions, solvent: MeOH (0.1% DEA), column: OJ-H (250 * 4.6 mm 5 μ m), R.t.: 4.42 min.

Example 36



[000521] A mixture of Compound **36A** (3 g, 30.6 mmol), thiourea (4.62 g, 61.1 mmol), I_2 (7.76 g, 30.6 mmol) was stirred at 120 °C overnight. The reaction mixture was cooled down, hot water (50 mL) was added and the mixture was stirred for 0.5 h, then extracted with ethyl acetate (50 mL x 3). The aqueous layer was basified by Na_2CO_3 , extracted with DCM (50 mL x 3), dried over anhydrous sodium sulfate, and concentrated to afford Compound **36B**. LC-MS (m/z): 155 $[M+1]^+$; ^1H NMR ($CDCl_3$, 400 MHz) major characteristic peaks: δ (ppm) 1.79 (m, 4H), 2.53 (m, 4H), 4.88 (br, 2H).

[000522] To a solution of Compound **36B** (460 mg, 3 mmol) and *p*-TsOH (1.55 g, 9 mmol) in MeCN (20 mL) was added a solution of KI (1.3 g, 7.8 mmol) and $NaNO_2$ (414 mg, 6 mmol) in water (3 mL) at 0 °C and the resultant mixture was stirred at room temperature overnight. To the mixture was added saturated aqueous Na_2SO_3 solution (20 mL) and saturated aqueous $NaHCO_3$ solution (20 mL), then the mixture was extracted with ethyl acetate (30 mL x 3), dried over anhydrous sodium sulfate, and purified with flash column chromatography (ethyl acetate in petroleum ether, 0 - 20% v/v) to render Compound **36C**. LC-MS (m/z): 266 $[M+1]^+$; ^1H NMR ($CDCl_3$, 400 MHz) major characteristic peaks: δ (ppm) 1.83 (m, 4H), 2.75 (m, 2H), 2.80 (m, 2H).

[000523] Compound **36D** was synthesized, by employing the procedure described for Compound **1B** using Compound **36C** in lieu of 1-chloro-4-iodobenzene. LC-MS (m/z): 267 $[M+1]^+$; ^1H NMR ($CDCl_3$, 400 MHz) major characteristic peaks: δ (ppm) 1.80 (m, 4H), 2.29 (m, 2H), 2.59 (s, 4H), 3.21 (m, 1H), 3.47 (m, 1H), 3.56 (m, 1H), 3.68 (m, 2H), 3.70 (s, 3H).

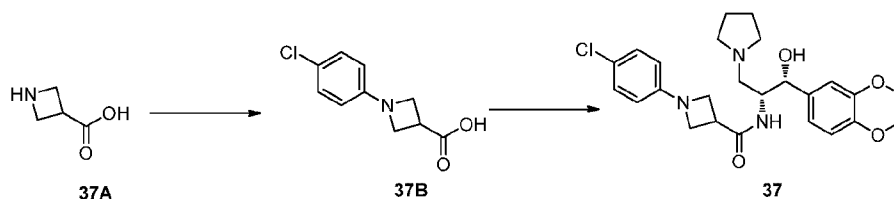
[000524] Compound **36E** was synthesized, by employing the procedure described for Compound **5C** using Compound **36D** in lieu of Compound **5B**. LC-MS (m/z): 253 $[M+1]^+$.

[000525] Compounds **36** and **36G** were synthesized, by employing the procedure described for Compound **1** using Compound **36E** in lieu of Compound **1B**.

[000526] Compound **36**. LC-MS (m/z): 513 $[M+1]^+$; ^1H NMR (CDCl_3 , 400 MHz) major characteristic peaks: δ (ppm) 1.78 (m, 8H), 2.16 (m, 3H), 2.58 (m, 6H), 2.83 (m, 2H), 2.93 (m, 1H), 3.48 (m, 5H), 4.17 (m, 1H), 4.25 (s, 4H), 4.93 (d, $J = 3.2$ Hz, 1H), 6.05 (d, $J = 7.6$ Hz, 1H), 6.74 (m, 1H), 6.83 (m, 2H). Chiral-HPLC conditions, solvent: EtOH (0.5% DEA), column: OJ-H 250 * 4.6 mm 5 μm , Rt: 4.38 min.

[000527] Compound **36G**. LC-MS (m/z): 513 $[M+1]^+$; ^1H NMR (CDCl_3 , 400 MHz) major characteristic peaks: δ (ppm) 1.78 (m, 8H), 2.11 (m, 3H), 2.57 (m, 6H), 2.81 (m, 2H), 2.92 (m, 1H), 3.41 (m, 5H), 4.20 (m, 1H), 4.24 (s, 4H), 4.93 (d, $J = 2.8$ Hz, 1H), 5.96 (d, $J = 7.2$ Hz, 1H), 6.75 (m, 1H), 6.83 (m, 2H). Chiral-HPLC conditions, solvent: EtOH (0.5% DEA), column: OJ-H 250 * 4.6 mm 5 μm , Rt: 6.72 min.

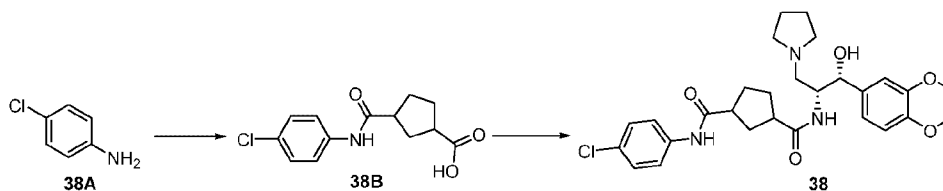
Example 37



[000528] Compound **37B** was synthesized, by employing the procedure described for Compound **1B** using Compound **37A** in lieu of Compound **1A**. LC-MS (m/z): 210 $[M-1]^-$.

[000529] Compound **37** was synthesized, by employing the procedure described for Compound **1** using Compound **37B** in lieu of Compound **1B**. LC-MS (m/z): 472 $[M+H]^+$; ^1H -NMR (CD_3OD , 400 MHz) major characteristic peaks: δ (ppm) 2.01 (m, 4H), 3.16 (m, 2H), 3.32 (m, 4H), 3.40 (m, 3H), 3.69 (m, 2H), 4.17 (m, 4H), 4.46 (m, 1H), 4.80 (s, 1H), 5.43 (m, 2H), 6.79 (m, 3H), 7.15 (m, 2H).

Example 38

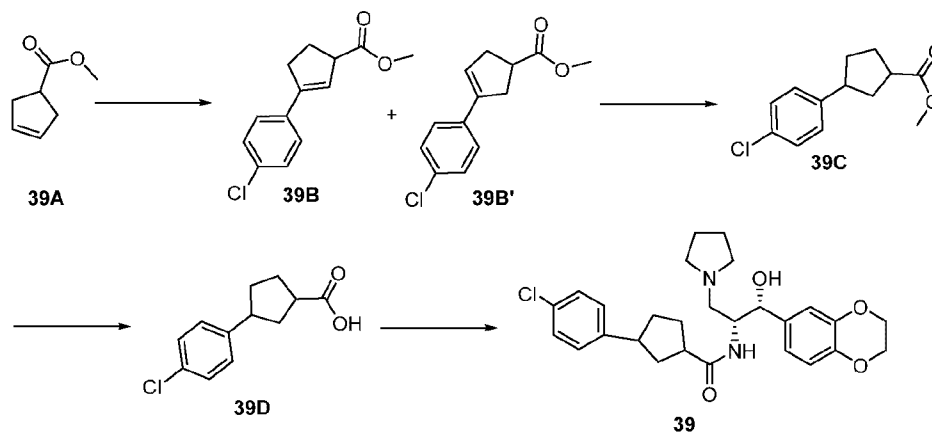


[000530] A mixture of cyclopentane-1,3-dicarboxylic acid (124 mg, 0.78 mmol), EDCI (227 mg, 1.18 mmol), HOBt (161 mg, 1.18 mmol), Compound **38A** (100 mg, 0.78 mmol) in DCM (20 mL) was stirred at room temperature overnight. After addition of water, the mixture

was extracted with DCM (50 mL x 2), washed with brine (50 mL), dried over Na₂SO₄, and concentrated to render a crude Compound **38B**. LC-MS (m/z): 268 [M+1]⁺.

[000531] Compound **38** was synthesized, by employing the procedure described for Compound **1** using Compound **38B** in lieu of Compound **1B**. LC-MS (m/z): 528 [M+1]⁺; ¹H NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 2.14 (m, 8H), 2.92 (m, 5H), 3.13 (s, 1H), 3.74 (m, 3H), 4.11 (s, 4H), 4.59 (m, 1H), 4.86 (m, 1H), 6.77 (s, 2H), 6.86 (s, 1H), 7.23 (s, 2H), 7.51 (m, 2H), 7.63 (d, *J* = 8.0 Hz, 0.5H), 7.96 (d, *J* = 8.0 Hz, 0.5H), 9.25 (s, 0.5H), 9.58 (s, 0.5H), 11.61 (s, 0.5 H), 11.78 (s, 0.5 H).

Example 39



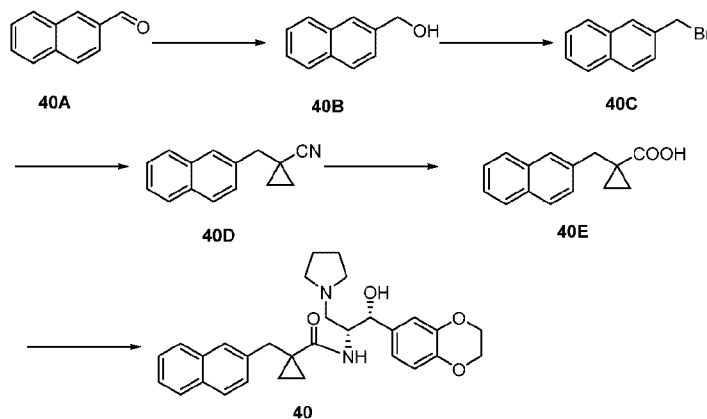
[000532] To a solution of Compound **39A** (1.26 g, 10 mmol) and 4-chloriodobenzene (3.57 g, 15 mmol) in Et₃N (30 mL) was added Pd(OAc)₂ (38 mg, 3 %) under N₂ atmosphere. The mixture was heated at 90 °C for 24 h in the dark. The mixture was cooled to room temperature, filtered, concentrated under reduced pressure, and purified by column chromatography on silica gel (dichloromethane in petroleum, 50 % v/v) to yield a mixture of Compounds **39B** and **39B'**. LC-MS (m/z): 237 [M+1]⁺.

[000533] To a solution of Compounds **39B** and **39B'** (200 mg, 0.85 mmol) in MeOH (20 mL) was added Pt/C (10 mg, 5%) under H₂ atmosphere. The mixture was stirred at 25 °C overnight. It was filtered and concentrated in *vacuo*. Diluted with water, the mixture was extracted with ethyl acetate (20 mL x 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated in *vacuo* to give a crude product Compound **39C**. LC-MS (m/z): 239 [M+1]⁺.

[000534] Compound **39D** was synthesized, by employing the procedure described for Compound **5C** using Compound **39C** in lieu of Compound **5B** (crude), which was used for next step without purification. LC-MS (m/z): 225 [M+1]⁺.

[000535] Compound **39** was synthesized, by employing the procedure described for Compound **1** using Compound **39D** in lieu of Compound **1B**. LC-MS (m/z): 485 $[M+1]^+$; ^1H NMR (CDCl_3 , 400 MHz) major characteristic peaks: δ (ppm) 1.54-1.73 (m, 4H), 1.90-1.97 (m, 6H), 2.65-2.71 (m, 1H), 2.86-2.98 (m, 3H), 3.18 (s, 1H), 3.54 (s, 1H), 3.74 (s, 2H), 4.19 (s, 4H), 4.39 (s, 1H), 4.88 (s, 1H), 6.75-6.85 (m, 3H), 7.08-7.16 (m, 2H), 7.22 (d, $J = 8$ Hz, 2H), 7.34 (s, 1H), 11.68 (s, 1H).

Example 40



[000536] To a solution of Compound **40A** (14.10 g, 90.38 mmol) in EtOH (100 mL) was added NaBH_4 (3.43 g, 90.83 mmol). The mixture was stirred at room temperature for 2 h. The mixture was diluted with ethyl acetate (300 mL), washed with water and brine, dried with anhydrous Na_2SO_4 , and evaporated to render Compound **40B**. LCMS (m/z): 159 $[M+1]^+$; ^1H -NMR (CDCl_3 , 400 MHz) major characteristic peaks: δ (ppm) 4.89 (s, 2H), 7.46-7.49 (m, 3H), 7.81-7.86 (m, 4H).

[000537] A mixture of Compound **40B** (6.00 g, 37.97 mmol) in conc. HBr (200 mL) was stirred at 90 °C overnight. The mixture was diluted with ethyl acetate (200 mL), washed with water and brine, and purified with silica gel column chromatography (ethyl acetate in petroleum ether, 5% v/v) to afford Compound **40C**. LCMS (m/z): 221 $[M+1]^+$; ^1H -NMR (CDCl_3 , 400 MHz) major characteristic peaks: δ (ppm) 4.67 (s, 2H), 7.48-7.52 (m, 3H), 7.80-7.85 (m, 4H).

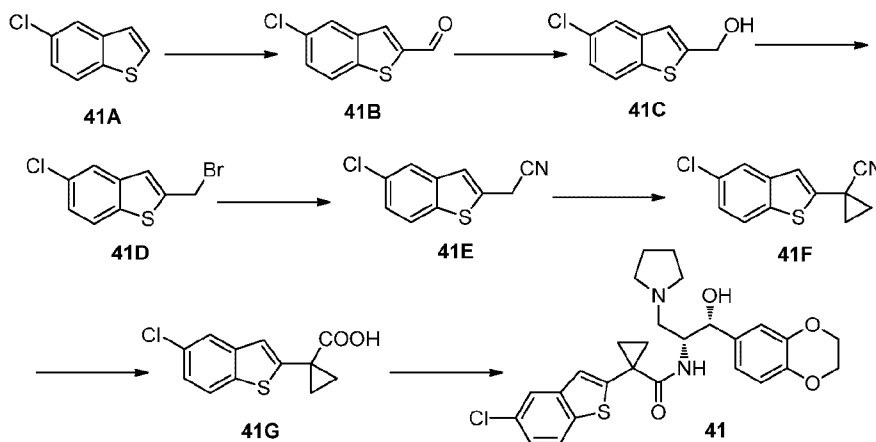
[000538] To a solution of Compound **40C** (550 mg, 2.50 mmol) and cyclopropanecarbonitrile (502 mg, 7.50 mmol) in dry THF (5 mL) was added LDA in THF (3.75 mL, 7.50 mmol, 2 M) dropwise at -10 °C. Then it was stirred at 0 °C for 5 h. It was quenched with water, diluted with ethyl acetate (150 mL), washed with water and brine, and purified with silica gel column chromatography (ethyl acetate in petroleum ether, 10% v/v) to yield Compound **40D**. LCMS (m/z): 208 $[M+1]^+$; ^1H -NMR (CDCl_3 , 400 MHz) major

characteristic peaks: δ (ppm) 0.99-1.02 (m, 2H), 1.30-1.33 (m, 2H), 2.99 (s, 2H), 7.40 (d, J = 10.2 Hz, 1H), 7.46-7.50 (m, 2H), 7.72 (s, 1H), 7.82-7.84 (m, 3H).

[000539] A mixture of Compound **40D** (400 mg, 1.93 mmol) and NaOH (4.00 g, 100 mmol) in EtOH/H₂O (1/5 mL) was added stirred at 100 °C overnight. Then it was adjusted to pH = 1 with conc.HCl, diluted with ethyl acetate (200 mL), washed with water and brine, dried with anhydrous Na₂SO₄, and evaporated to give Compound **40E**. LCMS (m/z): 225 [$M-1$], ¹H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 0.91-0.94 (m, 2H), 1.37-1.40 (m, 2H), 3.15 (s, 2H), 7.37-7.47 (m, 3H), 7.66 (s, 1H), 7.74-7.80 (m, 3H).

[000540] Compound **40** was synthesized, by employing the procedure described for Compound **1** using Compound **40E** in lieu of Compound **1B**. LCMS (m/z): 487 [$M+1$]⁺, ¹H NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 0.82-0.91 (m, 2H), 1.17-1.25 (m, 2H), 1.57-1.78 (m, 4H), 2.99 (br s, 1H), 2.51 (br s, 1H), 2.99-3.21 (m, 4H), 3.47 (br s, 1H), 4.06 (br s, 2H), 4.21 (s, 5H), 4.77 (s, 1H), 6.52 (d, J = 10.3 Hz, 1H), 6.66 (d, J = 8.0 Hz, 1H), 6.74 (s, 1H), 6.80 (d, J = 7.6 Hz, 1H), 7.40-7.50 (m, 3H), 7.75-7.80 (m, 4H).

Example 41



[000541] To a solution of Compound **41A** (500 mg, 2.97 mmol) in THF (30 mL) was added *n*-BuLi (1.42 mL, 3.56 mmol) at -78 °C under the protection of nitrogen. Then it was stirred at -78 °C for 1 h, DMF (434 mg, 5.94 mmol) was added to the mixture and stirred for another one hour at -78 °C. The reaction was quenched with sat. NH₄Cl. After separation, the organic phase was washed with brine, and dried over anhydrous Na₂SO₄, and purified by silica gel column chromatography (ethyl acetate in petroleum 20% v/v) to render Compound **41B**. ¹H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 7.47 (dd, J = 2.0, 8.8 Hz, 1H), 7.83 (d, J = 8.8 Hz, 1H), 7.93 (d, J = 2.0 Hz, 1H), 7.97 (s, 1H), 10.11 (s, 1H).

[000542] To a solution of Compound **41B** (500 mg, 2.54 mmol) in EtOH (10 mL) was added NaBH₄ (97 mg, 2.54 mmol) at 0 °C under N₂ and stirred at 25 °C for 1 h. The reaction

was quenched with water (10 mL). The mixture was extracted with ethyl acetate (50 mL x 3). The combined organic phase was washed with brine, and dried over anhydrous Na₂SO₄, and concentrated to afford Compound **41C**. ¹H-NMR (CDCl₃, 400 MHz) major characteristic peaks: δ (ppm) 2.00 (br s, 1H), 4.93 (s, 2H), 7.15 (s, 1H), 7.27 (dd, J = 2.4, 8.8 Hz, 1H), 7.71(m, 2H).

[000543] To a solution of Compound **41C** (5.83 g, 0.29.7 mmol) in ether (100 mL) was added a solution of PBr₃ (6.71 mL) in 50 mL of ether at 0 °C. The mixture was stirred at 0 °C for 2 h. The reaction was poured into ice-water (300 mL) and the mixture was extracted with ether (100 mL x 3). The combined organic layers were washed with water and brine, and dried over anhydrous Na₂SO₄. The crude product Compound **41D** was used for the next step of reaction without further purification. Compound **41D**. ¹H-NMR (DMSO-*d*₆, 400 MHz) major characteristic peaks: δ (ppm) 5.10 (s, 2H), 7.41 (dd, J = 2.0, 8.8 Hz, 1H), 7.53 (s, 1H), 7.94 (s, 1H), 8.00 (d, J = 8.8 Hz, 1H).

[000544] To a stirred solution of Compound **41D** (5.12 g, 19.6 mmol) in CHCl₃ (60 mL) was added a mixture of NaCN (1.45 g, 29.5 mmol), KOH (275 mg, 4.91 mmol), *n*-Bu₄NHSO₄ (1.68 g, 4.91 mmol) and water (60 mL). After one hour at 25 °C, the mixture was heated to reflux for 30 min. The mixture was cooled and partitioned between DCM and water. The aqueous phase was extracted with DCM (100 mL x 3). The combined organic phase was washed with water and brine, and dried over anhydrous Na₂SO₄, and purified by column chromatography on silica gel (ethyl acetate in petroleum, 20% v/v) to give Compound **41E**. ¹H-NMR (DMSO-*d*₆, 400 MHz) major characteristic peaks: δ (ppm) 4.46 (s, 2H), 7.41 (m, 2H), 7.96 (s, 1H), 8.01 (d, J = 8.8 Hz, 1H).

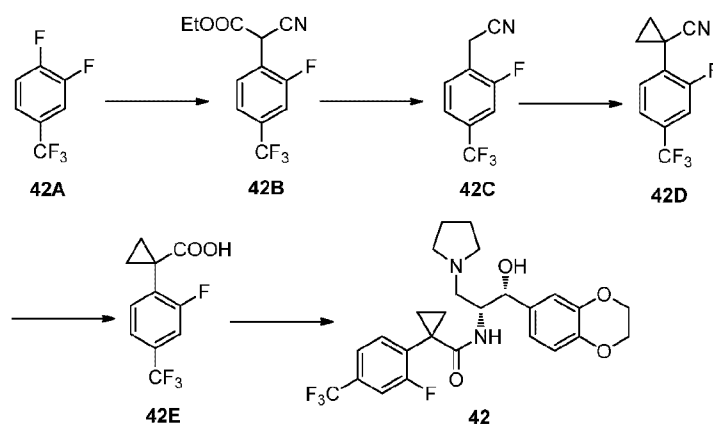
[000545] To a solution of Compound **41E** (1.5 g, 7.25 mmol) in dry DMF (30 mL) was added NaH (60 %, 870 mg, 21.74 mmol) at 0 °C under nitrogen protection. After stirring for 90 min at 30 °C, 1,2-dibromoethane (1.88 g, 21.74 mmol) was added dropwise at 0 °C, and the mixture was warmed to 25 °C and stood overnight. The reaction was quenched with 1 M HCl. It was extracted with ethyl acetate (100 mL x 3). The extracts were washed with water and brine, and dried over anhydrous Na₂SO₄. The crude product was purified by column chromatography on silica gel (ethyl acetate in petroleum, 20% v/v) to yield Compound **41F**. ¹H-NMR (DMSO-*d*₆, 400 MHz) major characteristic peaks: δ (ppm) 1.65 (m, 2H), 1.95 (m, 2H), 7.40 (dd, J = 2.0, 8.8 Hz, 1H), 7.43 (s, 1H), 7.89 (s, 1H), 8.00 (d, J = 8.4 Hz, 1H).

[000546] To a solution of Compound **41F** (570 mg, 2.75 mmol) in water (30 mL) was added NaOH (3 g, 75 mmol). The mixture was stirred at reflux overnight. After reaction, cooled and adjusted pH to 3 with conc. HCl, filtered and washed with water, then dried to

furnish Compound **41G**. $^1\text{H-NMR}$ ($\text{DMSO-}d_6$, 400 MHz) major characteristic peaks: δ (ppm) 1.42 (m, 2H), 1.65 (m, 2H), 7.26 (s, 1H), 7.33 (dd, $J = 1.6, 8.4$ Hz, 1H), 7.81 (s, 1H), 7.91 (d, $J = 8.4$ Hz, 1H) 12.80 (br s, 1H).

[000547] Compound **41** was synthesized, by employing the procedure described for Compound **1** using Compound **41G** in lieu of Compound **1B**. LCMS: 513 $[\text{M}+1]^+$; $^1\text{H-NMR}$ ($\text{DMSO-}d_6$, 400 MHz) major characteristic peaks: δ (ppm) 1.16 (m, 2H), 1.38 (m, 2H), 1.65 (m, 4H), 2.21 (m, 1H), 2.61 (m, 3H), 2.66 (m, 1H), 3.89 (m, 1H), 4.23 (m, 5H), 4.70 (s, 1H), 5.53 (s, 1H), 6.47 (d, $J = 8.4$ Hz, 1H), 6.60 (d, $J = 8.4$ Hz, 1H), 6.63 (s, 1H), 6.73 (d, $J = 8.0$ Hz, 1H), 7.34 (s, 1H), 7.40 (d, $J = 8.4$ Hz, 1H), 7.90 (s, 1H), 8.00 (d, $J = 8.4$ Hz, 1H).

Example 42



[000548] A suspension of Compound **42A** (2.5 g, 13.7 mmol), ethyl cyanacetate (1.35 mL, 12.5 mmol), benzyltriethylammonium chloride (285 mg, 1.25 mmol) and K_2CO_3 (5.18 g, 37.5 mmol) in DMSO (60 mL) was stirred at 90 °C under N_2 overnight. The mixture was diluted with ethyl acetate (100 mL), and then further cooled to 5 °C. Aqueous HCl solution (6 M) was added to the mixture, leading to precipitation of a white solid. The resulting suspension was stirred for 30 min until the precipitate dissolved. The organic layer was separated and washed with water (150 mL x 3) and brine (200 mL), dried over anhydrous Na_2SO_4 , and concentrated to give a crude Compound **42B**. LC-MS (m/z): 276 $[\text{M}+1]^+$.

[000549] To a solution of Compound **42B** (2.75 g, 10 mmol) in DMSO (50 mL) was added NaCl (820 mg, 14 mmol) and the mixture was heated to 110 °C for 15 h. The mixture was then cooled to 25 °C and diluted with dichloromethane (100 mL), followed by water (50 mL). The organic and aqueous phases were separated. The aqueous phase was extracted with dichloromethane (100 mL) and the combined organic phase were washed with water (200 mL) and brine (100 mL), dried over anhydrous Na_2SO_4 , and concentrated to give a crude Compound **42C**. LC-MS (m/z): 204 $[\text{M}+1]^+$. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) major

characteristic peaks: δ (ppm) 3.837 (s, 2H), 7.384 (d, $J = 9.6$ MHz, 1H), 7.384 (d, $J = 8.0$ MHz, 1H), 7.625 (t, $J = 8.0$ MHz, 1H).

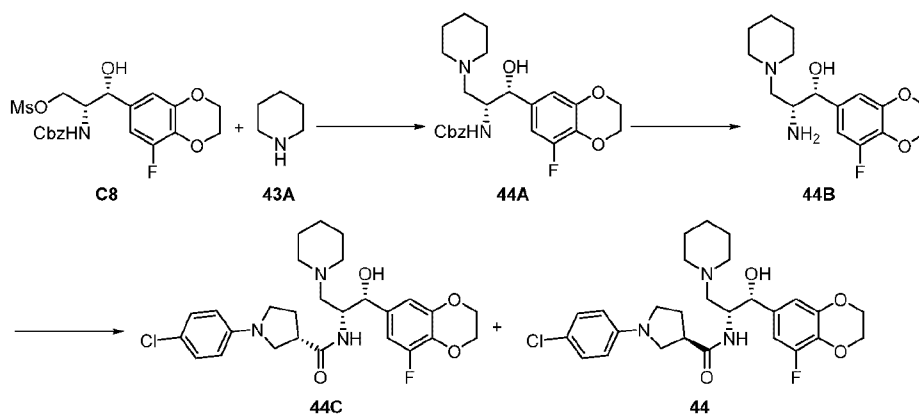
[000550] To a solution of Compound **42C** (1 g, 5 mmol) in THF (20 mL) at 0 °C was added NaH (60%, 0.6 g, 15 mmol) and the mixture was stirred at 0 °C for 5 min, followed by the addition of 1,2-dibromoethane (2.8 g, 15 mmol) in THF (2 mL). The mixture was stirred at 0 °C for 2 h and continued for 16 h at room temperature. It was quenched with addition of water (1 mL) and then concentrated. The resulting slurry was dissolved in ethyl acetate (50 mL) and washed with water (15 mL), dried over anhydrous Na_2SO_4 , and concentrated to yield a crude Compound **42D**. LC-MS (m/z): 230 $[\text{M}+1]^+$

[000551] A suspension of Compound **42D** (1 g, 4 mmol) in aq. NaOH solution (3 M, 20 mL) was heated to reflux for 18 h, and then cooled to room temperature. The resulting solution was adjusted to pH = 3 with aq. HCl solution (1 M) and extracted with ethyl acetate (50 mL x 3), dried over anhydrous Na_2SO_4 , and concentrated to give Compound **42E**. LC-MS (m/z): 249 $[\text{M}+1]^+$; ^1H -NMR (CDCl_3 , 400 MHz) major characteristic peaks: δ (ppm) 1.282 (q, $J = 4.0$ MHz, 2H), 1.780 (q, $J = 4.0$ MHz, 2H), 7.310 (d, $J = 9.6$ MHz, 1H), 7.380 ~ 7.415 (m, 3H).

[000552] Compound **42** was synthesized, by employing the procedure described for Compound **1** using Compound **42E** in lieu of Compound **1B**. LC-MS (m/z): 509 $[\text{M}+1]^+$; ^1H -NMR (CDCl_3 , 400 MHz) major characteristic peaks: δ (ppm) 0.971~1.078 (m, 2H), 1.601 (m, 2H), 1.856 (m, 4H), 2.813 (m, 4H), 2.954 (m, 2H), 4.113 (m, 1H), 4.252 (s, 4H), 4.916 (s, 1H), 5.712 (d, $J = 6.8$ MHz, 1H), 6.535 (m, 1H), 6.600 (d, $J = 2$ MHz, 1H), 6.730 (d, $J = 8.4$ MHz, 1H), 7.380 (m, 1H), 7.451 (m, 2H).

Hz, 2H), 6.81-6.84 (m, 2H), 6.94 (s, 1H), 7.12(d, $J = 8.8$ Hz, 2H). Chiral-HPLC condition, solvent: MeOH (0.1% DEA), column: OJ-H (250 * 4.6 mm 5 μ m), Rt: 4.9 min.

Example 44



[000558] Compounds **44A** and **44B** were synthesized, by employing the procedures described for Intermediate **A9** and **A** using Intermediate **C8**, Compound **43A**, and **44A** in lieu of Intermediate **A8**, pyrrolidine, and Intermediate **A9**.

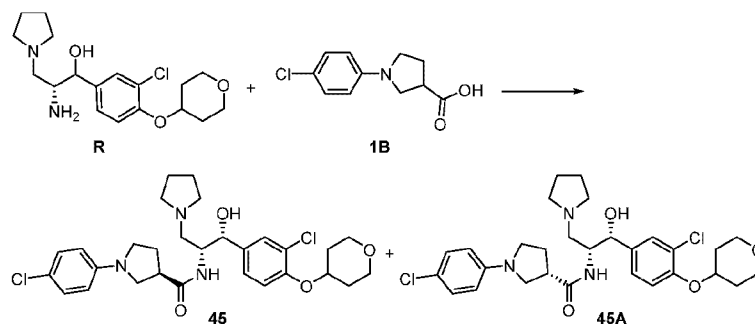
[000559] Compound **44A**. LC-MS (ESI) m/z : 445 $[M+H]^+$.

[000560] Compound **44B**, which was directly used for the next step without further purification. LC-MS (ESI) m/z : 311 $[M+H]^+$.

[000561] Compounds **44C** and **44** were synthesized, by employing the procedures described for Compound **1** using Compound **43B** in lieu of Intermediate **A**.

[000562] Compound **44C**. LC-MS (ESI) m/z : 518 $[M+H]^+$; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) : δ (ppm) 1.43 (s, 1H), 1.88 (s, 5H), 2.03 (s, 1H), 2.12 (s, 2H), 2.98-3.07 (m, 3H), 3.18-3.30 (m, 3H), 3.40-3.50 (m, 2H), 3.69 (s, 1H), 4.23 (s, 5H), 4.50 (s, 1H), 4.79 (s, 1H), 6.44 (d, $J = 8$ Hz, 2H), 6.66-6.71 (m, 2H), 7.14 (d, $J = 8$ Hz, 2H), 7.78 (s, 1H), 10.78 (s, 1H).

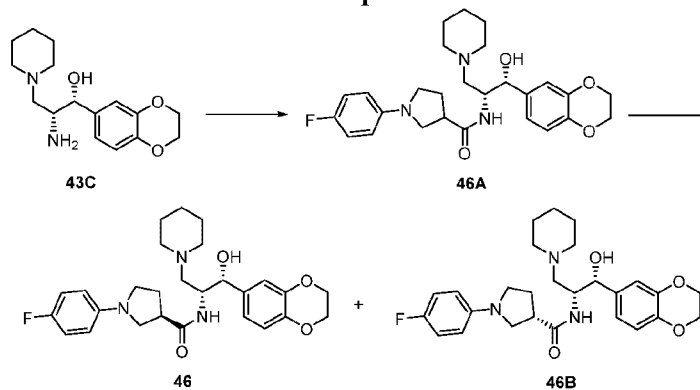
[000563] Compound **44**. LC-MS (ESI) m/z : 518 $[M+H]^+$; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ (ppm) 1.40 (s, 1H), 1.85 (s, 4H), 1.98 (s, 2H), 2.14 (s, 1H), 2.61 (s, 1H), 3.06 (s, 2H), 3.23-3.37 (m, 4H), 3.50 (s, 2H), 3.68 (s, 1H), 4.22-4.26 (s, 4H), 4.52 (s, 1H), 4.79 (s, 1H), 6.47 (d, $J = 8$ Hz, 2H), 6.65-6.71 (m, 2H), 7.14 (d, $J = 8$ Hz, 2H), 7.78 (s, 1H), 10.69 (s, 1H).

Example 45

[000564] Compounds **45** and **45A** were synthesized, by employing the procedures described for Compound **1** using Intermediate **R** in lieu of Intermediate **A**.

[000565] Compound **45**. LC-MS (ESI) m/z : 562 $[M+H]^+$; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ (ppm) 1.78-1.87 (m, 6H), 1.96-2.01 (m, 2H), 2.07-2.20 (m, 2H), 2.67-2.70 (m, 4H), 2.83-2.87 (m, 1H), 2.93-2.97 (m, 2H), 3.16-3.38 (m, 4H), 3.55-3.61 (m, 2H), 3.97-4.02 (m, 2H), 4.19-4.23 (m, 1H), 4.46-4.51 (m, 1H), 5.00 (d, $J = 2.4$ Hz, 1H), 6.30 (d, $J = 8.0$ Hz, 1H), 6.45 (d, $J = 8.8$ Hz, 2H), 6.85 (d, $J = 8.8$ Hz, 1H), 7.07 (dd, $J = 8.0, 2.0$ Hz, 1H), 7.16 (d, $J = 9.2$ Hz, 2H), 7.41 (d, $J = 2.0$ Hz, 1H); Chiral-HPLC condition, solvent: MeOH (0.1% DEA), column: OZ-H (250 * 4.6 mm 5 μm), Rt: 4.04 min.

[000566] Compound **45A**. LC-MS (ESI) m/z : 562 $[M+H]^+$; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ (ppm) 1.77 (m, 3H), 1.88-1.96 (m, 2H), 2.02-2.10 (m, 4H), 2.92-2.03 (m, 3H), 3.22-3.24 (m, 3H), 3.36-3.38 (m, 2H), 3.56-4.10 (m, 8H), 4.47-4.52 (m, 2H), 4.93 (s, 1H), 6.52 (d, $J = 8.8$ Hz, 2H), 6.87 (d, $J = 8.4$ Hz, 1H), 7.12-7.17 (m, 3H), 7.40 (s, 1H), 7.55 (d, $J = 7.6$ Hz, 1H), 11.08 (s, 1H); Chiral-HPLC condition, solvent: MeOH (0.1% DEA), column: AD-H (250 * 4.6 mm 5 μm), Rt: 5.65 min.

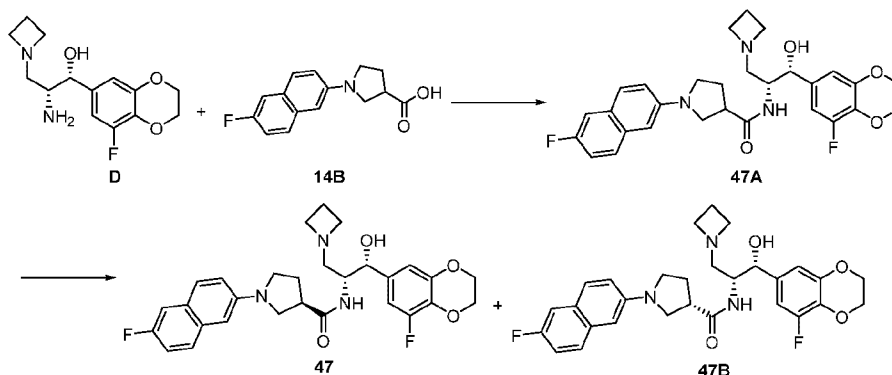
Example 46

[000567] Compounds **46** and **46B** were synthesized, by employing the procedures described for Compound **1** using Compounds **43C** and **24A** in lieu of Intermediate **A** and Compound **1B**.

[000568] Compound **46**. LC-MS (ESI) m/z : 484 $[M+H]^+$; ^1H -NMR (MeOD, 400 MHz) δ (ppm) 1.48-1.52 (m, 2H), 1.59-1.62 (m, 4H), 2.05-2.17 (m, 2H), 2.47-2.62 (m, 6H), 3.00-3.02 (m, 1H), 3.09-3.24 (m, 1H), 3.31-3.38 (m, 2H), 4.18-4.21 (m, 4H), 4.22-4.23 (m, 1H), 4.80 (d, $J = 3.2$ Hz, 1H), 6.51-6.54 (m, 2H), 6.77-6.78 (m, 2H), 6.90-6.95 (m, 3H). Chiral-HPLC condition, solvent: MeOH (0.1% DEA), column OJ-H (250 * 4.6 mm 5 μ m), Rt: 2.71 min.

[000569] Compound **46B**. LC-MS (ESI) m/z : 484 $[M+H]^+$; ^1H -NMR (MeOD, 400 MHz) δ (ppm) 1.37-1.38 (m, 2H), 1.50-1.53 (m, 4H), 1.83-1.89 (m, 1H), 2.01-2.09 (m, 1H), 2.46-2.52 (m, 6H), 3.08-3.25 (m, 5H), 4.08-4.09 (m, 4H), 4.18-4.21 (m, 1H), 4.67 (d, $J = 3.6$ Hz, 1H), 6.38-6.41 (m, 2H), 6.67-6.68 (m, 2H), 6.75-6.82 (m, 3H). Chiral-HPLC condition, solvent: MeOH (0.1% DEA), column OJ-H (250 * 4.6 mm 5 μ m), Rt: 4.44 min.

Example 47

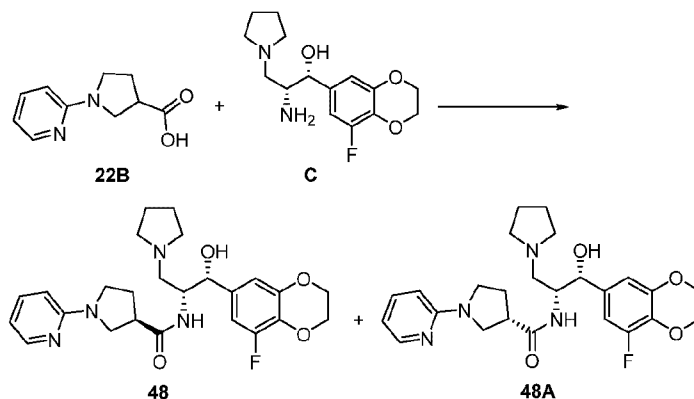


[000570] Compounds **47** and **47B** were synthesized, by employing the procedures described for Compound **1** using Intermediate **D** and Compound **14B** in lieu of Intermediate **A** and Compound **1B**.

[000571] Compound **47**. LC-MS (ESI) m/z : 506 $[M+H]^+$; ^1H -NMR (MeOD, 400 MHz) δ (ppm) 2.03-2.21 (m, 4H), 2.59-2.69 (m, 2H), 2.72-2.88 (m, 1H), 3.01-3.11 (m, 1H), 3.23-3.32 (m, 5H), 3.37-3.45 (m, 2H), 3.97-4.09 (m, 5H), 4.67 (s, 1H), 6.61 (s, 1H), 6.68-6.72 (m, 2H), 6.97 (d, $J = 8.4$ Hz, 1H), 7.04-7.09 (m, 1H), 7.24 (d, $J = 8.8$ Hz, 1H), 7.58 (d, $J = 8.8$ Hz, 2H).

[000572] Compound **47B**. LC-MS (ESI) m/z : 506 $[M+H]^+$; ^1H -NMR (MeOD, 400 MHz) δ (ppm) 1.84-2.15 (m, 4H), 2.53-2.67 (m, 2H), 3.04-3.07 (m, 1H), 3.24-3.35 (m, 6H), 3.40-3.43 (m, 2H), 3.93-3.97 (m, 1H), 4.17 (s, 1H), 6.62 (s, 1H), 6.61-6.70 (m, 3H), 6.97 (d, $J = 9.2$ Hz, 1H), 7.02-7.07 (m, 1H), 7.23 (d, $J = 9.2$ Hz, 1H), 7.52-7.57 (m, 2H).

Example 48

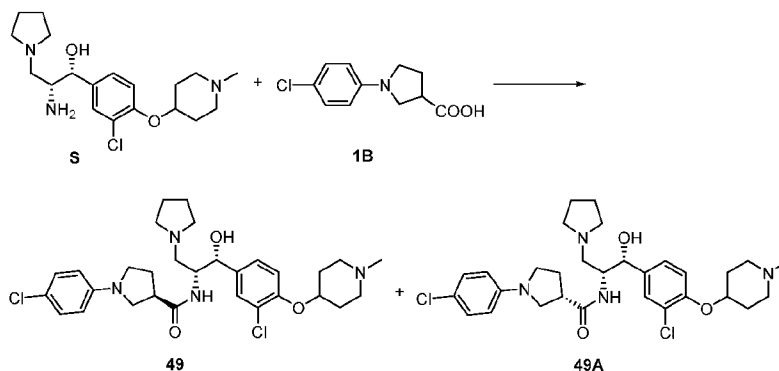


[000573] Compounds **48** and **48A** were synthesized, by employing the procedures described for Compound **7** using Intermediate **C** and Compound **22B** in lieu of Intermediate **A** and Compound **7B**.

[000574] Compound **48**. LC-MS (ESI) m/z : 471 $[M+H]^+$; $^1\text{H-NMR}$ (MeOD, 400 MHz) δ (ppm) 1.70-1.76 (m, 4H), 2.10-2.20 (m, 2H), 2.52-2.68 (m, 6H), 3.02-3.04 (m, 2H), 3.28-3.31 (m, 1H), 3.47-3.48 (m, 2H), 4.13-4.16 (m, 5H), 4.47 (d, $J = 2.4$ Hz, 1H), 6.35-6.37 (m, 1H), 6.46-6.49 (m, 1H), 6.59-6.64 (m, 2H), 7.41-7.43 (m, 1H), 7.88-7.89 (m, 1H). Chiral-HPLC condition, solvent: IPA (0.1% DEA), column: OD-H 250 * 4.6 mm 5 μm , Rt: 7.33 min.

[000575] Compound **48A**. LC-MS (ESI) m/z : 471 $[M+H]^+$; $^1\text{H-NMR}$ (MeOD, 400 MHz) δ (ppm) 1.68-1.72 (m, 4H), 1.78-1.87 (m, 1H), 2.02-2.12 (m, 1H), 2.47-2.65 (m, 6H), 3.01-3.03 (m, 1H), 3.25-3.47 (m, 4H), 4.12-4.15 (m, 5H), 4.67 (d, $J = 3.2$ Hz, 1H), 6.34-6.36 (m, 1H), 6.45-6.47 (m, 1H), 6.59-6.64 (m, 2H), 7.39-7.40 (m, 1H), 7.86-7.87 (m, 1H). Chiral-HPLC condition, solvent: IPA (0.1% DEA), column: OD-H 250 * 4.6 mm 5 μm , Rt: 8.33 min.

Example 49

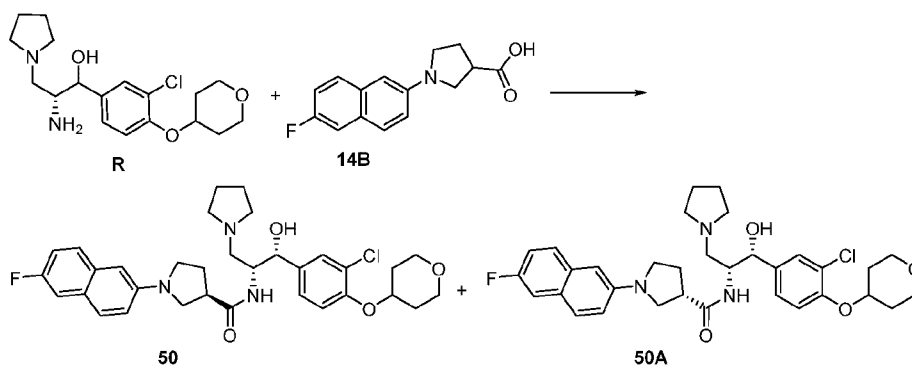


[000576] Compounds **49** and **49A** were synthesized, by employing the procedures described for Compound **1** using Intermediate **S** in lieu of Intermediate **A**.

[000577] Compound **49**. LC-MS (ESI) m/z : 575 $[M+H]^+$; $^1\text{H-NMR}$ (MEOD, 400 MHz) δ (ppm) 2.04-2.22 (m, 10H), 2.51-2.55 (m, 1H), 2.85 (s, 2H), 2.88 (s, 1H), 3.10-3.30 (m, 7H), 3.32-3.76 (m, 7H), 4.56-4.59 (m, 1H), 4.71 (m, 1H), 6.48-6.52 (m, 2H), 7.05-7.07 (d, $J = 8.4$ Hz, 1H), 7.14-7.18 (m, 2H), 7.30-7.33 (m, 1H), 7.57-7.59 (m, 1H); Chiral-HPLC condition, solvent: MeOH (0.5% DEA), column: AD-H (250 * 4.6 mm 5 μm), R_t : 2.39 min.

[000578] Compound **49A**. LC-MS (ESI) m/z : 575 $[M+H]^+$; $^1\text{H-NMR}$ (MEOD, 400 MHz) δ (ppm) 1.64-1.65 (m, 1H), 2.02-2.19 (m, 9H), 2.89 (s, 1H), 2.91 (s, 2H), 3.12-3.30 (m, 6H), 3.30-3.74 (m, 8H), 4.53-4.56 (m, 1H), 4.80 (m, 1H), 4.91 (d, $J = 2.0$ Hz, 1H), 6.47-6.49 (d, $J = 8.8$ Hz, 2H), 7.10-7.15 (m, 2H), 7.32-7.35 (m, 1H), 7.53-7.55 (m, 1H); Chiral-HPLC condition, solvent: MeOH (0.5% DEA), column: AD-H (250 * 4.6 mm 5 μm), R_t : 3.82 min.

Example 50



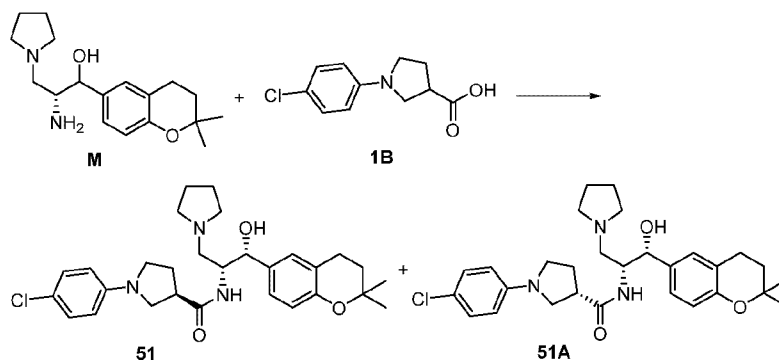
[000579] Compounds **50** and **50A** were synthesized, by employing the procedures described for Compound **1** using Intermediate **R** and Compound **14B** in lieu of Intermediate **A** and Compound **1B**.

[000580] Compound **50**. LC-MS (ESI) m/z : 596 $[M+H]^+$; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ (ppm) 1.72 (m, 4H), 1.77-1.85 (m, 2H), 1.92-1.99 (m, 2H), 2.11-2.25 (m, 2H), 2.63-2.71

(m, 4H), 2.83-2.87 (m, 1H), 2.94-3.01 (m, 2H), 3.30-3.42 (m, 3H), 3.48-3.57 (m, 3H), 3.95-4.01 (m, 2H), 4.21-4.26 (m, 1H), 4.41-4.46 (m, 1H), 5.01 (d, $J = 2.4$ Hz, 1H), 6.35 (d, $J = 8.0$ Hz, 1H), 6.77 (d, $J = 2.4$ Hz, 1H), 6.84 (d, $J = 8.4$ Hz, 1H), 7.00 (dd, $J = 8.8, 2.0$ Hz, 1H), 7.09 (dd, $J = 8.8, 2.4$ Hz, 1H), 7.14-7.19 (m, 1H), 7.31 (dd, $J = 10.0, 2.4$ Hz, 1H), 7.44 (d, $J = 2.0$ Hz, 1H), 7.62-7.66 (m, 2H); Chiral-HPLC condition, solvent: *n*-hexane (0.1% DEA): EtOH (0.1% DEA) = 70:30, column (OZ-H 250 * 4.6 mm 5 μ m), Rt: 7.22 min.

[000581] Compound **50A**. LC-MS (ESI) m/z : 596 $[M+H]^+$; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ (ppm) 1.80 (m, 6H), 1.93-2.00 (m, 2H), 2.05-2.11 (m, 1H), 2.17-2.23 (m, 1H), 2.65-2.75 (m, 4H), 2.86-2.92 (m, 2H), 2.99-2.03 (m, 1H), 3.31-3.37 (m, 1H), 3.43-3.59 (m, 5H), 3.96-4.02 (m, 2H), 4.21-4.25 (m, 1H), 4.39-4.44 (m, 1H), 4.99 (d, $J = 2.8$ Hz, 1H), 6.35 (d, $J = 8.0$ Hz, 1H), 6.76-6.79 (m, 2H), 7.00 (dd, $J = 9.2, 2.4$ Hz, 1H), 7.07 (dd, $J = 8.4, 2.0$ Hz, 1H), 7.13-7.18 (m, 1H), 7.31 (dd, $J = 10.0, 2.4$ Hz, 1H), 7.38 (d, $J = 2.0$ Hz, 1H), 7.59-7.65 (m, 2H); Chiral-HPLC condition, solvent: *n*-hexane (0.1% DEA): EtOH (0.1% DEA) = 70:30, column (OZ-H 250 * 4.6 mm 5 μ m), Rt: 8.27 min.

Example 51



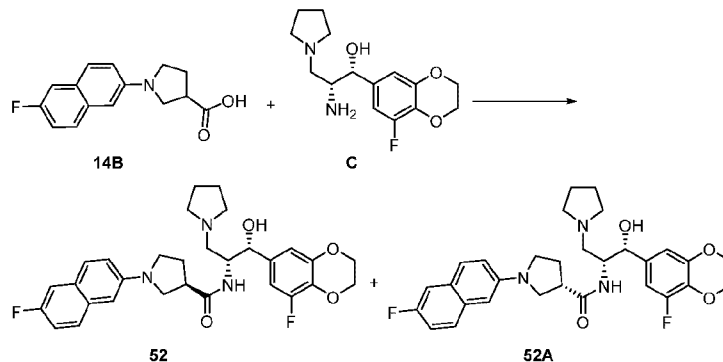
[000582] Compounds **51** and **51A** were synthesized, by employing the procedures described for Compound **1** using Intermediate **M** in lieu of Intermediate **A**.

[000583] Compound **51**. LC-MS (ESI) m/z : 512 $[M+H]^+$; $^1\text{H-NMR}$ ($\text{DMSO-}d_6$, 400 MHz) δ (ppm) 1.16 (s, 3H), 1.28 (s, 3H), 1.76-1.81 (m, 6H), 2.11-2.19 (m, 2H), 2.59-2.88 (m, 6H), 2.95-2.99 (m, 1H), 2.97-2.99 (m, 1H), 3.06-3.13 (m, 1H), 3.20-3.34 (m, 4H), 4.26-4.31 (m, 1H), 4.81 (s, 1H), 6.47 (d $J = 9.2$ Hz, 2H), 6.68 (d $J = 8.8$ Hz, 1H), 7.14-7.13 (m, 4H). Chiral-HPLC condition, solvent MeOH (0.1% DEA), column OJ-H (250 * 4.6 mm 5 μ m), Rt: 2.78 min.

[000584] Compound **51A**. LC-MS (ESI) m/z : 512 $[M+H]^+$; $^1\text{H-NMR}$ ($\text{DMSO-}d_6$, 400 MHz) δ (ppm) 1.21 (s, 6H), 1.69-1.72 (m, 6H), 1.82-1.87 (m, 1H), 2.03-2.10 (m, 1H), 2.49-2.69 (m, 6H), 3.00-3.06 (m, 1H), 3.13-3.17 (m, 2H), 3.22-3.28 (m, 4H), 4.17-4.22 (m, 1H),

4.70 (s, 1H), 6.40 (d, $J = 8.8$ Hz, 2H), 6.57 (d, $J = 8.8$ Hz, 1H), 6.95-7.03 (m, 4H). Chiral-HPLC condition, solvent MeOH (0.1% DEA), column OJ-H (250 * 4.6 mm 5 μ m), Rt: 3.49 min.

Example 52

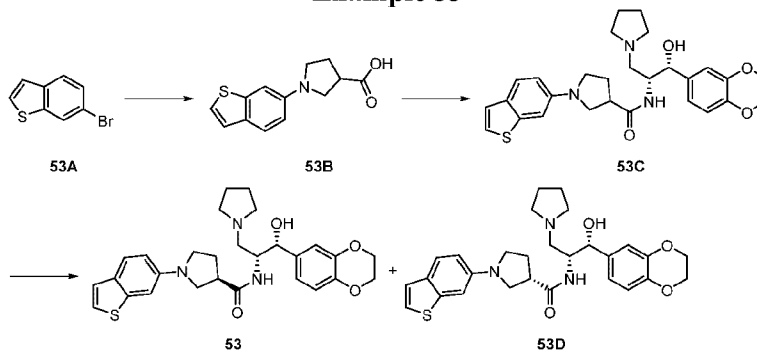


[000585] Compounds **52** and **52A** were synthesized, by employing the procedures described for Compound **1** using Compound **14B** and Intermediate **C** in lieu of Compound **1B** and Intermediate **A**.

[000586] Compound **52**. LC-MS (ESI) m/z : 538 $[M+H]^+$; $^1\text{H-NMR}$ (MeOD, 400 MHz) δ (ppm) 1.72 (s, 4H), 2.01-2.17 (m, 2H), 2.50-2.64 (m, 5H), 2.83-2.86 (m, 1H), 3.01-3.09 (m, 1H), 3.34-3.42 (m, 4H), 4.05-4.17 (m, 5H), 4.71 (s, 1H), 6.60-6.70 (m, 3H), 6.95 (d $J = 8.4$ Hz, 1H), 7.02-7.06 (m, 1H), 7.20-7.23 (m, 1H), 7.54-7.58 (m, 2H); Chiral-HPLC condition, solvent: MeOH (0.1% DEA), column AD-H (4.6 * 250 mm 5 μ m), Rt: 6.63 min.

[000587] Compound **52A**. LC-MS (ESI) m/z : 538 $[M+H]^+$; $^1\text{H-NMR}$ (MeOD, 400 MHz) δ (ppm) 1.71 (s, 4H), 1.85-1.90 (m, 1H), 1.92-2.15 (m, 1H), 2.48-2.65 (m, 6H), 3.00-3.08 (m, 1H), 3.29-3.39 (m, 4H), 4.14 (s, 5H), 4.67 (s, 1H), 6.59-6.67 (m, 3H), 6.93 (d, $J = 8.4$ Hz, 1H), 6.99-7.04 (m, 1H), 7.18 (d, $J = 8.0$ Hz, 1H), 7.19-7.53 (m, 2H); Chiral-HPLC condition, solvent: MeOH (0.1% DEA), column AD-H (4.6 * 250 mm 5 μ m), Rt: 13.47 min.

Example 53



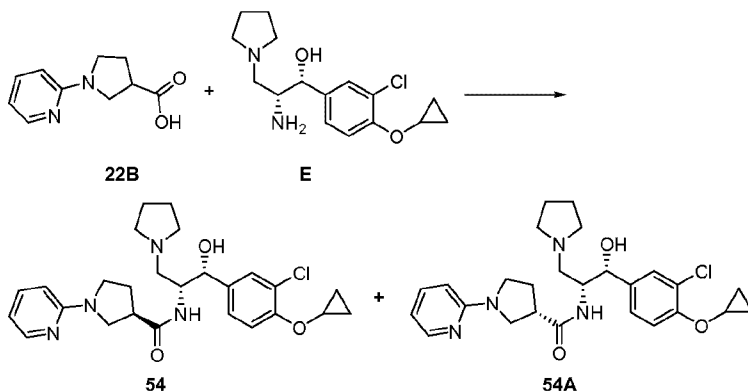
[000588] Compounds **53B**, **53**, and **53D** were synthesized, by employing the procedures described for Compound **1B** and Compound **1** using Compound **53A** and **53B** in lieu of 1-chloro-4-iodobenzene and Compound **1B**.

[000589] Compound **53B**. LC-MS (ESI) m/z : 248 $[M+H]^+$; ^1H -NMR (DMSO- d_6 , 400 MHz) δ (ppm) 2.05-2.15 (m, 2H), 2.87-2.95 (m, 1H), 2.23-2.29 (m, 2H), 2.38-2.41 (m, 2H), 6.67-6.69 (m, 1H), 6.97 (d, $J = 2$ Hz, 1H), 7.19-7.24 (m, 2H) 7.60-7.63 (m, 1H).

[000590] Compound **53**. LC-MS (ESI) m/z : 508 $[M+H]^+$; ^1H -NMR (MeOD, 400 MHz) δ (ppm) 1.70 (s, 4H), 1.85-1.90 (m, 1H), 2.06-2.09 (m, 1H), 2.25-2.66 (m, 6H), 2.98-3.02 (m, 1H), 3.20-3.21 (m, 4H), 4.09 (s, 4H), 4.15-4.18 (m, 1H), 4.67 (d, $J = 3.2$ Hz, 1H), 6.58-6.61 (m, 1H), 6.66-6.69 (m, 2H), 6.77 (d, $J = 1.6$ Hz, 2H), 6.85 (d, $J = 1.2$ Hz, 2H), 6.99-7.02 (m, 2H), 7.48-7.50 (m, 1H). Chiral-HPLC condition, solvent: MeOH (0.5% DEA), column AS-H (250 * 4.6 mm 5 μ m), Rt: 5.58 min.

[000591] Compound **53D**. LC-MS (ESI) m/z : 508 $[M+H]^+$; ^1H -NMR (MeOD, 400 MHz) δ (ppm) 1.91-2.12 (m, 6H), 2.59-2.63 (m, 1H), 3.04-3.14 (m, 3H), 3.32-3.38 (m, 4H), 3.46-3.59 (m, 2H), 3.67-3.74 (m, 1H), 4.07-4.17 (m, 4H), 4.38-4.42 (m, 1H), 4.76 (d, $J = 2.4$ Hz, 1H), 6.63-6.65 (m, 1H), 6.75-6.78 (m, 2H), 6.87-6.89 (m, 2H), 7.05-7.06 (m, 2H), 7.53-7.55 (m, 1H). Chiral-HPLC condition, solvent: MeOH (0.5% DEA), column AS-H (250 * 4.6 mm 5 μ m), Rt: 6.85 min.

Example 54



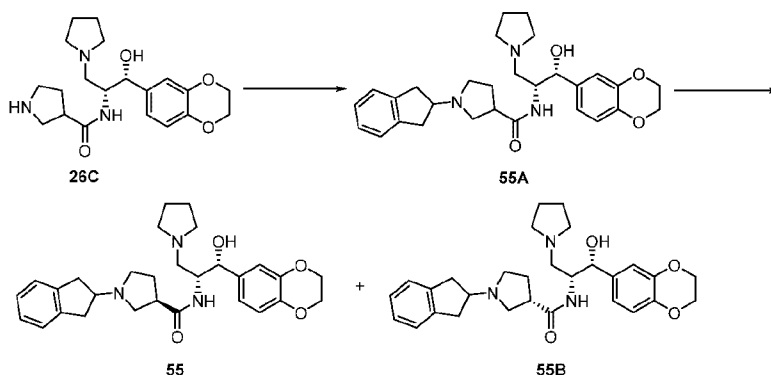
[000592] Compounds **54** and **54A** were synthesized, by employing the procedures described for Compound **7** using Compound **22B** and Intermediate **E** in lieu of Compound **7B** and Intermediate **A**.

[000593] Compound **54**. LC-MS (ESI) m/z : 485 $[M+H]^+$; ^1H -NMR (MeOD, 400 MHz) δ (ppm) 0.56-0.60 (m, 4H), 1.92-2.08 (m, 4H), 2.10-2.37 (m, 2H), 2.90-3.00 (m, 1H), 3.01-3.20 (m, 3H), 3.32-3.74 (m, 9H), 4.45 (d, $J = 2.8$ Hz 1H), 6.78-6.81 (m, 1H), 6.84-6.87 (m,

1H), 7.21-7.22 (m, 2H), 7.39 (s, 1H), 7.79-7.80 (m, 1H), 7.88-7.92 (m, 1H). Chiral-HPLC condition, solvent: IPA (0.5% DEA), column: OZ-H 250 * 4.6 mm 5 um, Rt: 3.88 min.

[000594] Compound **54A**. LC-MS (ESI) m/z: 485 [M+H]⁺; ¹H-NMR (MeOD, 400 MHz) δ (ppm) 0.60-0.72 (m, 4H), 1.64-1.80 (m, 5H), 2.00-2.10 (m, 1H), 2.51-2.73 (m, 6H), 3.01-3.08 (m, 1H), 3.25-3.32 (m, 2H), 3.36-3.47 (m, 2H), 3.73-3.76 (m, 1H), 4.18-4.19 (m, 1H), 4.76 (d, J = 2.8 Hz 1H), 6.34-6.36 (m, 1H), 6.44-6.47 (m, 1H), 7.15-7.16 (m, 1H), 7.21-7.22 (m, 1H), 7.30 (s, 1H), 7.37-7.39 (m, 1H), 7.86-7.87 (m, 1H). Chiral-HPLC condition, solvent: IPA (0.5% DEA), column: OZ-H 250 * 4.6 mm 5 um, Rt: 5.25 min.

Example 55

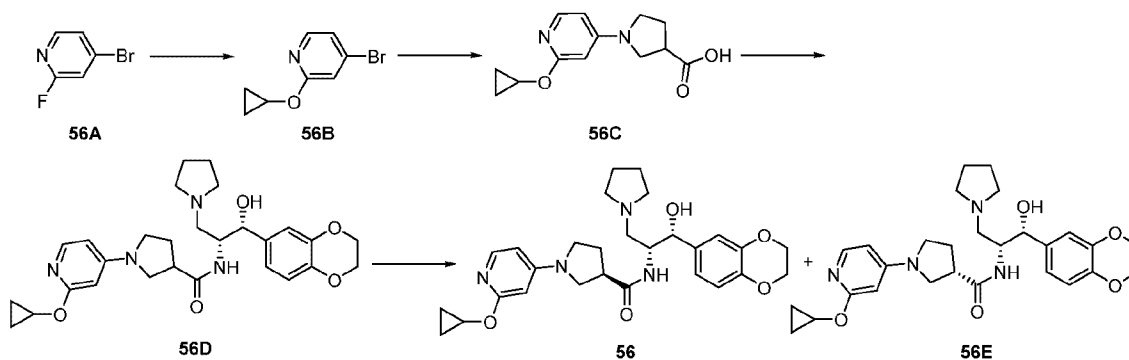


[000595] Compounds **55** and **55B** were synthesized, by employing the procedures described for Compound **9B** using Compound **26C** and 1H-inden-2(3H)-one in lieu of Compound **5A** and tetrahydro-4H-pyran-4-one.

[000596] Compounds **55**. LC-MS (ESI) m/z: 492 [M+H]⁺; ¹H-NMR (CDCl₃, 400 MHz) δ (ppm) 2.02 (m, 4H), 2.28 (m, 2H), 3.21 (m, 10H), 3.76 (m, 6H), 4.18 (m, 4H), 4.48 (m, 1H), 4.81 (m, 1H), 6.79 (m, 3H), 7.20 (m, 4H), 7.90-11.44 (m, 2H); Chiral-HPLC condition, solvent: EtOH (0.5% DEA), column IC (150 * 4.6 mm 5 um), Rt: 4.97 min.

[000597] Compounds **55B**. LC-MS (ESI) m/z: 492 [M+H]⁺; ¹H-NMR (CDCl₃, 400 MHz) δ (ppm) 1.58 (m, 1H), 1.95 (m, 5H), 3.17 (m, 11H), 3.70 (m, 5H), 4.09 (m, 4H), 4.41 (m, 1H), 4.73 (m, 1H), 6.71 (m, 3H), 7.11 (m, 4H), 7.73-11.59 (m, 2H). Chiral-HPLC condition, solvent: EtOH (0.5% DEA), column IC (150 * 4.6 mm 5 um), Rt: 5.8 min.

Example 56



[000598] To a mixture of cyclopropanol (1.5 g, 25.8 mmol) and Compound **56A** (3.0 g, 17.2 mmol) in *N*-methyl-2-pyrrolidone (20 mL) was added potassium *tert*-butoxide (2.9 g, 25.8 mmol) in tetrahydrofuran (25 mL) dropwise and the resultant mixture was stirred at room temperature for 0.5 h under nitrogen protection. Then it was diluted with ethyl acetate (50 mL) and petroleum ether (50 mL), washed with water (30 mL) and brine (30 mL), dried over anhydrous sodium sulfate, evaporated and purified with flash column chromatography on silica gel (petroleum ether, 100% v/v) to furnish Compound **56B**. LC-MS: (*m/z*) 216 [*M*+2]⁺; ¹H-NMR (DMSO-*d*₆, 400 MHz) δ (ppm) 0.66-0.69 (m, 2H), 0.75-0.78 (m, 2H), 4.19-4.22 (m, 1H), 7.16 (m, 1H), 7.26-7.28 (m, 1H), 8.11-8.12 (d, *J* = 5.2 Hz, 1H).

[000599] Compounds **56C**, **56**, and **56E** were synthesized, by employing the procedures described for Compound **1B** and **1** using Compound **56B** and **56C** in lieu of 1-chloro-4-iodobenzene and Compound **1B**.

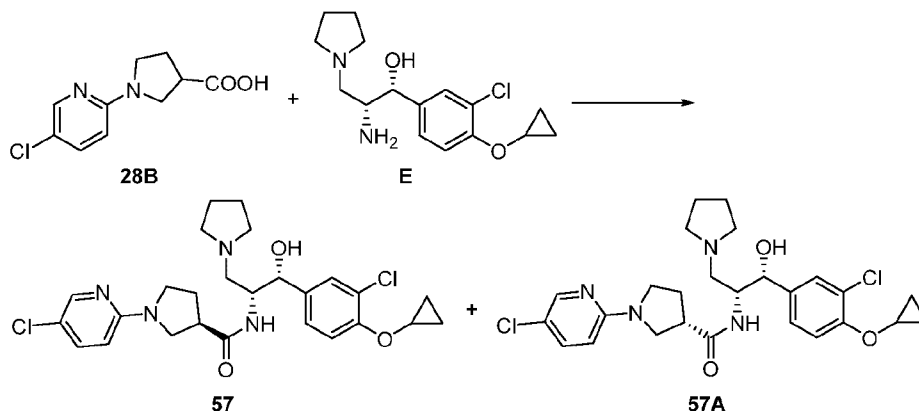
[000600] Compound **56C**. LC-MS (ESI) *m/z*: 249 [*M*+H]⁺; ¹H-NMR (DMSO-*d*₆, 400 MHz) δ (ppm) 0.84-0.91 (m, 4H), 2.19-2.30 (m, 2H), 3.53-3.73 (m, 5H), 4.31 (s, 1H), 6.27-6.78 (m, 2H), 7.80-8.15 (m, 1H), 12.72-12.95 (m, 1H).

[000601] Compound **56**. LC-MS (ESI) *m/z*: 509 [*M*+H]⁺; ¹H-NMR (CDCl₃, 400 MHz) δ (ppm) 0.73-0.77 (m, 4H), 1.78-1.79 (m, 4H), 2.16-2.20 (m, 2H), 2.64-2.69 (m, 4H), 2.87-2.92 (m, 2H), 3.20-3.29 (m, 2H), 3.37-3.41 (m, 2H), 4.12-4.14 (m, 2H), 4.23-4.26 (m, 4H), 4.97-4.98 (m, 1H), 5.79 (s, 1H), 6.09-6.11 (m, 2H), 6.77-6.86 (m, 3H), 7.87-7.89 (m, 1H). Chiral-HPLC condition, solvent: *n*-hexane (0.1% DEA) : EtOH (0.1% DEA) = 30:70 column AD-H (4.6 * 250 mm 5 μ m), Rt: 7.54 min.

[000602] Compound **56E**. LC-MS (ESI) *m/z*: 509 [*M*+H]⁺; ¹H-NMR (CDCl₃, 400 MHz) δ (ppm) 0.71-0.75 (m, 4H), 1.79-1.80 (m, 4H), 2.00-2.14 (m, 2H), 2.67-2.75 (m, 4H), 2.87-2.95 (m, 2H), 3.24-3.47 (m, 4H), 4.06-4.12 (m, 2H), 4.20-4.23 (m, 4H), 4.94-4.94 (m, 1H), 5.77-5.79 (m, 1H), 6.08-6.22 (m, 2H), 6.76-6.84 (m, 3H), 7.85-7.87 (m, 1H). Chiral-HPLC

condition, solvent: *n*-hexane (0.1% DEA) : EtOH (0.1% DEA) = 30:70 column AD-H (4.6 * 250 mm 5 um), Rt: 26.19 min.

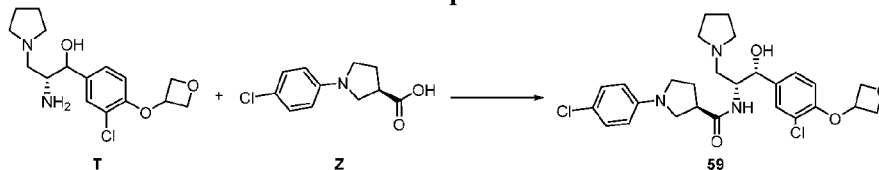
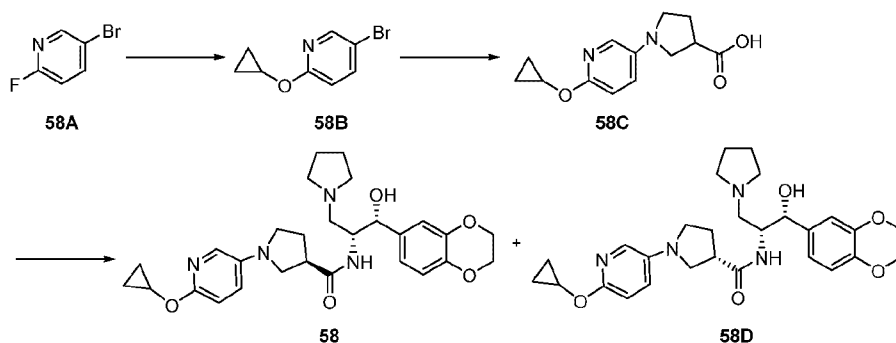
Example 57



[000603] Compounds **57** and **57A** were synthesized, by employing the procedures described for Compound **1** using Compound **28B** and Intermediate **E** in lieu of Compound **1B** and Intermediate **A**.

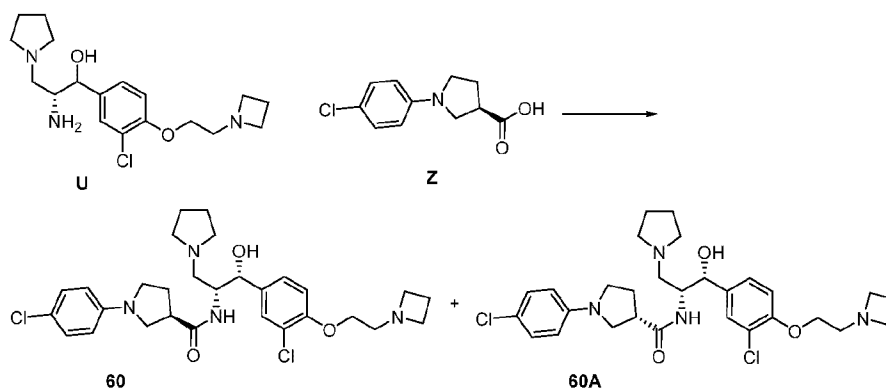
[000604] Compound **57**. LC-MS (ESI) m/z : 519 $[M+H]^+$; ^1H -NMR ($CDCl_3$, 400 MHz) δ (ppm) 0.81-0.85 (m, 4H), 1.72-1.74 (m, 5H), 2.21-2.23 (m, 2H), 2.61-2.65 (m, 4H), 2.72-2.73 (m, 2H), 2.93-2.96 (m, 1H), 3.40-3.52 (m, 4H), 3.72-3.73 (m, 1H), 4.10-4.13 (m, 1H), 4.75 (d, J = 4.8 Hz, 1H), 6.15-6.18 (m, 1H), 6.26 (d, J = 8.8 Hz, 1H), 7.21-7.23 (m, 3H), 7.26 (s, 1H), 7.43-7.44 (m, 1H), 7.94 (s, 1H); Chiral-HPLC condition, solvent: MeOH (0.5% DEA), column OJ-H (4.6 * 250 mm 5 um), Rt: 4.24 min.

[000605] Compound **57A**. LC-MS (ESI) m/z : 519 $[M+H]^+$; ^1H -NMR ($CDCl_3$, 400 MHz) δ (ppm) 0.83-0.85 (m, 4H), 1.77-1.79 (m, 5H), 2.16-2.18 (m, 2H), 2.56-2.59 (m, 4H), 2.68-2.71 (m, 2H), 2.93-2.94 (m, 1H), 3.40-3.57 (m, 4H), 3.76-3.77 (m, 1H), 4.11-4.13 (m, 1H), 4.73 (d, J = 4.8 Hz, 1H), 6.11-6.15 (m, 1H), 6.30 (d, J = 8.8 Hz, 1H), 7.24-7.24 (m, 3H), 7.26 (s, 1H), 7.36-7.37 (m, 1H), 8.02 (s, 1H); Chiral-HPLC condition, solvent: MeOH (0.1% DEA), column AS-H (4.6 * 250 mm 5 um), Rt: 4.90 min.



[000611] Compound **59** was synthesized, by employing the procedure described for Compound **1** using Intermediate **T** and Intermediate **Z** in lieu of Intermediate **A** and Compound **1B**. LC-MS (ESI) m/z : 534 $[M+H]^+$; ^1H -NMR (MeOD, 400 MHz) δ (ppm) 2.02-2.06 (m, 6H), 2.15-2.19 (m, 1H), 2.92-2.99 (m, 1H), 3.10-3.26 (m, 5H), 3.31-3.35 (m, 1H), 3.68-3.71 (m, 3H), 4.46-4.50 (m, 2H), 4.62-4.69 (m, 2H), 4.92-4.99 (m, 2H), 5.11-5.12 (m, 1H), 6.38-6.41 (d, $J = 9.2$ Hz, 1H), 6.57-6.60 (d, $J = 8.4$ Hz, 1H), 7.11-7.14 (m, 2H), 7.26-7.45 (m, 1H), 7.44-7.45 (d, $J = 2.0$ Hz, 1H), 8.07-8.09 (d, $J = 9.6$ Hz, 1H).

Example 60

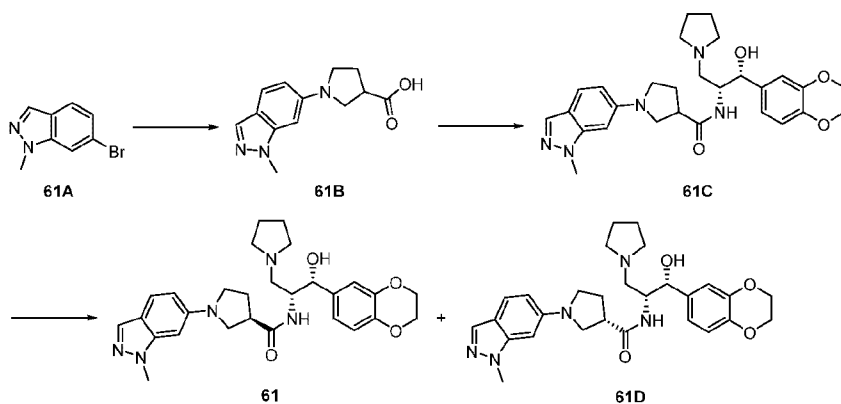


[000612] Compounds **60** and **60A** were synthesized, by employing the procedures described for Compound **1** using intermediates **U** and **Z** in lieu of intermediate **A** and Compound **1B**.

[000613] Compound **60**. LC-MS (ESI) m/z : 561 $[M+H]^+$. ^1H -NMR (MeOD, 400 MHz) δ (ppm) 1.77-1.78 (m, 4H), 2.05-2.12 (m, 4H), 2.58-2.62 (m, 4H), 2.71-2.84 (m, 4H), 3.01-3.07 (m, 1H), 3.14-3.19 (m, 1H), 3.25-3.31 (m, 3H), 3.39 (t, $J = 7.2$ Hz, 4H), 3.94 (t, $J = 5.6$ Hz, 2H), 4.20-4.25 (m, 1H), 4.82 (d, $J = 2.4$ Hz, 1H), 6.44 (d, $J = 8.8$ Hz, 2H), 6.86 (d, $J = 8.8$ Hz, 1H), 7.08 (d, $J = 9.2$ Hz, 2H), 7.15 (dd, $J = 8.4, 2.0$ Hz, 1H), 7.41 (d, $J = 1.6$ Hz, 1H). Chiral-HPLC condition, solvent: *n*-hexane (0.1% DEA) : EtOH (0.1% DEA) = 30:70, column IA (4.6 * 250 mm 5 μ m), R_t : 6.41 min.

[000614] Compound **60A**. LC-MS (ESI) m/z : 561 $[M+H]^+$. ^1H -NMR (MeOD, 400 MHz) δ (ppm) 1.75-1.77 (m, 4H), 1.81-1.86 (m, 1H), 2.07-2.12 (m, 3H), 2.55-2.61 (m, 4H), 2.68-2.70 (m, 2H), 2.84 (t, $J = 4.8$ Hz, 2H), 3.02-3.09 (m, 1H), 3.16-3.20 (m, 2H), 3.27-3.30 (m, 3H), 3.39 (t, $J = 6.8$ Hz, 4H), 3.99 (t, $J = 5.2$ Hz, 2H), 4.20-4.21 (m, 1H), 4.81 (d, $J = 2.0$ Hz, 1H), 6.43 (d, $J = 8.4$ Hz, 2H), 6.91 (d, $J = 8.4$ Hz, 1H), 7.06 (d, $J = 8.4$ Hz, 2H), 7.17 (d, $J = 7.8$ Hz, 1H), 7.38 (s, 1H). Chiral-HPLC condition, solvent: *n*-hexane (0.1% DEA) : EtOH (0.1% DEA) = 30:70, column O IA (4.6 * 250 mm 5 μ m), R_t : 10.69 min.

Example 61



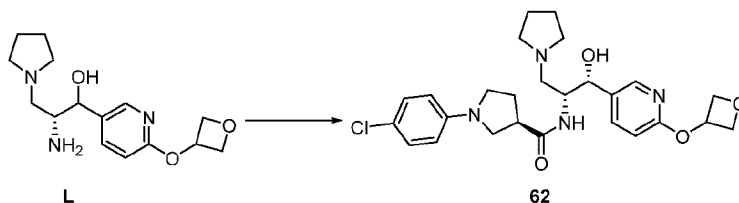
[000615] Compounds **61B**, **61** and **61D** were synthesized, by employing the procedures described for Compound **1B** and **1** using Compound **61A** and **61B** in lieu of Compound **1A** and **1B**.

[000616] Compound **61B**. LC-MS (ESI) m/z : 246 $[M+H]^+$; $^1\text{H-NMR}$ (DMSO- d_6 , 400 MHz) δ (ppm) 2.17-2.25 (m, 2H), 3.20-3.24 (m, 1H), 3.32-3.41 (m, 2H), 3.47-3.56 (m, 2H), 3.89 (s, 3H), 6.43 (s, 1H), 6.58 (dd, $J_1 = 9.6$ Hz, $J_2 = 2.0$ Hz, 1H), 7.50 (d, $J = 9.6$ Hz, 1H), 7.76 (d, $J = 2.0$ Hz, 1H).

[000617] Compound **61**. LC-MS (ESI) m/z : 506 $[M+H]^+$; $^1\text{H-NMR}$ (MeOD, 400 MHz) δ (ppm) 1.85-1.86 (m, 4H), 1.94-2.01 (m, 1H), 2.20-2.25 (m, 1H), 2.68-2.83 (m, 6H), 3.14-3.31 (m, 1H), 3.37-3.41 (m, 1H), 3.48-3.50 (m, 2H), 3.91 (s, 1H), 4.22 (s, 1H), 4.28-4.31 (m, 1H), 4.79 (d, $J = 3.2$ Hz, 1H), 6.32 (s, 1H), 6.62 (dd, $J_1 = 8.8$ Hz, $J_2 = 2.0$ Hz, 1H), 6.76-6.83 (m, 2H), 6.89 (d, $J = 2.0$ Hz, 1H), 7.51 (d, $J = 8.8$ Hz, 1H), 7.75 (d, $J = 0.8$ Hz, 1H).

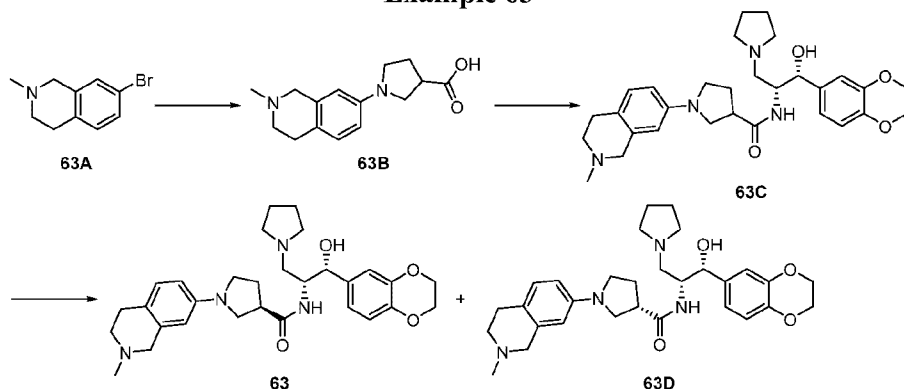
[000618] Compound **61D**. LC-MS (ESI) m/z : 506 $[M+H]^+$; $^1\text{H-NMR}$ (MeOD, 400 MHz) δ (ppm) 1.93-1.98 (m, 4H), 2.20-2.23 (m, 2H), 2.88-2.92 (m, 1H), 2.90-3.19 (m, 8H), 3.31-3.34 (m, 1H), 3.45-3.50 (m, 2H), 3.95 (s, 3H), 4.09-4.15 (m, 4H), 4.38-4.42 (m, 1H), 4.82 (d, $J = 2.8$ Hz, 1H), 6.28 (s, 1H), 6.62 (dd, $J_1 = 8.8$ Hz, $J_2 = 2.0$ Hz, 1H), 6.81-6.90 (m, 3H), 7.53 (d, $J = 8.8$ Hz, 1H), 7.76 (d, $J = 0.8$ Hz, 1H).

Example 62



[000619] Compound **62** was synthesized, by employing the procedure described for Compound **1** using Intermediate **L** and **Z** in lieu of Intermediate **A** and Compound **1B**. LC-MS (ESI) m/z : 502 $[M+H]^+$; ^1H -NMR (MeOD, 400 MHz) δ (ppm) 2.01-2.10 (m, 6H), 2.82-2.84 (m, 1H), 3.10-3.18 (m, 5H), 3.21-3.27 (m, 1H), 3.45-3.46 (m, 1H), 3.53-3.70 (m, 4H), 3.87-3.96 (m, 1H), 4.58-4.64 (m, 1H), 4.72-4.74 (m, 2H), 4.97-4.98 (m, 1H), 5.29-5.34 (m, 1H), 6.38-6.43 (m, 2H), 7.04-7.08 (m, 2H), 7.17-7.26 (m, 1H), 8.29-8.34 (m, 1H), 8.49 (s, 1H).

Example 63



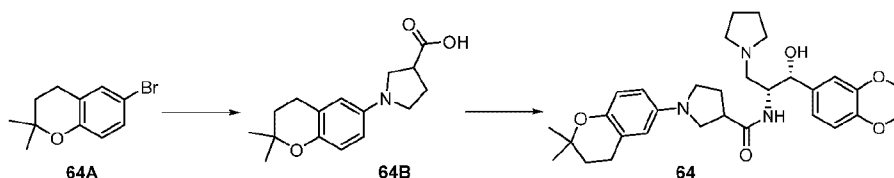
[000620] Compounds **63B**, **63**, and **63D** were synthesized, by employing the procedures described for Compounds **1B** and **1** using Compounds **63A** and **63B** in lieu of 1-chloro-4-iodobenzene and Compound **1B**.

[000621] Compound **63B**. LC-MS (ESI) m/z : 261 $[M+H]^+$; ^1H -NMR ($CDCl_3$, 400 MHz) δ (ppm) 2.05-2.15 (m, 3H), 2.53 (s, 3H), 2.62 (s, 2H), 2.81-2.97 (m, 4H), 3.35-3.37 (m, 2H), 3.75-3.81 (m, 2H), 6.17 (s, 1H), 6.37-6.39 (m, 1H), 7.85-6.89 (m, 1H).

[000622] Compound **63**. LC-MS (ESI) m/z : 521 $[M+H]^+$; ^1H -NMR (MeOD, 400 MHz) δ (ppm) 2.03-2.20 (m, 6H), 2.68-2.72 (m, 1H), 3.05 (s, 4H), 3.14-3.25 (m, 5H), 3.32-3.33 (m, 3H), 3.36-3.37 (m, 1H), 3.56-3.62 (m, 1H), 3.67-3.81 (m, 3H), 4.19-4.30 (m, 5H), 4.47-4.52 (m, 2H), 4.84 (d, J = 2.8 Hz, 1H), 6.28-6.29 (m, 1H), 6.55-6.58 (m, 1H), 6.82-6.92 (m, 3H), 7.09-7.11 (m, 1H). Chiral-HPLC condition, solvent: MeOH (0.5% DEA), column AD-H (250 * 4.6 mm 5 μ m), Rt: 2.56 min.

[000623] Compound **63D**. LC-MS (ESI) m/z : 521 $[M+H]^+$; ^1H -NMR (MeOD, 400 MHz) δ (ppm) 1.74-1.79 (m, 1H), 2.02-2.18 (m, 5H), 2.98-3.02 (s, 4H), 3.14-3.20 (m, 6H), 3.35-3.44 (m, 4H), 3.54-3.75 (m, 4H), 4.22-4.26 (m, 5H), 4.43-4.51 (m, 2H), 4.81 (d, J = 2.4 Hz, 1H), 6.30 (s, 1H), 6.54-6.56 (m, 1H), 6.78-6.94 (m, 3H), 7.05-7.08 (m, 1H). Chiral-HPLC condition, solvent: MeOH (0.5% DEA), column AD-H (250 * 4.6 mm 5 μ m), Rt: 6.78 min.

Example 64

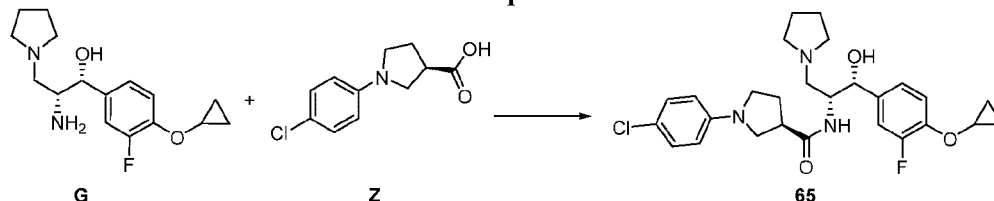


[000624] Compounds **64B** and **64** were synthesized, by employing the procedures described for Compounds **1B** and **1** using Compounds **64A** and **64B** in lieu of 1-chloro-4-iodobenzene and Compound **1B**.

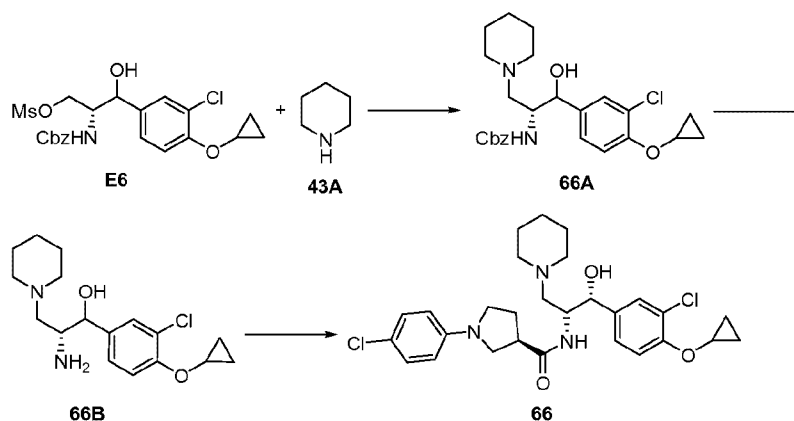
[000625] Compound **64B**. LC-MS (ESI) m/z : 276 $[M+H]^+$; $^1\text{H-NMR}$ (DMSO- d_6 , 400 MHz) δ (ppm) 1.21 (s, 6H), 1.90 (t, $J = 6.8$ Hz, 2H), 1.94-2.08 (m, 2H), 2.66 (t, $J = 6.8$ Hz, 2H), 3.07-3.27 (m, 5H), 6.18-6.27 (m, 2H), 6.49 (d, $J = 8.8$ Hz, 1H).

[000626] Compound **64**. LC-MS (ESI) m/z : 536 $[M+H]^+$; $^1\text{H-NMR}$ (MeOD, 400 MHz) δ (ppm) 1.32-1.35 (m, 6H), 1.83 (s, 2H), 2.16-2.41 (m, 6H), 2.83 (m, 2H), 3.21 (s, 3H), 3.40-3.46 (m, 2H), 3.58-3.69 (m, 5H), 3.80-3.91 (m, 1H), 3.88-4.10 (m, 4H), 4.19-4.55 (m, 1H), 4.83 (s, 1H), 6.76-7.30 (m, 6H).

Example 65



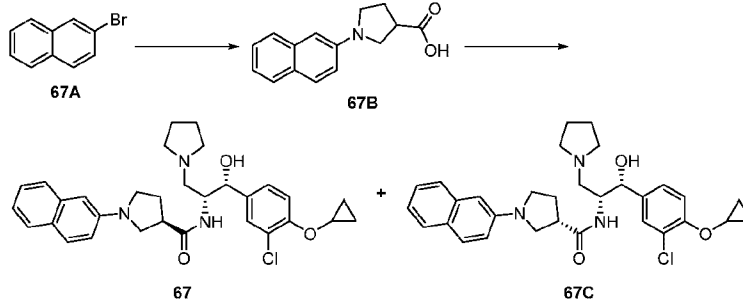
[000627] Compound **65** was synthesized, by employing the procedure described for Compound **1** using Intermediate **G** and **Z** in lieu of Intermediate **A** and Compound **1B**. LC-MS (ESI) m/z : 502 $[M+H]^+$; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ (ppm) 0.75-0.81 (m, 4H), 1.99-2.25 (m, 6H), 2.89-3.31 (m, 7H), 3.62 (m, 1H), 3.69-3.77 (m, 3H), 4.45 (s, 1H), 4.95 (s, 1H), 6.44 (d, $J = 8.8$ Hz, 2H), 6.98 (d, $J = 8.0$ Hz, 1H), 7.09-7.23 (m, 4H), 7.56 (s, 1H), 11.55 (s, 1H).

Example 66

[000628] Compound **66A** was synthesized, by employing the procedure described for Intermediate **A9** using Intermediate **E6** and Compound **43A** in lieu of Intermediate **A8** and pyrrolidine. LC-MS (ESI) m/z : 459 $[M+H]^+$.

[000629] Compound **66B** was synthesized, by employing the procedure described for Intermediate **E** using Compound **66A** in lieu of Intermediate **E7**, which was directly used for the next step without further purification. LC-MS (ESI) m/z : 325 $[M+H]^+$.

[000630] Compound **66** was synthesized, by employing the procedure described for Compound **1** using Compound **66B** and Intermediate **Z** in lieu of Intermediate **A** and Compound **1B**. LC-MS (ESI) m/z : 532.1 $[M+H]^+$; $^1\text{H-NMR}$ (MeOD, 400 MHz) δ (ppm) 0.55-0.83 (m, 4H), 1.53-1.59 (m, 1H), 1.71-1.74 (m, 1H), 1.84-1.85 (m, 1H), 1.87-1.98 (m, 4H), 2.05-2.21 (m, 2H), 2.54 (m, 1H), 2.94-3.32 (m, 6H), 3.46-3.54 (m, 3H), 3.72-3.88 (m, 2H), 4.58-4.63 (m, 1H), 6.44 (d, $J = 8.8$ Hz, 2H), 7.12 (d, $J = 9.2$ Hz, 2H), 7.33 (s, 2H), 7.53 (s, 1H).

Example 67

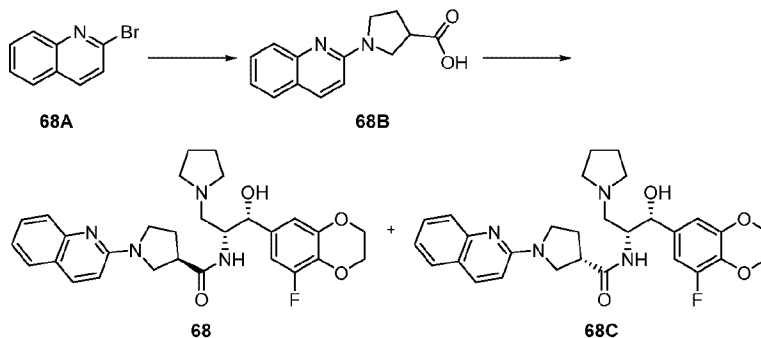
[000631] Compounds **67B**, **67**, and **67C** were synthesized, by employing the procedures described for Compounds **1B** and **1** using Compounds **67A**, **67B**, and Intermediate **E** in lieu of 1-chloro-4-iodobenzene, Compound **1B**, and Intermediate **A**.

[000632] Compound **67B**. LC-MS (ESI) m/z : 242 $[M+H]^+$; ^1H -NMR ($CDCl_3$, 400 MHz) δ (ppm) 2.17-2.20 (m, 2H), 2.98-3.02 (m, 1H), 3.25-3.30 (m, 1H), 3.39-3.52 (m, 3H), 6.65 (s, 1H), 6.90-6.92 (m, 1H), 6.96-7.00 (m, 1H), 7.15-7.19 (m, 1H), 7.47-7.55 (m, 3H).

[000633] Compound **67**. LC-MS (ESI) m/z : 534 $[M+H]^+$; ^1H -NMR (MeOD, 400 MHz) δ (ppm) 0.44-0.55 (m, 4H), 1.78-1.82 (m, 4H), 2.00-2.03 (m, 2H), 2.11-2.13 (m, 2H), 2.63-2.71 (m, 4H), 2.77-2.81 (m, 3H), 3.01-3.05 (m, 1H), 3.24-3.36 (m, 3H), 3.49-3.51 (m, 1H), 4.24-4.25 (m, 1H), 4.80 (d, $J = 2.0$ Hz, 1H), 6.62 (s, 1H), 6.85-6.88 (m, 1H), 7.00-7.04 (m, 1H), 7.08-7.14 (m, 2H), 7.19-7.23 (m, 1H), 7.37 (s, 1H), 7.53-7.57 (m, 3H). Chiral HPLC condition, solvent: *n*-hexane (0.1% DEA) : EtOH (0.1% DEA) = 30:70, column IA-H 250 * 4.6 mm 5 μ m), Rt: 4.88 min.

[000634] Compound **67C**. LC-MS (ESI) m/z : 534 $[M+H]^+$; ^1H -NMR (MeOD, 400 MHz) δ (ppm) 0.60-0.67 (m, 4H), 1.70-1.72 (m, 4H), 1.87-2.19 (m, 2H), 2.47-2.62 (m, 4H), 2.64-2.67 (m, 2H), 3.01-3.08 (m, 1H), 3.27-3.40 (m, 4H), 3.65-3.70 (m, 1H), 4.14-4.21 (m, 1H), 4.76 (d, $J = 2.8$ Hz, 1H), 6.63 (s, 1H), 6.88-6.90 (m, 1H), 7.00-7.04 (m, 1H), 7.14-7.20 (m, 3H), 7.30 (s, 1H), 7.47-7.56 (m, 3H). Chiral HPLC condition, solvent: *n*-hexane (0.1% DEA) : EtOH (0.1% DEA) = 40:60, column OZ-H 250 * 4.6 mm 5 μ m), Rt: 11.57 min.

Example 68



[000635] Compounds **68B**, **68**, and **68C** were synthesized, by employing the procedures described for Compounds **1B** and **7** using Compounds **68A**, **68B**, and Intermediate **C** in lieu of 1-chloro-4-iodobenzene, Compound **1B**, and Intermediate **A**.

[000636] Compound **68B**. LC-MS (ESI) m/z : 242 $[M+H]^+$; ^1H -NMR (MeOD, 400 MHz) δ (ppm) 2.24-2.27 (m, 2H), 3.09-3.12 (m, 1H), 3.54-3.80 (m, 4H), 6.85-6.87 (d, $J = 9.6$ Hz, 1H), 7.21-7.27 (t, 1H), 7.52-7.56 (t, 1H), 7.62 (d, $J = 9.6$ Hz, 1H), 7.68 (d, $J = 9.6$ Hz, 1H), 7.99 (d, $J = 9.6$ Hz, 1H).

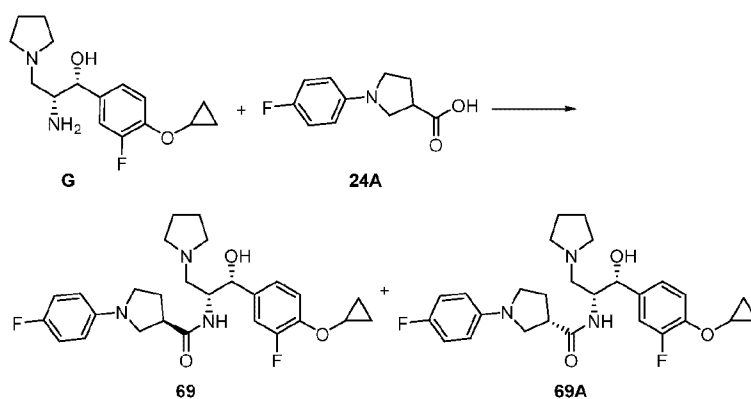
[000637] Compound **68**. LC-MS (ESI) m/z : 521 $[M+H]^+$; ^1H -NMR (MeOD, 400 MHz) δ (ppm) 1.76-1.79 (m, 4H), 2.07-2.15 (m, 2H), 2.57-2.79 (m, 6H), 3.06-3.21 (m, 2H), 3.43-3.49 (m, 1H), 3.65-3.72 (m, 2H), 4.09-4.18 (m, 5H), 4.68 (d, $J = 2.8$ Hz, 1H), 6.61-6.73 (m,

3H), 7.09-7.11 (m, 1H), 7.41-7.42 (m, 1H), 7.53-7.59 (m, 2H), 7.86 (d, $J = 9.2$ Hz, 1H).

Chiral-HPLC condition, solvent: MeOH (0.1% DEA), column AS-H 250 * 4.6 mm 5 μ m, Rt: 4.37 min.

[000638] Compound **68C**. LC-MS (ESI) m/z : 521 $[M+H]^+$; $^1\text{H-NMR}$ (MeOD, 400 MHz) δ (ppm) 1.79-1.81 (m, 4H), 1.97-2.05 (m, 1H), 2.11-2.23 (m, 1H), 2.55-2.80 (m, 7H), 3.15-3.19 (m, 1H), 3.56-3.78 (m, 5H), 4.23-4.27 (m, 5H), 4.78 (d, $J = 2.8$ Hz, 1H), 6.71-6.84 (m, 3H), 7.16-7.20 (m, 1H), 7.48-7.52 (m, 1H), 7.61-7.67 (m, 2H), 7.93 (d, $J = 9.2$ Hz, 1H). Chiral-HPLC condition, solvent: MeOH (0.1% DEA), column AS-H 250 * 4.6 mm 5 μ m, Rt: 4.55 min.

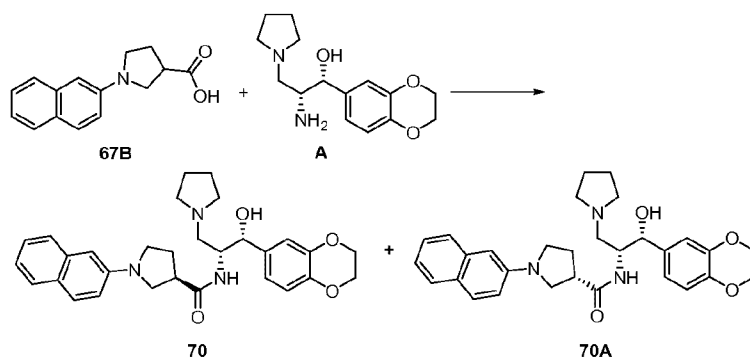
Example 69



[000639] Compounds **69** and **69A** were synthesized, by employing the procedures described for Compound **7** using Compound **24A** and Intermediate **G** in lieu of Compound **7B**, and Intermediate **A**.

[000640] Compound **69**. LC-MS (ESI) m/z : 486 $[M+H]^+$; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ (ppm) 0.78-0.82 (m, 4H), 1.82-1.87 (m, 3H), 2.02-2.19 (m, 4H), 2.85-3.36 (m, 1H), 3.75-3.78 (m, 1H), 4.26-4.28 (m, 1H), 5.06 (d, $J = 2.8$ Hz, 1H), 6.45-6.48 (m, 2H), 6.51-6.52 (m, 1H), 6.92-6.99 (m, 3H), 7.10-7.13 (dd, $J = 12.4, 2.0$ Hz, 1H), 7.19 (t, $J = 8.4$ Hz, 1H); Chiral-HPLC condition, solvent: MeOH (0.5% DEA), column OJ-H 250 * 4.6 mm 5 μ m, Rt: 2.62 min.

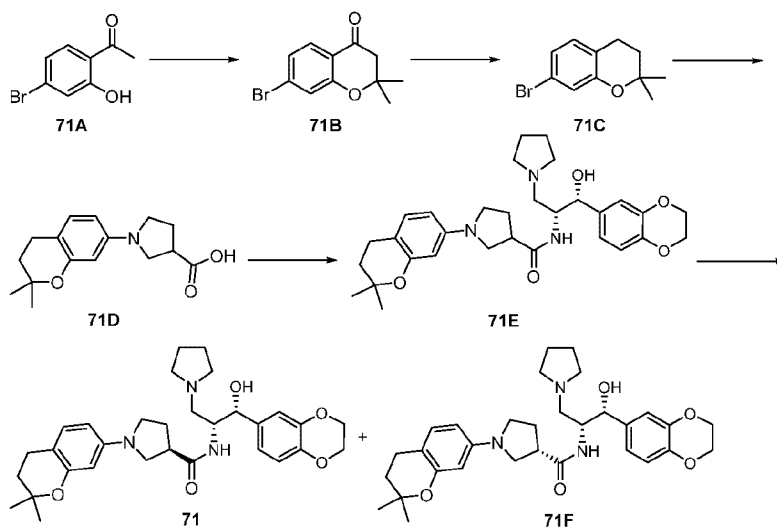
[000641] Compound **69A**. LC-MS (ESI) m/z : 486 $[M+H]^+$; $^1\text{H-NMR}$ (MEOD, 400 MHz) δ (ppm) 0.69-0.83 (m, 4H), 1.64-1.69 (m, 1H), 2.02-2.15 (m, 5H), 3.14-3.24 (m, 5H), 3.36-3.87 (m, 7H), 4.52-4.55 (m, 1H), 4.89 (d, $J = 2.8$ Hz, 1H), 6.60 (m, 2H), 6.92-6.95 (m, 2H), 7.16-7.23 (m, 2H), 7.33 (t, $J = 8.8$ Hz, 1H); Chiral-HPLC condition, solvent: MeOH (0.5% DEA), column OJ-H 250 * 4.6 mm 5 μ m, Rt: 4.62 min.

Example 70

[000642] Compounds **70** and **70A** were synthesized, by employing the procedures described for Compound **7** using Compound **67B** in lieu of Compound **7B**.

[000643] Compound **70**. LC-MS (ESI) m/z : 502 $[M+H]^+$; $^1\text{H-NMR}$ (MeOD, 400 MHz) δ (ppm) 1.69-1.78 (m, 4H), 1.99-2.22 (m, 2H), 2.61-2.70 (m, 4H), 2.75-2.77 (m, 2H), 2.91-2.93 (m, 1H), 3.02-3.03 (m, 1H), 3.25-3.28 (m, 1H), 3.38-3.44 (m, 2H), 4.03-4.10 (m, 4H), 4.20-4.21 (m, 1H), 4.72 (d, $J = 2.8$ Hz, 1H), 6.64 (s, 1H), 6.69-6.73 (m, 2H), 6.81 (s, 1H), 6.89-6.92 (m, 1H), 7.01-7.04 (m, 1H), 7.19-7.23 (m, 1H), 7.51-7.59 (m, 3H). Chiral-HPLC condition, solvent: MeOH (0.1% DEA), column IC-H 250 * 4.6 mm 5 μm , Rt: 4.9 min

[000644] Compound **70A**. LC-MS (ESI) m/z : 502 $[M+H]^+$; $^1\text{H-NMR}$ (MeOD, 400 MHz) δ (ppm) 1.69-1.76 (m, 4H), 1.88-2.18 (m, 2H), 2.61-2.71 (m, 4H), 2.74-2.76 (m, 2H), 3.03-3.07 (m, 1H), 3.25-3.32 (m, 2H), 3.39-3.41 (m, 2H), 4.09-4.11 (m, 4H), 4.19-4.20 (m, 1H), 4.69 (d, $J = 3.6$ Hz, 1H), 6.63 (s, 1H), 6.66-6.73 (m, 2H), 6.79 (s, 1H), 6.87-6.90 (m, 1H), 6.99-7.03 (m, 1H), 7.16-7.21 (m, 1H), 7.47-7.56 (m, 3H). Chiral-HPLC condition, solvent: MeOH (0.1% DEA), column IC-H 250 * 4.6 mm 5 μm , Rt: 7.09 min.

Example 71

[000645] A solution of Compound **71A** (4.50 g, 20.93 mmol), acetone (12.14 g, 0.209 mol), and pyrrolidine (1.51 g, 20.93 mmol) in toluene (50 mL) was stirred at 80 °C for 16 h. It was purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, from 0% to 8% v/v) to furnish Compound **71B**. ¹H-NMR (CDCl₃, 400 MHz) δ (ppm) 1.46 (s, 6H), 2.71 (s, 2H), 7.10-7.14 (m, 2H), 27.72 (d, J = 8.4 Hz, 1H).

[000646] A mixture of Compound **71B** (3.80 g, 5.90 mmol) and TES (5 mL) in TFA (5 mL) was stirred at 30 °C for 16 h. It was purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, from 0% to 5% v/v) to furnish Compound **71C**. ¹H-NMR (CDCl₃, 400 MHz) δ (ppm) 1.32 (s, 6H), 1.79 (t, J = 6.8 Hz, 2H), 2.71 (t, J = 6.8 Hz, 2H), 6.91-6.95 (m, 3H).

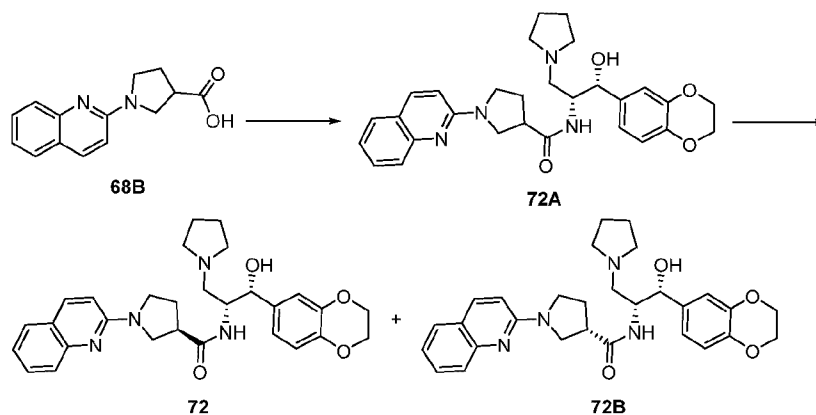
[000647] Compounds **71D**, **71**, and **71F** were synthesized, by employing the procedures described for Compounds **1B** and **1** using Compounds **71C** and **71D** in lieu of 1-chloro-4-iodobenzene and Compound **1B**.

[000648] Compound **71D**. LC-MS (ESI) m/z : 276 [M+H]⁺; ¹H-NMR (CDCl₃, 400 MHz) δ (ppm) 1.32 (s, 6H), 1.77 (t, J = 6.8 Hz, 2H), 2.26-2.30 (m, 2H), 2.68 (t, J = 6.8 Hz, 2H), 3.20-3.39 (m, 3H), 3.50-3.53 (m, 2H), 6.04 (s, 1H), 6.15 (d, J = 8.4 Hz, 1H), 6.91 (d, J = 8.4 Hz, 1H).

[000649] Compound **71**. LC-MS (ESI) m/z : 536 [M+H]⁺; ¹H-NMR (CDCl₃, 400 MHz) δ (ppm) 1.32 (s, 6H), 1.78 (t, J = 6.0 Hz, 2H), 2.09 (s, 4H), 2.23-2.30 (m, 2H), 2.73 (s, 2H), 2.87-2.97 (m, 2H), 3.11-3.23 (m, 3H), 3.31 (s, 1H), 3.49 (s, 2H), 3.66-3.79 (m, 4H), 4.11-4.23 (m, 4H), 4.48 (s, 1H), 4.86 (s, 1H), 6.51-6.59 (m, 2H), 6.72-6.80 (m, 2H), 6.91 (s, 1H), 7.01-7.04 (m, 1H), 7.71 (d, J = 8.8 Hz, 1H), 11.03 (s, 1H); Chiral-HPLC condition, solvent EtOH (0.1% DEA), column OZ-H (250 * 4.6 mm 5 μ m), RT: 4.94 min.

[000650] Compound **71F**. LC-MS (ESI) m/z : 536 [M+H]⁺; ¹H-NMR (CDCl₃, 400 MHz) δ (ppm) 1.32 (s, 6H), 1.78 (t, J = 6.0 Hz, 2H), 1.98-2.08 (m, 5H), 2.25-2.33 (m, 1H), 2.73 (s, 2H), 2.91-2.99 (m, 3H), 3.16 (s, 1H), 3.28 (s, 1H), 3.42-3.50 (m, 2H), 3.64-3.84 (m, 5H), 4.21 (s, 4H), 4.50 (s, 1H), 4.86 (s, 1H), 6.64-6.70 (m, 2H), 6.81 (s, 2H), 6.90 (s, 1H), 7.04 (d, J = 8.8 Hz, 1H), 7.80 (s, 1H), 10.89 (s, 1H); Chiral-HPLC condition, solvent EtOH (0.1% DEA), column OZ-H (250 * 4.6 mm 5 μ m), RT: 6.11 min.

Example 72

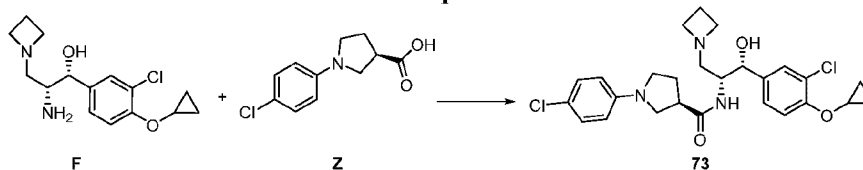


[000651] Compounds **72** and **72B** were synthesized, by employing the procedures described for Compound **1** using Compound **68B** in lieu of Compound **1B**.

[000652] Compound **72**. LC-MS (ESI) m/z : 503 $[M+H]^+$; $^1\text{H-NMR}$ (MeOD, 400 MHz) δ (ppm) 1.94 (m, 2H), 2.05 (m, 2H), 2.20 (m, 1H), 2.30 (m, 1H), 3.08 (m, 2H), 3.22 (m, 2H), 3.31-3.34 (m, 1H), 3.49-3.51 (m, 1H), 3.64 (m, 3H), 3.77-3.84 (m, 3H), 4.00-4.02 (m, 2H), 4.08-4.12 (m, 1H), 4.38-4.41 (m, 1H), 4.71 (m, 1H), 6.68-6.71 (m, 1H), 6.79-6.82 (m, 1H), 6.97-7.09 (m, 1H), 7.45 (t, $J = 7.6$ Hz, 1H), 7.72 (t, $J = 7.6$ Hz, 1H), 7.82 (d, $J = 7.6$ Hz, 2H), 8.29-8.35 (m, 1H); Chiral-HPLC condition, solvent: *n*-hexane (0.1% DEA) : EtOH (0.1% DEA) = 10: 90, column (S, S)-Whelk-O1 (250 * 4.6 mm 5 μm), R_t : 7.19 min.

[000653] Compound **72B**. LC-MS (ESI) m/z : 503 $[M+H]^+$; $^1\text{H-NMR}$ (MeOD, 400 MHz) δ (ppm) 1.76-1.81 (m, 1H), 1.92-1.94 (m, 2H), 2.04 (m, 2H), 2.24-2.26 (m, 1H), 3.05-3.10 (m, 2H), 3.27-3.33 (m, 2H), 3.44-3.54 (m, 2H), 3.62-3.74 (m, 4H), 3.88 (m, 1H), 4.12 (s, 4H), 4.42 (m, 1H), 4.72 (d, $J = 3.2$ Hz, 1H), 6.69 (d, $J = 8.0$ Hz, 1H), 6.77-6.79 (m, 1H), 6.87 (s, 1H), 7.03 (m, 1H), 7.42 (t, $J = 7.8$ Hz, 1H), 7.69 (t, $J = 7.8$ Hz, 1H), 7.78 (d, $J = 7.2$ Hz, 2H), 8.23-8.25 (m, 1H); Chiral-HPLC condition, solvent: *n*-hexane (0.1% DEA) : EtOH (0.1% DEA) = 10: 90, column (S, S)-Whelk-O1 (250 * 4.6 mm 5 μm), R_t : 8.56 min.

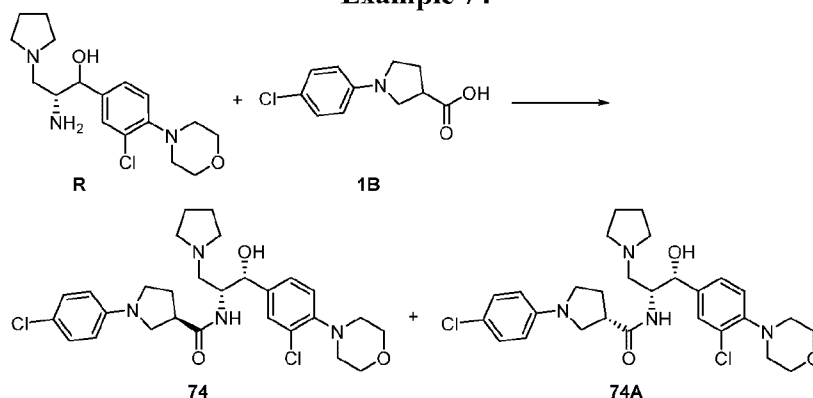
Example 73



[000654] Compound **73** was synthesized, by employing the procedure described for Compound **1** using Intermediates **F** and **Z** in lieu of Intermediate **A** and Compound **1B**. LC-MS (ESI) m/z : 504 $[M+H]^+$; $^1\text{H-NMR}$ (MeOD, 400 MHz) δ (ppm) 0.57-0.81 (m, 4H), 2.05-2.08 (m, 1H), 2.18-2.43 (m, 1H), 2.42-2.62 (m, 3H), 3.08-3.32 (m, 4H), 3.45-3.50 (m, 1H),

3.65-3.60 (m, 1H), 3.69-3.72 (m, 1H), 4.16-4.37 (m, 5H), 4.89 (d, $J = 2.4$ Hz, 1H), 6.42 (d, $J = 8.8$ Hz, 2H), 7.11 (d, $J = 8.8$ Hz, 2H), 7.25 (s, 2H), 7.50 (d, $J = 0.8$ Hz, 1H).

Example 74

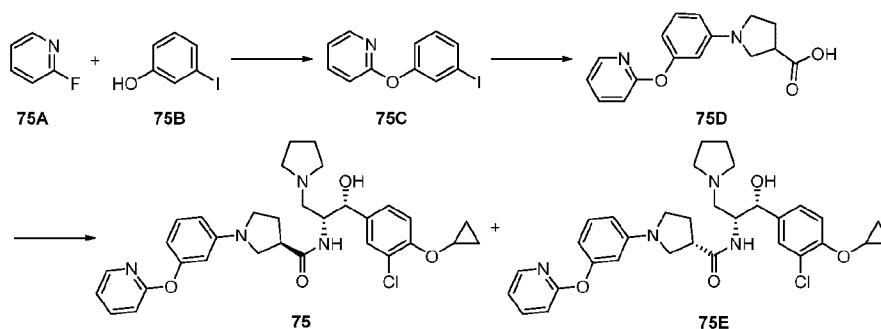


[000655] Compounds **74** and **74A** were synthesized, by employing the procedures described for Compound **1** using Intermediate **R** in lieu of Intermediate **A**.

[000656] Compound **74**. LC-MS (ESI) m/z : 547 $[M+H]^+$; $^1\text{H-NMR}$ (MeOD, 400 MHz) δ (ppm) 1.83 (s, 4H), 2.04-2.20 (m, 2H), 2.60-2.70 (m, 4H), 2.76-2.83 (m, 3H), 2.85-2.89 (m, 4H), 2.92-2.98 (m, 1H), 3.06-3.11 (m, 2H), 3.31-3.38 (m, 1H), 3.82 (t, $J = 10.4$ Hz, 4H), 4.27-4.31 (m, 1H), 4.88-4.91 (m, 1H), 6.50 (d $J = 9.2$ Hz, 2H), 7.02 (d $J = 8.4$ Hz, 1H), 7.12-7.14 (m, 2H), 7.23-7.25 (m, 1H), 7.46 (s, 1H); Chiral-HPLC condition, solvent MeOH (0.5% DEA), column AD-H 250 * 4.6 mm 5 μm , RT: 3.48 min.

[000657] Compound **74A**. LC-MS (ESI) m/z : 547 $[M+H]^+$; $^1\text{H-NMR}$ (MeOD, 400 MHz) δ (ppm) 1.76-1.84 (m, 5H), 2.08-2.15 (m, 1H), 2.55-2.72 (m, 6H), 2.94-2.97 (m, 4H), 3.03-3.09 (m, 1H), 3.16-3.19 (m, 2H), 3.26-3.31 (m, 2H), 3.78-3.80 (m, 4H), 4.21-4.25 (m, 1H), 4.83 (s, 1H), 6.43 (d $J = 8.8$ Hz, 2H), 7.01-7.07 (m, 3H), 7.19-7.21 (m, 1H), 7.40 (s, 1H); Chiral-HPLC condition, solvent MeOH (0.5% DEA), column AD-H 250 * 4.6 mm 5 μm , RT: 5.45 min.

Example 75



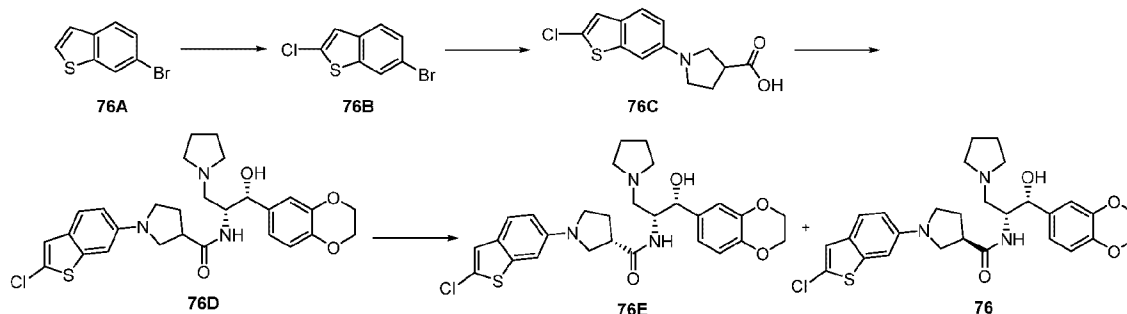
[000658] To a mixture of Compound **75B** (1.5 g, 6.82 mmol) and potassium *tert*-butoxide (1.53 g, 13.64 mmol) in DMSO (20 mL) was added Compound **75A** (662 mg, 6.82 mmol). The reaction mixture was heated at 100 °C for 6 hours. It was quenched with a saturated aqueous solution of ammonium chloride (100 mL) and extracted with ethyl acetate (80 mL x 3). The organic phase was washed with a saturated aqueous solution of ammonium chloride (100 mL x 5), dried over anhydrous sodium sulfate, filtered, and concentrated. The crude product was purified with silica gel column chromatography eluting with petroleum ether/ethyl acetate (20:1) to furnish Compound **75C**. LC-MS (ESI) *m/z*: 298 [M+H]⁺.

[000659] Compounds **75D**, **75**, and **75E** were synthesized, by employing the procedures described for Compounds **1B** and **1** using Compounds **75C**, **75D**, and Intermediate **E** in lieu of Compounds **1A**, **1B**, and Intermediate **A**.

[000660] Compound **75D**. LC-MS *m/z*: 283 [M-H]⁺; ¹H-NMR (CDCl₃, 400 MHz) δ (ppm) 8.23 (dd, *J* = 4.9, 1.5 Hz, 1H), 7.66 (ddd, *J* = 8.4, 7.2, 2.0 Hz, 1H), 7.22 (t, *J* = 8.1 Hz, 1H), 6.98 (ddd, *J* = 7.1, 5.0, 0.7 Hz, 1H), 6.86 (d, *J* = 8.3 Hz, 1H), 6.47-6.37 (m, 2H), 6.33 (t, *J* = 2.2 Hz, 1H), 3.55 (d, *J* = 7.3 Hz, 2H), 3.48-3.26 (m, 2H), 3.20 (p, *J* = 7.4 Hz, 1H), 2.36-2.21 (m, 2H), 2.07 (s, 1H).

[000661] Compound **75**. LC-MS (ESI) *m/z*: 577 [M+H]⁺; ¹H-NMR (MeOD, 400 MHz) δ (ppm) 8.16 (dd, *J* = 5.1, 1.4 Hz, 1H), 7.84-7.76 (m, 1H), 7.40 (d, *J* = 1.9 Hz, 1H), 7.3-7.17 (m, 3H), 7.11 (dd, *J* = 6.8, 5.5 Hz, 1H), 6.87 (d, *J* = 8.4 Hz, 1H), 6.43 (dd, *J* = 8.2, 2.1 Hz, 1H), 6.37-6.32 (m, 1H), 6.30 (t, *J* = 2.2 Hz, 1H), 4.87 (s, 1H), 4.29 (s, 1H), 3.77 (dd, *J* = 7.5, 4.4 Hz, 2H), 3.41-3.34 (m, 2H), 3.27-3.20 (m, 1H), 3.10 (m, 2H), 2.9-2.63 (m, 8H), 2.17-2.09 (m, 2H), 1.85 (s, 4H), 0.77-0.61 (m, 4H). Chiral-HPLC condition, solvent: *n*-hexane (0.1% DEA): EtOH (0.1% DEA) = 60:40, column IC 4.6 * 250 mm 5 μ m, Rt: 8.512 min.

[000662] Compound **75E**. LC-MS (ESI) *m/z*: 577 [M+H]⁺; ¹H-NMR (MeOD, 400 MHz) δ (ppm) 8.18-8.12 (m, 1H), 7.84-7.73 (m, 1H), 7.40 (d, *J* = 1.9 Hz, 1H), 7.35-7.16 (m, 3H), 7.10 (dd, *J* = 6.8, 5.5 Hz, 1H), 6.85 (d, *J* = 8.4 Hz, 1H), 6.42 (d, *J* = 8.6 Hz, 1H), 6.33 (d, *J* = 8.0 Hz, 1H), 6.27 (d, *J* = 2.2 Hz, 1H), 4.86 (d, *J* = 2.8 Hz, 1H), 4.28 (s, 1H), 3.89-3.78 (m, 1H), 3.39-3.36 (m, 1H), 3.24 (m, 2H), 3.15-3.04 (m, 2H), 2.85-2.53 (m, 6H), 2.22-2.11 (m, 1H), 1.83 (s, 3H), 0.84-0.59 (m, 4H). Chiral-HPLC condition, solvent: *n*-hexane (0.1% DEA): EtOH (0.1% DEA) = 60:40, column IC 4.6 * 250 mm 5 μ m, Rt: 21.180 min.

Example 76

[000663] To a mixture of LDA (7.8 mL, 15.5 mmol) in tetrahydrofuran (10 mL) was added Compound **76A** (3.0 g, 14.1 mmol) in tetrahydrofuran (5 mL) dropwise at -78°C and the mixture was stirred under nitrogen protection for 1 h. The solution was added to a mixture of carbon tetrachloride (5.5 mL, 56.6 mmol) in tetrahydrofuran (15 mL) at -78°C and the reaction mixture was stirred under nitrogen protection for 1.5 h. It was quenched with ammonium chloride solution (50 mL), warmed to room temperature, extracted with DCM (100 mL x 2), washed with water (30 mL) and brine (30 mL), dried over anhydrous sodium sulfate, evaporated and purified with flash column chromatography on silica gel (petroleum ether, 100% v/v) to furnish Compound **76B**. $^1\text{H-NMR}$ ($\text{DMSO-}d_6$, 400 MHz) δ (ppm) 7.55-7.58 (m, 2H), 7.72-7.74 (d, $J = 8.0$ Hz, 1H), 8.27 (m, 1H).

[000664] Compounds **76C**, **76E**, and **76** were synthesized, by employing the procedures described for Compounds **1B** and **1** using Compounds **76B**, and **76C** in lieu of Compounds **1A** and **1B**.

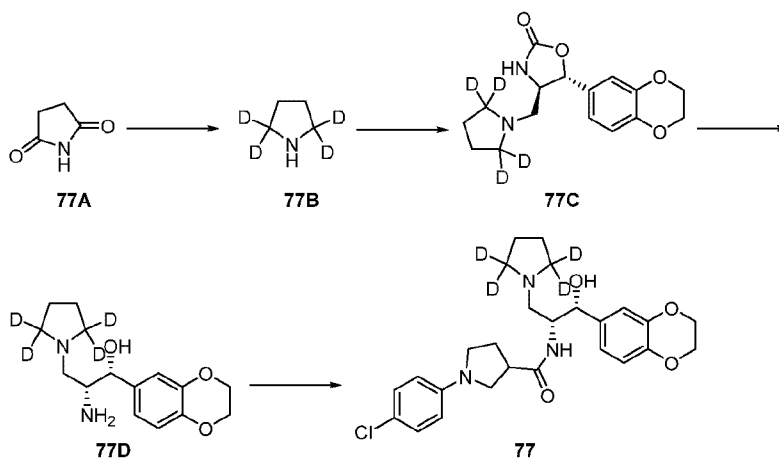
[000665] Compound **76C**. LC-MS (ESI) m/z : 282 $[\text{M}+\text{H}]^+$; $^1\text{H-NMR}$ ($\text{DMSO-}d_6$, 400 MHz) δ (ppm) 0.62-0.72 (m, 4H), 2.14-2.19 (m, 2H), 3.16-3.27 (m, 3H), 3.36-3.42 (m, 2H), 4.07 (s, 1H), 6.51-6.90 (m, 2H), 7.12-7.14 (m, 1H).

[000666] Compound **76E**. LC-MS (ESI) m/z : 542 $[\text{M}+\text{H}]^+$; $^1\text{H-NMR}$ (MeOD, 400 MHz) δ (ppm) 1.97-2.29 (m, 6H), 2.65-2.69 (m, 1H), 3.11-3.30 (m, 4H), 3.32-3.64 (m, 4H), 3.71-3.85 (m, 2H), 4.14-4.27 (m, 4H), 4.48-4.56 (m, 1H), 4.86 (m, 1H), 6.68-6.70 (m, 1H), 6.83-6.85 (m, 2H), 6.89-6.91 (m, 1H), 6.97-6.98 (m, 1H), 7.07-7.08 (m, 1H), 7.51-7.53 (m, 1H), 8.02-8.05 (m, 1H). Chiral-HPLC condition, solvent: MeOH (0.1% DEA) column OJ-H (4.6 * 250 mm 5 μm), Rt: 6.20 min.

[000667] Compound **76**. LC-MS (ESI) m/z : 542 $[\text{M}+\text{H}]^+$; $^1\text{H-NMR}$ (MeOD, 400 MHz) δ (ppm) 1.75-1.83 (m, 1H), 2.01-2.09 (m, 2H), 2.16-2.22 (m, 3H), 3.11-3.30 (m, 4H), 3.37-3.62 (m, 4H), 3.69-3.81 (m, 2H), 4.19-4.25 (m, 4H), 4.45-4.53 (m, 1H), 4.82-4.83 (m, 1H), 6.65-6.72 (m, 1H), 6.79-6.81 (m, 1H), 6.81-6.88 (m, 2H), 6.94-6.97 (m, 1H), 7.04 (m, 1H),

7.48-7.50 (m, 1H), 8.01-8.05 (m, 1H). Chiral-HPLC condition, solvent: MeOH (0.1% DEA) column OJ-H (4.6 * 250 mm 5 um), Rt: 4.02 min.

Example 77



[000668] To a solution of succinimide **77A** (0.99 g, 10 mmol) in THF (50 mL) was added lithium aluminum deuteride. The reaction mixture was stirred at 0 °C for 1 h and room temperature for 2 h, and heated to reflux for overnight. The reaction mixture was quenched with deuterium oxide, filtered, and washed with THF (50 mL x 2). The filtrate (**77B**) was directly used for the next step.

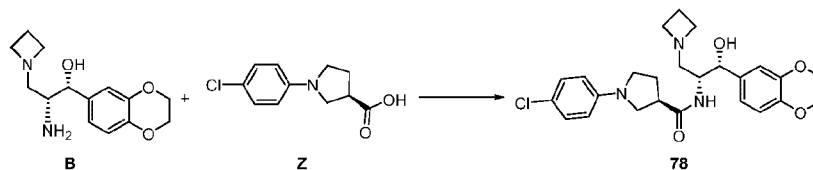
[000669] To a solution of Compound **77B** in THF (150 mL) was added Compound **A8** (880 mg, 2 mmol). The reaction was stirred at 55 °C for 15 hours. The solvent was evaporated under reduced pressure and the residue was extracted with acetate ethyl (50 mL x 3). The extracts were washed with brine (50 mL) and dried over sodium sulfate. Evaporation of the solvent under reduced pressure afforded the crude product. The crude product was purified with silica gel column chromatography (ethyl acetate in petroleum ether, from 20% to 60% v/v) to furnish Compound **77C**. LC-MS (ESI) m/z : 309 $[M+H]^+$.

[000670] To a solution of Compound **77C** (150 mg, 0.487 mmol) in methanol- d_4 (5.0 mL) was added Lithium hydroxide monohydrate (210 mg, 5.0 mmol). The reaction was stirred at reflux for 24 h. The solvent was evaporated under reduced pressure and the residue was extracted with THF (50 mL x 3). The extracts were dried over sodium sulfate. Evaporation of the solvent under reduced pressure afforded a crude product. The crude product Compound **77D** was directly used for the next step. LC-MS (ESI) m/z : 283 $[M+H]^+$.

[000671] Compound **77** was synthesized, by employing the procedure described for Compound **7** using Compound **77D** in lieu of Intermediate **A**. LC-MS (ESI) m/z : 486 $[M+H]^+$; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ (ppm) 7.16 (d, J = 8.8 Hz, 2 H), 6.85-6.75 (m, 3 H),

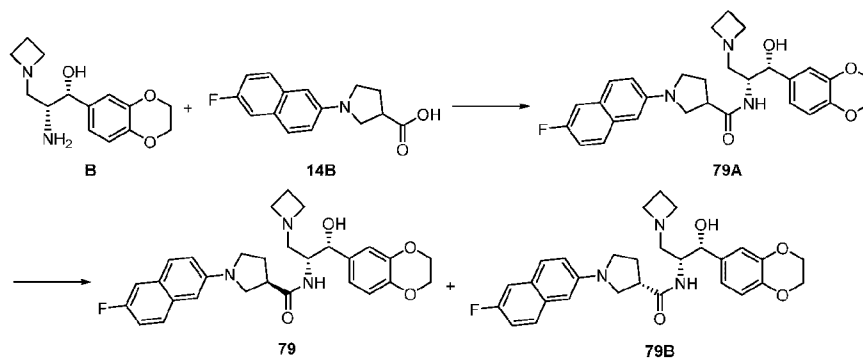
6.45 (d, $J = 8.8$ Hz, 2 H), 6.21 (m, 1 H), 4.98-4.95 (m, 5 H), 3.4-3.2 (m, 4 H), 2.98-2.89 (m, 3 H), 2.17-2.14 (m, 2 H), 1.80 (d, $J = 10.4$ Hz, 4 H).

Example 78



[000672] Compound **78** was synthesized, by employing the procedure described for Compound **1** using Intermediates **B** and **Z** in lieu of Intermediate **A** and Compound **1B**. LC-MS (ESI) m/z : 472 $[M+H]^+$; ^1H -NMR (MeOD, 400 MHz) δ (ppm) 2.07-2.24 (m, 2H), 2.39-2.44 (m, 1H), 2.57-2.71 (m, 2H), 3.12-3.24 (m, 1H), 3.31-3.32 (m, 1H), 3.33-3.35 (m, 2H), 3.45-3.48 (m, 1H), 3.54-3.58 (m, 1H), 4.19-4.28 (m, 9H), 4.81 (d, $J = 2.8$ Hz, 1H), 6.48-6.50 (m, 2H), 6.80-6.86 (m, 2H), 6.92 (s, 1H), 7.13-7.16 (m, 2H).

Example 79

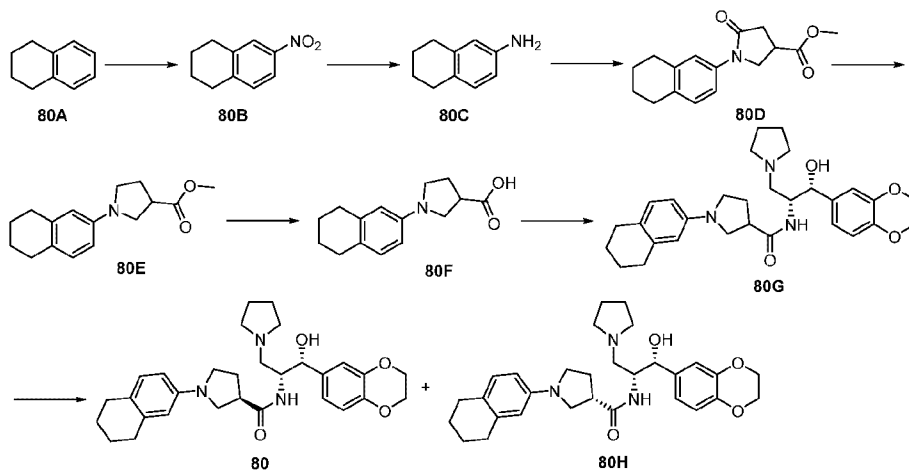


[000673] Compounds **79** and **79B** were synthesized, by employing the procedures described for Compound **1** using Intermediate **B** and Compound **14B** in lieu of Intermediate **A** and Compound **1B**.

[000674] Compound **79**. LC-MS (ESI) m/z : 506 $[M+H]^+$; ^1H -NMR (MeOD, 400 MHz) δ (ppm) 2.08-2.11 (m, 2H), 2.54-2.60 (m, 3H), 2.89-2.98 (m, 2H), 3.16-3.22 (m, 6H), 3.30-3.37 (m, 2H), 3.96-4.07 (m, 5H), 4.63 (d, $J = 2.8$ Hz, 1H), 6.64-6.78 (m, 4H), 6.90-6.92 (m, 1H), 7.01-7.05 (m, 1H), 7.18-7.21 (m, 1H), 7.51-7.53 (m, 2H). Chiral-HPLC, solvent: MeOH (0.1% DEA), column OJ-H (250 * 4.6 mm 5 μ m), Rt: 3.57 min.

[000675] Compound **79B**. LC-MS (ESI) m/z : 506 $[M+H]^+$; ^1H -NMR (MeOD, 400 MHz) δ (ppm) 1.79-1.84 (m, 1H), 2.19-2.23 (m, 1H), 2.37-2.44 (s, 1H), 2.57-2.62 (m, 1H), 3.17-3.19 (m, 1H), 3.33-3.57 (m, 6H), 4.11-4.32 (m, 9H), 4.80 (d, $J = 3.2$ Hz, 1H), 6.79-6.94 (m, 3H), 7.08-7.17 (m, 2H), 7.32-7.35 (m, 1H), 7.66-7.68 (m, 1H). Chiral-HPLC condition, solvent: MeOH (0.1% DEA), column OJ-H (250 * 4.6 mm 5 μ m), Rt: 7.04 min.

Example 80



[000676] To a solution of Compound **80A** (1.32 g, 10 mmol) in Ac₂O (10 mL) was added dropwise a solution of HNO₃ (3.15 g, 50 mmol) in Ac₂O (1 mL) at 0 °C. The mixture was stirred at 25 °C for 2 h, poured onto ice, extracted with ethyl acetate (50 mL x 2), washed with saturated aqueous sodium bicarbonate solution (50 mL x 2) and water (50 mL x 1), dried over anhydrous sodium sulfate, concentrated, and purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, 0-18% v/v) to furnish Compound **80B**. ¹H-NMR (CDCl₃, 400 MHz) δ (ppm) 1.84 (m, 4H), 2.85 (m, 4H), 7.18 (d, *J* = 8.0 Hz, 1H), 7.91 (m, 2H).

[000677] A mixture of Compound **80B** (10 g, 56.5 mmol), Pd/C (10%, 0.7 g) in MeOH (100 mL) was stirred at 25 °C under H₂ overnight. The mixture was filtered to remove the catalyst. The filtrate was concentrated and the resulting residue was purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, 15% v/v) to furnish Compound **80C**. LC-MS (ESI) *m/z*: 148 [M+H]⁺; ¹H-NMR (CDCl₃, 400 MHz) δ (ppm) 1.66 (m, 4H), 2.58 (m, 4H), 3.38 (br, 2H), 6.35 (d, *J* = 2.4 Hz, 1H), 6.39 (m, 1H), 6.78 (d, *J* = 8.0 Hz, 1H).

[000678] A mixture of Compound **80C** (1 g, 6.8 mmol), dimethyl 2-methylenesuccinate (1 g, 6.3 mmol) was stirred at 180 °C overnight. The mixture was purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, 60% v/v) to furnish Compound **80D**. LC-MS (ESI) *m/z*: 274 [M+H]⁺; ¹H-NMR (CDCl₃, 400 MHz) δ (ppm) 1.76 (m, 4H), 2.73 (m, 4H), 2.83 (m, 2H), 3.31 (m, 1H), 3.77 (s, 3H), 3.97 (m, 1H), 4.06 (m, 1H), 7.05 (d, *J* = 8.4 Hz, 1H), 7.24 (m, 2H).

[000679] To a solution of Compound **80D** (770 mg, 2.8 mmol) in THF (50 mL) was added BH₃ (1 M in THF, 5.1 mL, 5.1 mmol). The mixture was stirred at 60 °C for 3 h and

quenched with MeOH (5 mL) and water (50 mL). The mixture was concentrated to remove THF, extracted with DCM (50 mL x 3), dried over anhydrous sodium sulfate, and purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, 0-20% v/v) to furnish Compound **80E**. LC-MS (ESI) m/z : 260 $[M+H]^+$; ^1H -NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.76 (m, 4H), 2.27 (m, 2H), 2.73 (m, 4H), 3.18 (m, 1H), 3.36 (m, 2H), 3.51 (m, 2H), 3.72 (s, 3H), 6.29 (d, $J = 2.4$ Hz, 1H), 6.38 (m, sH), 6.92 (d, $J = 8.0$ Hz, 1H).

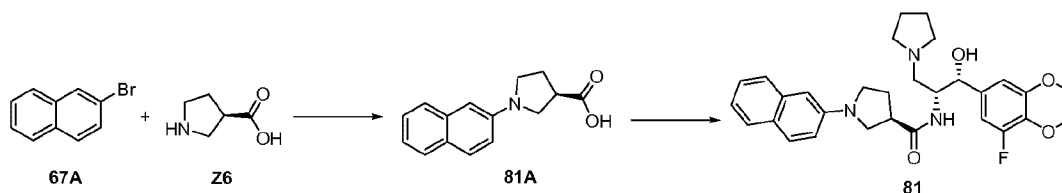
[000680] To a solution of Compound **80E** (470 mg, 1.8 mmol) in THF (10 mL) and water (2 mL) was added LiOH water (87 mg, 3.6 mmol). The mixture was stirred at 25 °C overnight, acidified by 1 M HCl, extracted with DCM (20 mL x 3), dried over anhydrous sodium sulfate and concentrated to furnish Compound **80F**. LC-MS (ESI) m/z : 246 $[M+H]^+$.

[000681] Compounds **80** and **80H** were synthesized, by employing the procedures described for Compound **1** using Compound **80F** in lieu of Compound **1B**.

[000682] Compound **80**. LC-MS (ESI) m/z : 506 $[M+H]^+$; ^1H -NMR (MeOD, 400 MHz) δ (ppm) 1.79 (s, 5H), 2.02-2.32 (m, 5H), 2.74 (m, 4H), 3.20 (m, 3H), 3.45-3.80 (m, 8H), 4.21 (s, 4H), 4.50 (m, 1H), 4.82 (d, $J = 3.2$ Hz, 1H), 6.79-7.07 (m, 6H). Chiral-HPLC condition, solvent: MeOH (0.1% DEA), column AS-H 250 * 4.6 mm 5 μ m, Rt: 4.12 min.

[000683] Compound **80H**. LC-MS (ESI) m/z : 506 $[M+H]^+$; ^1H -NMR (MeOD, 400 MHz) δ (ppm) 1.70 (m, 4H), 1.92-2.27 (m, 6H), 2.65 (m, 4H), 2.78 (m, 1H), 3.06 (m, 1H), 3.23-3.66 (m, 8H), 3.78-3.96 (m, 4H), 4.38 (m, 1H), 4.72 (d, $J = 3.2$ Hz, 1H), 6.64-7.03 (m, 6H). Chiral-HPLC condition, solvent: MeOH (0.1% DEA), column AS-H 250 * 4.6 mm 5 μ m, Rt: 4.85 min.

Example 81

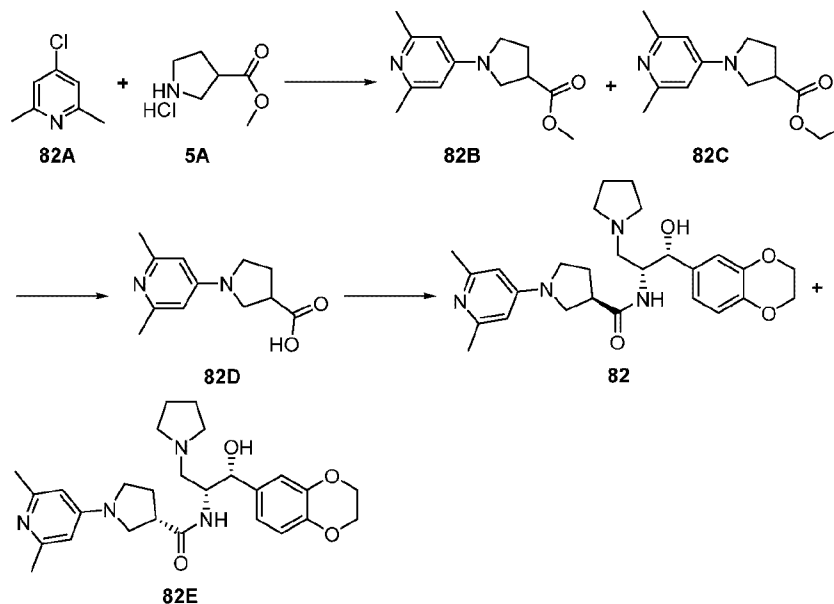


[000684] Compound **81A** was synthesized, by employing the procedure described for Compound **1B** using Compound **67A** and Intermediate **Z6** in lieu of 1-chloro-4-iodobenzene and Compound **1A**. LC-MS (ESI) m/z : 242 $[M+H]^+$;

[000685] Compound **81** was synthesized, by employing the procedure described for Compound **7** using Compound **81A** and Intermediate **C** in lieu of Compound **7B** and Intermediate **A**. LC-MS (ESI) m/z : 520 $[M+H]^+$; ^1H -NMR (MeOD, 400 MHz) δ (ppm) 1.72-1.78 (m, 4H), 1.97-2.13 (m, 2H), 2.57-2.65 (m, 4H), 2.72-2.74 (m, 2H), 2.85-2.87 (m, 1H), 3.02-3.06 (m, 1H), 3.27-3.28 (m, 1H), 3.37-3.42 (m, 2H), 4.04-4.19 (m, 5H), 4.71 (d, $J = 2.4$

Hz, 1H), 6.62-6.64 (m, 2H), 6.67-6.70 (m, 1H), 6.88-6.91 (m, 1H), 7.02-7.04 (m, 1H), 7.19-7.21 (m, 1H), 7.53-7.58 (m, 3H). Chiral-HPLC condition, solvent: MeOH (0.1% DEA), column OJ-H 250 * 4.6 mm 5 μ m, Rt: 5.44 min.

Example 82



[000686] A mixture of 4-chloro-2,6-dimethylpyridine (**82A**, 400 mg, 2.42 mmol), Compound **5A** (400 mg, 2.83 mmol), and triethylamine (708 mg, 7.01 mmol) in ethanol (6 mL) was stirred at 150 °C for 5 h. The reaction mixture was treated with water, and extracted with ethyl acetate (150 mL x 3). The extraction was washed with water, dried over sodium sulfate, concentrated, and purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, from 10% to 50% v/v) to furnish a mixture of Compound **82B** and **82C**. LC-MS (ESI) m/z : 235 $[M+H]^+$.

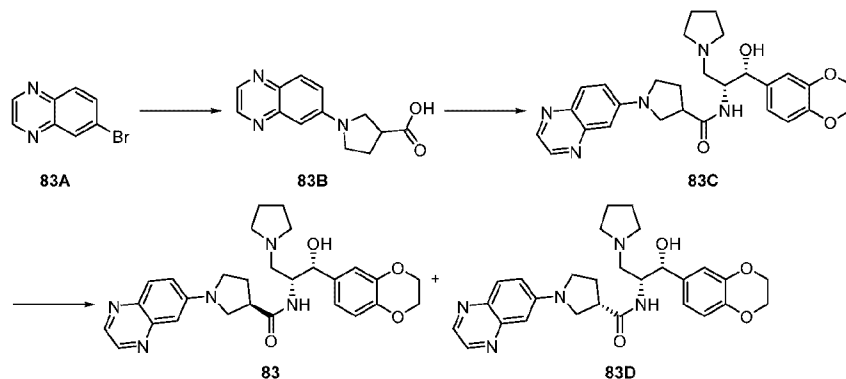
[000687] Compound **82D** was synthesized, by employing the procedure described for Compound **5C** using a mixture of Compound **82B** and **82C** in lieu of Compound **5B**. LC-MS (ESI) m/z : 221 $[M+H]^+$.

[000688] Compounds **82** and **82E** were synthesized, by employing the procedures described for Compound **7** using Compound **82D** in lieu of Compound **7B**,

[000689] Compound **82**. LC-MS (ESI) m/z : 481 $[M+H]^+$; $^1\text{H-NMR}$ (MeOD, 400 MHz) δ (ppm) 1.91-1.93 (m, 2H), 2.03-2.08 (m, 2H), 2.10-2.19 (m, 1H), 2.36 (s, 3H), 2.44 (s, 3H), 2.81-2.85 (m, 1H), 3.08-3.12 (m, 3H), 3.31-3.37 (m, 2H), 3.44-3.53 (m, 3H), 3.54-5.69 (m, 2H), 4.02-4.13 (m, 4H), 4.39-4.41 (m, 1H), 4.71 (d, $J = 2.8$ Hz, 1H), 6.25-6.26 (m, 1H), 6.42-6.43 (m, 1H), 6.71-6.73 (m, 1H), 6.78-6.79 (m, 1H), 6.82-6.84 (m, 1H). Chiral-HPLC condition, solvent: MeOD (0.1% DEA), column AD-H 250 * 4.6 mm 5 μ m, Rt: 2.81 min.

[000690] Compound **82E**. LC-MS (ESI) m/z : 481 $[M+H]^+$; ^1H -NMR (MeOD, 400 MHz) δ (ppm) 1.61-1.75 (m, 1H), 1.85-1.93 (m, 2H), 2.00-2.08 (m, 2H), 2.10-2.15 (m, 1H), 2.36 (s, 3H), 2.37 (s, 3H), 3.04-3.12 (m, 3H), 3.31-3.67 (m, 8H), 4.11 (s, 4H), 4.38-4.39 (m, 1H), 4.70 (d, J = 2.8 Hz, 1H), 6.37 (brs, 2H), 6.67-6.69 (m, 1H), 6.75-6.77 (m, 1H), 6.83-6.84 (m, 1H). Chiral-HPLC condition, solvent: MeOD (0.1% DEA), column AD-H 250 * 4.6 mm 5 μ m, Rt: 5.03 min.

Example 83



[000691] Compounds **83B**, **83**, and **83D** were synthesized, by employing the procedures described for Compounds **1B** and **1** using Compounds **83A** and **83B** in lieu of 1-chloro-4-iodobenzene and Compound **1B**.

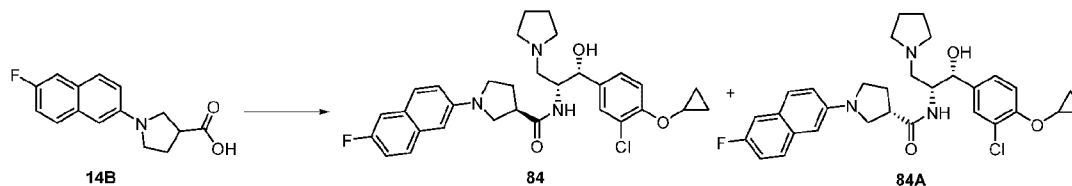
[000692] Compound **83B**. LC-MS (ESI) m/z : 244 $[M+H]^+$; ^1H -NMR (MeOD, 400 MHz) δ (ppm) 2.19-2.28 (m, 2H), 3.20-3.24 (m, 1H), 3.43-3.49 (m, 2H), 3.60-3.65 (m, 2H), 6.80 (d, J = 2.0 Hz, 1H), 7.35 (dd, J = 2.4, 9.2 Hz, 1H), 7.85 (d, J = 9.2 Hz, 1H), 8.50 (d, J = 1.6 Hz, 1H), 8.67 (d, J = 2.0 Hz, 1H).

[000693] Compound **83**. LC-MS (ESI) m/z : 504 $[M+H]^+$; ^1H -NMR (MeOD, 400 MHz) δ (ppm) 1.98-2.05 (m, 2H), 2.14-2.19 (m, 3H), 2.28-2.33 (m, 1H), 2.94-3.01 (m, 1H), 3.16-3.24 (m, 3H), 3.43-3.47 (m, 2H), 3.55-3.67 (m, 4H), 3.75-3.79 (m, 1H), 4.06-4.12 (m, 3H), 4.25-4.29 (m, 1H), 4.45-4.50 (m, 1H), 4.81 (d, J = 2.4 Hz, 1H), 6.79-6.88 (m, 3H), 6.93 (d, J = 2.0 Hz, 1H), 7.35-7.38 (m, 1H), 7.90 (d, J = 9.6 Hz, 1H), 8.51 (d, J = 2.0 Hz, 1H), 8.63 (d, J = 2.4 Hz, 1H); Chiral-HPLC condition, solvent: *n*-hexane (0.1% DEA) : EtOH (0.1% DEA) = 65:35, column OJ-H (4.6 * 250 mm 5 μ m), Rt: 7.84 min.

[000694] Compound **83D**. LC-MS (ESI) m/z : 504 $[M+H]^+$; ^1H -NMR (MeOD, 400 MHz) δ (ppm) 1.76-1.84 (m, 1H), 1.97-2.02 (m, 2H), 2.11-2.15 (m, 2H), 2.20-2.26 (m, 1H), 3.13-3.23 (m, 3H), 3.31-3.37 (m, 1H), 3.39-3.48 (m, 2H), 3.51-3.57 (m, 2H), 3.61-3.65 (m, 2H), 3.73-3.78 (m, 1H), 4.19 (s, 4H), 4.44-4.49 (m, 1H), 4.79 (d, J = 2.8 Hz, 1H), 6.77 (d, J = 8.0 Hz, 2H), 6.84 (dd, J = 1.6, 8.4 Hz, 1H), 7.38-7.41 (m, 1H), 7.87 (d, J = 9.2 Hz, 1H), 8.50

(d, $J = 2.4$ Hz, 1H), 8.57 (d, $J = 2.4$ Hz, 1H); Chiral-HPLC condition, solvent: *n*-hexane (0.1% DEA) : EtOH (0.1% DEA) = 65:35, column OJ-H (4.6 * 250 mm 5 μ m), Rt: 11.32 min.

Example 84

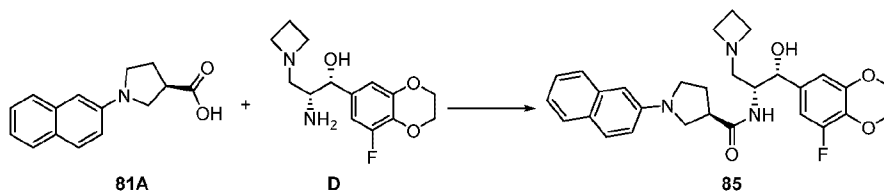


[000695] Compounds **84** and **84A** were synthesized, by employing the procedures described for Compound **1** using Compound **14B** and Intermediate **E** in lieu of Compound **1B** and Intermediate **A**.

[000696] Compound **84**. LC-MS (ESI) m/z : 552 $[M+H]^+$; ^1H -NMR (MeOD, 400 MHz) δ (ppm) 0.46-0.57 (m, 4H), 1.72 (s, 4H), 1.98-2.17 (m, 2H), 2.49-2.60 (m, 4H), 2.68-2.69 (m, 2H), 2.75-2.79 (m, 1H), 2.98-3.06 (m, 1H), 3.20-3.24 (m, 1H), 3.25-3.36 (m, 2H), 3.52-3.58 (m, 1H), 4.20-4.24 (m, 1H), 4.80 (s, 1H), 6.66 (s, 1H), 6.90-6.94 (m, 1H), 7.01-7.06 (m, 1H), 7.11 (s, 2H), 7.20 (d $J = 8.8$ Hz, 1H), 7.37 (s, 1H), 7.55 (d, $J = 8.8$ Hz, 1H), 7.60-7.64 (m, 1H); Chiral-HPLC condition, solvent: MeOH (0.5% DEA), column RegisCell (4.6 * 250 mm 5 μ m), RT: 4.78 min.

[000697] Compound **84A**. LC-MS (ESI) m/z : 552 $[M+H]^+$; ^1H -NMR (MeOD, 400 MHz) δ (ppm) 0.57-0.67 (m, 4H), 1.70 (s, 4H), 1.71-1.86 (m, 1H), 2.05-2.15 (m, 1H), 2.48-2.65 (m, 6H), 2.99-3.07 (m, 1H), 3.22-3.28 (m, 2H), 3.34-3.37 (m, 2H), 3.66-3.71 (m, 1H), 4.13-4.18 (m, 1H), 4.74 (d, $J = 4.8$ Hz, 1H), 6.66 (s, 1H), 6.90-6.92 (m, 1H), 6.97-7.02 (m, 1H), 7.10-7.19 (m, 3H), 7.28 (s, 1H), 7.48-7.52 (m, 2H); Chiral-HPLC condition, solvent: MeOH (0.5% DEA), column OJ-H (4.6 * 250 mm 5 μ m), RT: 5.99 min.

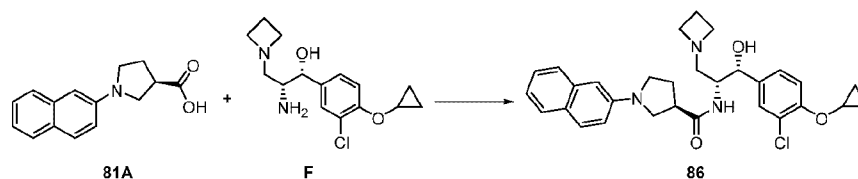
Example 85



[000698] Compound **85** was synthesized, by employing the procedure described for Compound **7** using Compound **81A** and Intermediate **D** in lieu of Compound **7B** and Intermediate **A**. LC-MS (ESI) m/z : 506 $[M+H]^+$; ^1H -NMR (MeOD, 400 MHz) δ (ppm) 2.01-2.13 (m, 4H), 2.78-2.83 (m, 3H), 3.03-3.05 (m, 1H), 3.25-3.28 (m, 1H), 3.40-3.46 (m, 6H), 4.02-4.10 (m, 5H), 4.65 (d, $J = 2.4$ Hz, 1H), 6.61-6.63 (m, 2H), 6.67-6.71 (m, 1H), 6.87-6.90

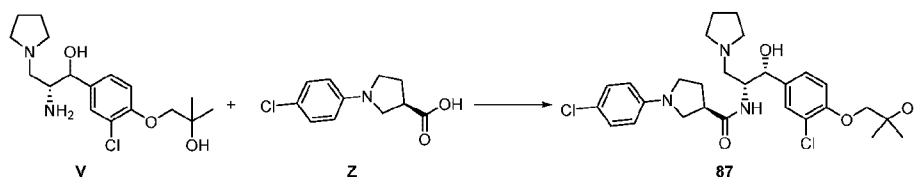
(m, 1H), 7.02-7.04 (m, 1H), 7.19-7.23 (m, 1H), 7.53-7.58 (m, 3H). Chiral-HPLC condition, solvent: MeOH (0.1% DEA), column AS-H 250 * 4.6 mm 5 μ m, Rt: 3.54 min.

Example 86

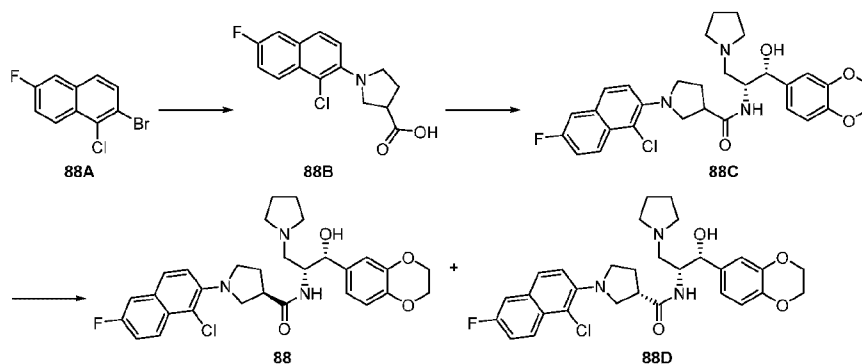


[000699] Compound **86** was synthesized, by employing the procedure described for Compound **7** using Compound **81A** and Intermediate **F** in lieu of Compound **7B** and Intermediate **A**. LC-MS (ESI) m/z : 520 $[M+H]^+$; ^1H -NMR (MeOD, 400 MHz) δ (ppm) 0.46-0.56 (m, 4H), 2.01-2.14 (m, 4H), 2.60-2.71 (m, 2H), 2.81-2.83 (m, 1H), 3.00-3.04 (m, 1H), 3.26-3.37 (m, 7H), 3.51-3.53 (m, 1H), 4.01-4.02 (m, 1H), 4.72 (d, $J = 2.4$ Hz, 1H), 6.62 (s, 1H), 6.86-6.89 (m, 1H), 7.00-7.04 (m, 1H), 7.10 (m, 2H), 7.20-7.21 (m, 1H), 7.35 (s, 1H), 7.53-7.57 (m, 3H). Chiral-HPLC condition, solvent: MeOH (0.1% DEA), column OZ-H 250 * 4.6 mm 5 μ m, Rt: 5.25 min.

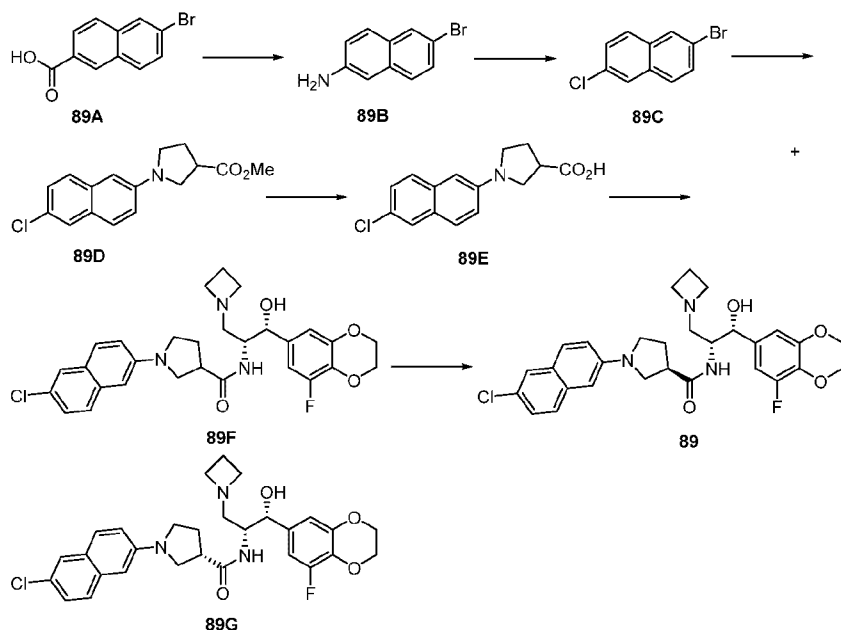
Example 87



[000700] Compound **87** was synthesized, by employing the procedure described for Compound **1** using Intermediates **Z** and **V** in lieu of Compound **7B** and Intermediate **A**. LC-MS (ESI) m/z : 550 $[M+H]^+$; ^1H -NMR (MeOD, 400 MHz) δ (ppm) 1.31 (s, 3H), 1.34 (s, 3H), 2.01-2.09 (m, 3H), 2.16-2.21 (m, 3H), 2.60-2.65 (m, 1H), 3.07-3.15 (m, 1H), 3.17-3.22 (m, 3H), 3.25-3.27 (m, 2H), 3.46-3.50 (m, 1H), 3.56-3.62 (m, 1H), 3.66-3.68 (m, 1H), 3.76-3.77 (m, 3H), 4.49-4.52 (m, 1H), 4.88 (d, $J = 2.4$ Hz, 1H), 6.46 (d, $J = 8.8$ Hz, 1H), 6.96 (d, $J = 8.0$ Hz, 1H), 7.12 (d, $J = 8.8$ Hz, 2H), 7.26 (dd, $J = 2.4, 8.4$ Hz, 1H), 7.51 (d, $J = 2.4$ Hz, 1H).



Example 89



[000705] To a solution of Compound **89A** (3.77 g, 15 mmol) and TEA (2.27 g, 22.5 mmol) in DMF (100 mL) was added DPPA (5.47 g, 22.5 mmol). The mixture was stirred at 25 °C for 3 h. Water (30 mL) was added, and the mixture was heated at 100 °C for 2 h. DMF was removed by distillation under vacuum. The residue was dissolved in ethyl acetate (300 mL) and saturated sodium bicarbonate (200 mL), and filtrated through celite. The organic phase was separated, washed with water (200 mL) and brine (200 mL), dried over anhydrous sodium sulfate, and evaporated to furnish Compound **89B**. LC-MS (ESI) m/z : 222 $[M+H]^+$; ^1H -NMR (DMSO- d_6 , 400 MHz) δ (ppm) 5.55 (s, 2H), 6.83 (s, 1H), 6.99 (d, J = 8.8 Hz, 1H), 7.36 (dd, J = 8.8, 1.6 Hz, 1H), 7.47 (d, J = 8.4 Hz, 1H), 7.59 (d, J = 8.8 Hz, 1H), 7.87 (s, 1H).

[000706] To a solution of Compound **89B** (2.04 g, 9.19 mmol) in 6 *N* HCl (20 mL) was added a solution of NaNO₂ (698 mg, 10.1 mmol) in water (10 mL) at 0 °C. The mixture was stirred at room temperature for 1 h. Then a solution of CuCl (4.55 g, 46 mmol) in 6 *N* HCl (10 mL) was added. The mixture was stirred at room temperature for 4 h, diluted with water (200 mL), and extracted with ethyl acetate (150 mL x 3). The organic layer was washed with water (150 mL x 3) and brine (150 mL x 1), dried over sodium sulfate, concentrated, and purified with flash column chromatography on silica gel (petroleum ether, 100% v/v) to yield Compound **89C**. ^1H -NMR (DMSO- d_6 , 400 MHz) δ (ppm) 7.60 (d, J = 8.8 Hz, 1H), 7.71 (d, J = 8.8 Hz, 1H), 7.90 (d, J = 8.8 Hz, 1H), 7.97 (d, J = 8.8 Hz, 1H), 8.11 (s, 1H), 8.28 (s, 1H).

[000707] A mixture of Compound **89C** (605 mg, 2.5 mmol), methyl pyrrolidine-3-carboxylate (355 mg, 2.75 mmol), Pd(OAc)₂ (56 mg, 0.25 mmol), XantPhos (145 mg, 0.25

mmol), and CsCO_3 (1.22 g, 3.75 mmol) in dioxane (30 mL) was refluxed for 18 h. After evaporation, the crude compound was suspended in water (50 mL), extracted with ethyl acetate (100 mL), and dried over anhydrous sodium sulfate. After evaporation of solvent, the crude product was purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, 8% v/v) to give Compound **89D**. LC-MS (ESI) m/z : 290 $[\text{M}+\text{H}]^+$; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ (ppm) 2.31-2.37 (m, 2H), 3.22-3.30 (m, 1H), 3.42-3.56 (m, 2H), 3.62-3.69 (m, 2H), 3.74 (s, 3H), 6.72 (d, $J = 2.0$ Hz, 1H), 6.98 (dd, $J = 8.8, 2.4$ Hz, 1H), 7.28 (dd, $J = 8.8, 2.0$ Hz, 1H), 7.54-7.65 (m, 3H).

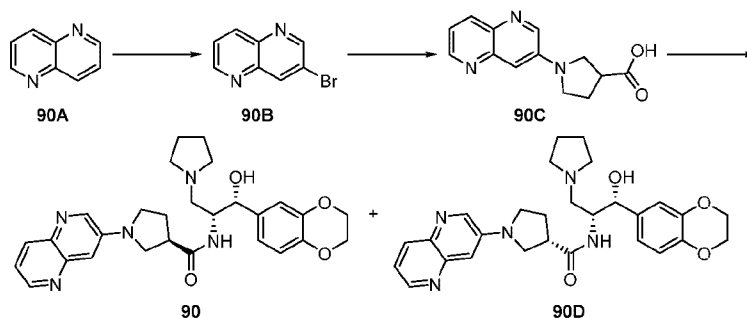
[000708] Compound **89E** was synthesized, by employing the procedure described for Compound **5C** using Compound **89D** in lieu of Compound **5B**. LC-MS (ESI) m/z : 276 $[\text{M}+\text{H}]^+$.

[000709] Compounds **89** and **89G** were synthesized, by employing the procedures described for Compound **1** using Intermediate **D** and Compound **89E** in lieu of Intermediate **A** and Compound **1B**.

[000710] Compound **89**. LC-MS (ESI) m/z : 540 $[\text{M}+\text{H}]^+$; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ (ppm) 2.10-2.21 (m, 4H), 2.82-2.86 (m, 2H), 2.95-3.01 (m, 2H), 3.25-3.52 (m, 8H), 4.02 (s, 1H), 4.22 (s, 4H), 4.92 (s, 1H), 6.21 (d, $J = 7.6$ Hz, 1H), 6.63 (s, 1H), 6.74 (m, 2H), 6.97 (dd, $J = 9.2, 2.0$ Hz, 1H), 7.29 (dd, $J = 8.8, 2.0$ Hz, 1H), 7.58-7.65 (m, 3H); Chiral-HPLC condition, solvent: MeOH (0.1% DEA), column: OJ-H (250 * 4.6 mm 5 μm), Rt: 3.44 min.

[000711] Compound **89G**. LC-MS (ESI) m/z : 540 $[\text{M}+\text{H}]^+$; $^1\text{H-NMR}$ (CD_3OD , 400 MHz) δ (ppm) 1.75-1.83 (m, 1H), 2.16-2.24 (m, 11H), 2.38-2.45 (m, 1H), 2.56-2.63 (m, 1H), 3.14-3.20 (m, 1H), 3.35-3.57 (m, 6H), 4.16-4.35 (m, 9H), 4.79 (d, $J = 2.4$ Hz, 1H), 6.75-6.81 (m, 3H), 7.04 (d, $J = 8.8$ Hz, 1H), 7.25 (dd, $J = 8.8, 2.4$ Hz, 1H), 7.57-7.65 (m, 3H), 8.01 (d, $J = 9.6$ Hz, 1H); Chiral-HPLC condition, solvent: MeOH (0.1% DEA), column: OJ-H (250 * 4.6 mm 5 μm), Rt: 6.20 min.

Example 90



[000712] To a solution of Compound **90A** (1.0 g, 7.69 mol) in acetic acid (8 mL) was added NaOAc (1.26 g, 15.38 mmol) and a solution of bromine (0.43 mL, 8.46 mmol) in acetic acid (2 mL) at 85 °C. The mixture was stirred at 85 °C for four hours, cooled to room temperature, and filtered. The filtrate was concentrated under vacuum and the residue was purified with flash column chromatography on silica gel (petroleum in ethyl acetate, 30% v/v) to render Compound **90B**. LC-MS (ESI) m/z : 209 $[M+H]^+$; ^1H -NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.70 (dd, $J = 4.0, 8.8$ Hz, 1H), 8.43 (d, $J = 8.4$ Hz, 1H), 8.63 (d, $J = 2.4$ Hz, 1H), 7.45 (t, $J = 2.4$ Hz, 1H).

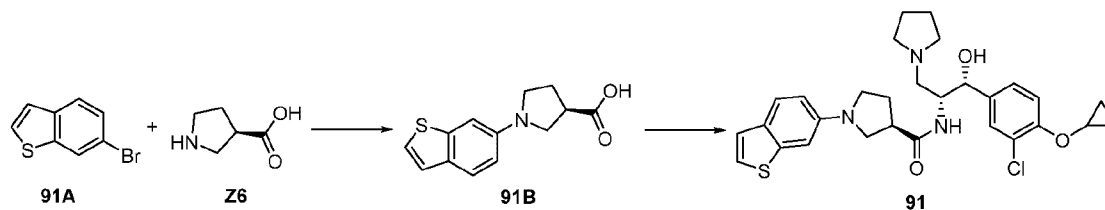
[000713] Compounds **90C**, **90**, and **90D** were synthesized, by employing the procedures described for Compounds **1B** and **1** using Compounds **90B** and **90C** in lieu of 1-chloro-4-iodobenzene and Compound **1B**.

[000714] Compound **90C**. LC-MS (ESI) m/z : 244 $[M+H]^+$.

[000715] Compound **90**. LC-MS (ESI) m/z : 504 $[M+H]^+$; ^1H -NMR (MeOD, 400 MHz) δ (ppm) 2.00-2.02 (m, 2H), 2.13-2.21 (m, 3H), 2.29-2.37 (m, 1H), 3.11-3.22 (m, 3H), 3.39-3.43 (m, 1H), 3.50-3.55 (m, 2H), 3.61-3.67 (m, 3H), 4.00-4.05 (m, 2H), 4.14-4.19 (m, 2H), 4.44-4.47 (m, 1H), 4.77 (d, $J = 2.8$ Hz, 1H), 6.75 (d, $J = 8.4$ Hz, 1H), 6.86-6.88 (m, 2H), 7.00 (d, $J = 2.0$ Hz, 1H), 7.67-7.70 (m, 1H), 8.15 (d, $J = 10.0$ Hz, 1H), 8.78-8.80 (m, 3H); Chiral-HPLC condition, solvent: MeOH (0.1% DEA), column RegisCell (4.6 * 250 mm 5 μ m), Rt: 4.53 min.

[000716] Compound **90D**. LC-MS (ESI) m/z : 504 $[M+H]^+$; ^1H -NMR (MeOD, 400 MHz) δ (ppm) 1.80-1.82 (m, 2H), 2.00-2.10 (m, 4H), 2.25-2.27 (m, 1H), 3.14-3.40 (m, 5H), 3.57-3.73 (m, 4H), 4.18 (s, 4H), 4.46-4.48 (m, 1H), 4.80 (m, 1H), 6.77-7.00 (m, 4H), 7.65 (m, 1H), 8.77 (m, 3H); Chiral-HPLC condition, solvent: MeOH (0.1% DEA), column RegisCell (4.6 * 250 mm 5 μ m), Rt: 5.63 min.

Example 91

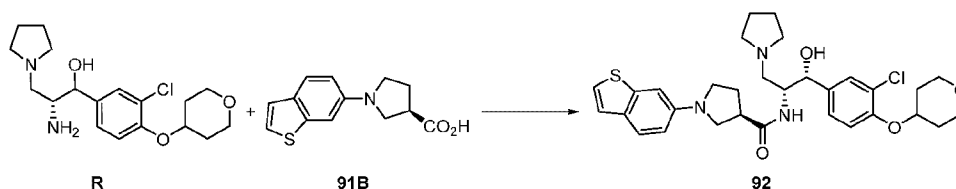


[000717] Compounds **91B** and **91** were synthesized, by employing the procedures described for Compounds **1B** and **1** using Compound **91A**, Intermediate **Z6**, Compound **91B**, and Intermediate **E** in lieu of 1-chloro-4-iodobenzene, Compounds **1A**, **1B**, and Intermediate **A**.

[000718] Compound **91B**. LC-MS (ESI) m/z : 248 $[M+H]^+$; $^1\text{H-NMR}$ (MeOD, 400 MHz) δ (ppm) 2.27-2.31 (m, 2H), 3.13-3.17 (m, 1H), 3.32-3.56 (m, 4H), 6.72-6.75 (m, 1H), 6.99 (s, 1H), 7.09-7.14 (m, 2H), 7.59-7.61 (m, 1H).

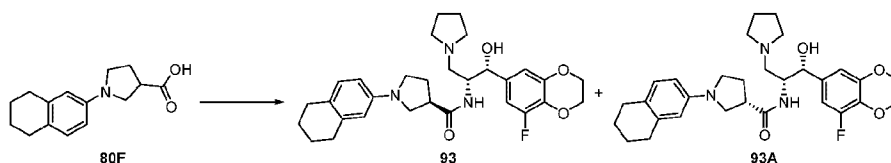
[000719] Compound **91**. LC-MS (ESI) m/z : 540 $[M+H]^+$; $^1\text{H-NMR}$ (MeOD, 400 MHz) δ (ppm) 0.50-0.68 (m, 4H), 2.05-2.28 (m, 6H), 2.62-2.66 (m, 1H), 3.13-3.25 (m, 4H), 3.39-3.63 (m, 6H), 3.79-3.87 (m, 1H), 4.55-4.60 (m, 1H), 4.93 (d, $J = 2.8$ Hz, 1H), 6.69-6.71 (m, 1H), 6.96 (s, 1H), 7.17 (s, 2H), 7.25-7.27 (m, 2H), 7.53 (s, 1H), 7.63-7.65 (m, 1H).

Example 92



[000720] Compound **92** was synthesized, by employing the procedure described for Compound **1** using Compound **91B** and Intermediate **R** in lieu of Compound **1B** and Intermediate **A**. LC-MS (ESI) m/z : 584 $[M+H]^+$; $^1\text{H-NMR}$ (MeOD, 400 MHz) δ (ppm) 1.57-1.72 (m, 2H), 1.84-1.89 (m, 2H), 2.03-2.29 (m, 7H), 2.65-2.69 (m, 1H), 3.12-3.29 (m, 3H), 3.36-3.52 (m, 5H), 3.61-3.89 (m, 5H), 4.40-4.47 (m, 1H), 4.55-4.59 (m, 1H), 4.91 (s, 1H), 6.76 (d, $J = 8.8$ Hz, 1H), 6.98 (d, $J = 8.4$ Hz, 1H), 7.03 (s, 1H), 7.19 (s, 2H), 7.27 (dd, $J = 8.4$, 2.0 Hz, 1H), 7.56 (d, $J = 2.0$ Hz, 1H), 7.65 (d, $J = 8.8$ Hz, 1H).

Example 93

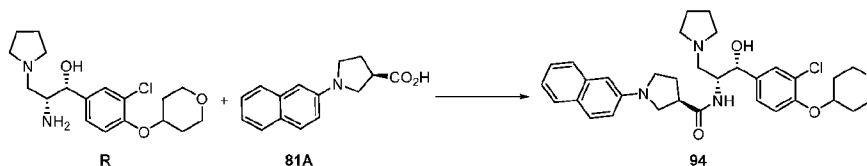


[000721] Compounds **93** and **93A** were synthesized, by employing the procedures described for Compound **1** using Compound **80F** and Intermediate **C** in lieu of Compound **1B** and Intermediate **A**.

[000722] Compound **93**. LC-MS (ESI) m/z : 524 $[M+H]^+$; $^1\text{H-NMR}$ (MeOD, 400 MHz) δ (ppm) 1.79 (m, 4H), 2.05-2.22 (m, 6H), 2.62-2.76 (m, 5H), 3.11-3.29 (m, 5H), 3.37-3.49 (m, 2H), 3.56-3.62 (m, 1H), 3.68-3.81 (m, 2H), 4.18 (m, 4H), 4.49 (m, 1H), 4.83 (d, $J = 2.4$ Hz, 1H), 6.35 (d, $J = 2.0$ Hz, 1H), 6.44 (m, 1H), 6.75 (s, 1H), 6.82 (m, 1H), 6.90 (d, $J = 8.0$ Hz, 1H), Chiral-HPLC condition, solvent: MeOH (0.5% DEA), column AD-H (250 * 4.6 mm 5 μm), Rt: 3.74 min.

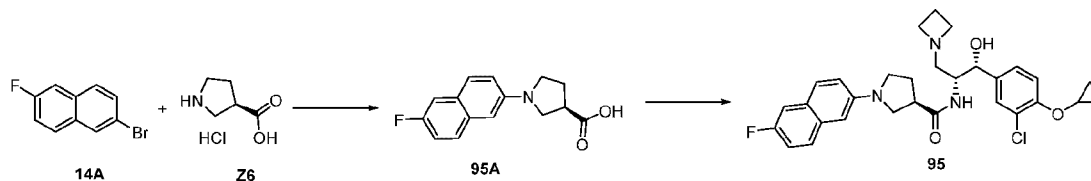
[000723] Compound **93A**. LC-MS (ESI) m/z : 524 $[M+H]^+$; $^1\text{H-NMR}$ (MeOD, 400 MHz) δ (ppm) 1.79 (m, 5H), 2.02-2.32 (m, 5H), 2.73 (m, 4H), 3.18 (m, 2H), 3.42-3.77 (m, 8H), 4.25 (s, 4H), 4.50 (m, 1H), 4.81 (d, $J = 2.4$ Hz, 1H), 6.79-7.07 (m, 5H). Chiral-HPLC condition, solvent: MeOH (0.5% DEA), column AD-H (250 * 4.6 mm 5 μm), R_t : 6.18 min.

Example 94



[000724] Compound **94** was synthesized, by employing the procedure described for Compound **1** using Compound **81A** and Intermediate **R** in lieu of Compound **1B** and Intermediate **A**. LC-MS (ESI) m/z : 578 $[M+H]^+$; $^1\text{H-NMR}$ (CD_3OD , 400 MHz) δ (ppm) 1.55-1.68 (m, 2H), 1.79-1.85 (m, 2H), 2.04-2.31 (m, 6H), 2.73-2.77 (m, 1H), 3.19-3.26 (m, 2H), 3.36-3.54 (m, 6H), 3.62-3.88 (m, 6H), 4.37-4.41 (m, 1H), 4.56-4.60 (m, 1H), 4.93 (s, 1H), 6.99 (dd, $J = 14.4, 4.4$ Hz, 2H), 7.15-7.17 (m, 1H), 7.28-7.34 (m, 2H), 7.57 (d, $J = 2.0$ Hz, 1H), 7.66-7.73 (m, 3H).

Example 95



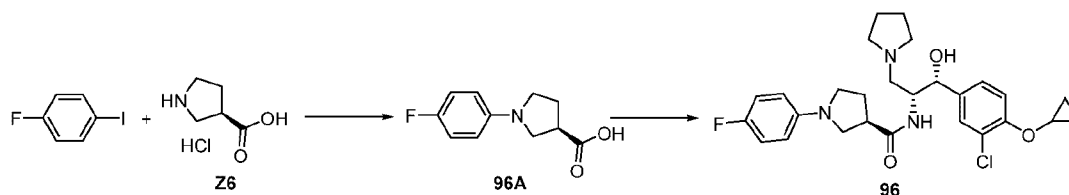
[000725] Compounds **95A** and **95** were synthesized, by employing the procedures described for Compounds **1B** and **1** using Compound **14A**, Intermediate **Z6**, Compound **95A**, and Intermediate **F** in lieu of 1-chloro-4-iodobenzene, Compounds **1A**, **1B**, and Intermediate **A**.

[000726] Compound **95A**. LC-MS (ESI) m/z : 260 $[M+H]^+$; $^1\text{H-NMR}$ ($\text{DMSO}-d_6$, 400 MHz) δ (ppm) 2.14-2.30 (m, 2H), 3.20-3.27 (m, 1H), 3.33-3.44 (m, 2H), 3.49-3.58 (m, 2H), 6.84 (s, 1H), 7.09 (d, $J = 8.8$ Hz, 1H), 7.21-7.27 (m, 1H), 7.48 (d, $J = 8.8$ Hz, 1H), 7.67-7.73 (m, 2H), 12.50 (s, 1H).

[000727] Compound **95**. LC-MS (ESI) m/z : 538 $[M+H]^+$; $^1\text{H-NMR}$ (CD_3OD , 400 MHz) δ (ppm) 0.48-0.69 (m, 4H), 2.07-2.15 (m, 1H), 2.23-2.30 (m, 1H), 2.40-2.49 (m, 1H), 2.56-2.66 (m, 2H), 3.10-3.18 (m, 1H), 3.31-3.38 (m, 2H), 3.42-3.62 (m, 4H), 4.16-4.42 (m, 5H), 4.92 (s, 1H), 6.73 (s, 1H), 6.98-7.01 (m, 1H), 7.13-7.19 (m, 1H), 7.25 (s, 2H), 7.32 (d, $J =$

10.0 Hz, 1H), 7.56 (s, 1H), 7.65 (d, $J = 9.2$ Hz, 1H), 7.73-7.77 (m, 1H), 8.03 (d, $J = 10.0$ Hz, 1H).

Example 96

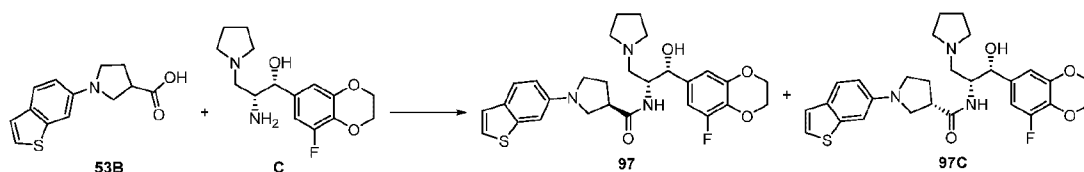


[000728] Compounds **96A** and **96** were synthesized, by employing the procedures described for Compounds **1B** and **1** using 1-fluoro-4-iodobenzene, Intermediate **Z6**, Compound **96A**, and Intermediate **E** in lieu of 1-chloro-4-iodobenzene, Compounds **1A**, **1B**, and Intermediate **A**.

[000729] Compound **96A**. LC-MS (ESI) m/z : 208 $[M-H]^+$; ^1H -NMR (CD_3OD , 400 MHz): δ (ppm) 2.25-2.32 (m, 2H), 3.20-3.36 (m, 3H), 3.47-3.49 (m, 2H), 6.54-6.57 (m, 2H), 6.90-6.94 (m, 2H).

[000730] Compound **96**. LC-MS (ESI) m/z : 502 $[M+H]^+$; ^1H -NMR (CD_3OD , 400 MHz) δ (ppm) 0.69-0.79 (m, 4H), 2.08-2.15 (m, 6H), 2.51-2.52 (m, 1H), 3.12-3.24 (m, 6H), 3.48-3.82 (m, 5H), 4.53-4.56 (m, 1H), 4.93-4.94 (m, 1H), 6.56 (m, 2H), 6.94 (m, 2H), 7.30 (m, 2H), 7.53 (m, 1H). Chiral-HPLC condition, solvent: MeOH (0.1% DEA), column: OZ-H 250 * 4.6 mm 5 μm , Rt: 4.31 min.

Example 97

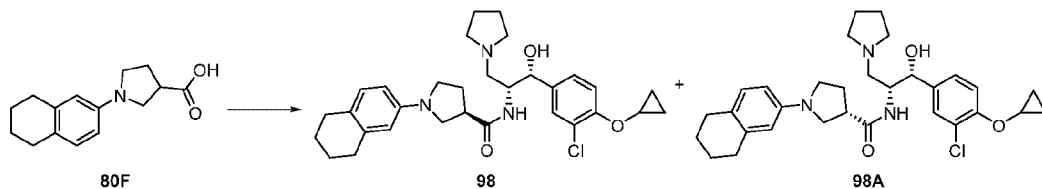


[000731] Compounds **97** and **97C** were synthesized, by employing the procedures described for Compound **1** using Compound **53B** and Intermediate **C** in lieu of Compound **1B** and Intermediate **A**.

[000732] Compound **97**. LC-MS (ESI) m/z : 526 $[M+H]^+$; ^1H -NMR (CD_3OD , 400 MHz) δ (ppm) 2.04-2.26 (m, 6H), 2.67-2.71 (m, 1H), 3.17-3.19 (m, 3H), 3.35-3.44 (m, 4H), 3.48-3.61 (m, 3H), 4.17-4.30 (m, 4H), 4.51-4.53 (m, 1H), 4.84 (d, $J = 2.8$ Hz, 1H), 6.73-6.86 (m, 3H), 7.00 (d, $J = 1.6$ Hz, 1H), 7.17-7.18 (m, 2H), 7.64-7.66 (m, 1H). Chiral-HPLC condition, solvent: *n*-hexane (0.1% DEA): EtOH (0.1% DEA) = 10:90, column: (S, S)-Whelk-01 250 * 4.6 mm 5 μm , Rt: 8.26 min.

[000733] Compound **97C**. LC-MS (ESI) m/z : 526 $[M+H]^+$; $^1\text{H-NMR}$ (CD_3OD , 400 MHz) δ (ppm) 1.73-1.86 (m, 6H), 2.08-2.12 (m, 1H), 2.57-2.63 (m, 5H), 3.01-3.07 (m, 1H), 3.22-3.34 (m, 4H), 4.15 (s, 5H), 4.68 (d, $J = 2.8$ Hz, 1H), 6.60-6.61 (m, 3H), 6.86 (d, $J = 2.0$ Hz, 1H), 7.01-7.03 (m, 2H), 7.48-7.50 (m, 1H). Chiral-HPLC condition, solvent: *n*-hexane (0.1% DEA): EtOH (0.1% DEA) = 10:90, column: (S, S)-Whelk-01 250 * 4.6 mm 5 μm), Rt: 12.87 min.

Example 98

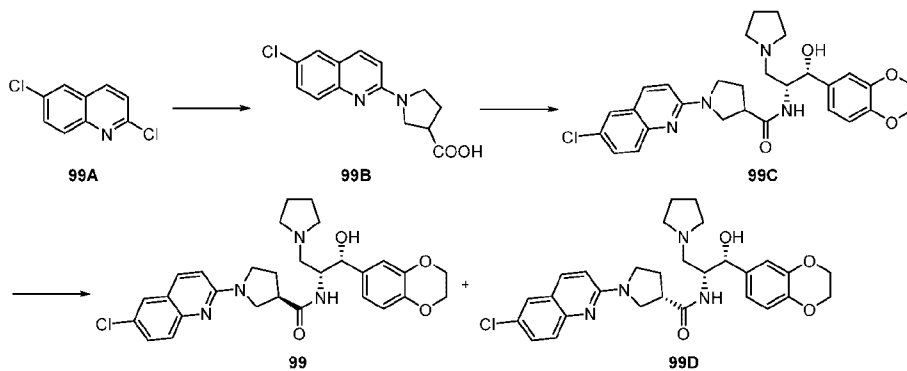


[000734] Compounds **98** and **98A** were synthesized, by employing the procedures described for Compound **1** using Compound **80F** and Intermediate **E** in lieu of 1-chloro-4-iodobenzene, Compound **1B**, and Intermediate **A**.

[000735] Compound **98**. LC-MS (ESI) m/z : 538 $[M+H]^+$; $^1\text{H-NMR}$ (CD_3OD , 400 MHz) δ (ppm) 0.61-0.75 (m, 4H), 2.81 (m, 4H), 2.06-2.34 (m, 6H), 2.65-2.79 (m, 5H), 3.19-3.28 (m, 4H), 3.45-3.81 (m, 8H), 4.53-4.57 (m, 1H), 6.65 (m, 2H), 7.01 (d, $J = 8.0$ Hz, 1H), 7.29 (m, 2H), 7.49 (s, 1H). Chiral-HPLC condition, solvent: *n*-hexane (0.1% DEA) : EtOH (0.1% DEA) = 90 : 10, column: IC (250 * 4.6 mm 5 μm), Rt: 11.74 min.

[000736] Compound **98A**. LC-MS (ESI) m/z : 538 $[M+H]^+$; $^1\text{H-NMR}$ (CD_3OD , 400 MHz) δ (ppm) 0.70-0.83 (m, 4H), 1.66-1.79 (m, 5H), 2.03-2.29 (m, 5H), 2.72-2.76 (m, 4H), 3.19-3.28 (m, 5H), 3.43-3.84 (m, 8H), 4.52-4.56 (m, 1H), 6.75-6.81 (m, 2H), 7.03 (d, $J = 8.4$ Hz, 1H), 7.34 (m, 2H), 7.49 (d, $J = 1.2$ Hz, 1H). Chiral-HPLC condition, solvent: *n*-hexane (0.1% DEA) : EtOH (0.1% DEA) = 90 : 10, column: IC (250 * 4.6 mm 5 μm), Rt: 14.51 min.

Example 99



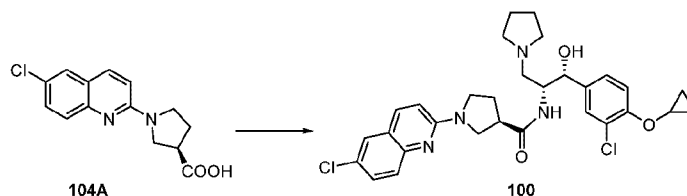
[000737] Compounds **99B**, **99**, and **99D** were synthesized, by employing the procedures described for Compounds **1B** and **1** using Compounds **99A** and **99B** in lieu of 1-chloro-4-iodobenzene and Compound **1B**.

[000738] Compound **99B**. LC-MS m/z : 275 $[M-H]^+$; ^1H -NMR (DMSO- d_6 , 400 MHz) δ (ppm) 1.96-2.14 (m, 2H), 2.67-2.71 (m, 1H), 3.43-3.54 (m, 4H), 3.65-3.69 (m, 1H), 6.85-6.88 (m, 1H), 7.41-7.44 (m, 1H), 7.48-7.50 (m, 1H), 7.73 (m, 1H), 7.91-7.93 (m, 1H).

[000739] Compound **99**. LC-MS (ESI) m/z : 537 $[M+H]^+$; ^1H -NMR (CD₃OD, 400 MHz) δ (ppm) 1.96-2.23 (m, 4H), 2.31-2.44 (m, 2H), 3.11-3.23 (m, 2H), 3.32-3.40 (m, 2H), 3.42-3.45 (m, 1H), 3.56-3.62 (t, J = 12.0 Hz, 1H), 3.65-3.77 (m, 3H), 3.83-3.96 (m, 2H), 4.00-4.22 (m, 4H), 4.48-4.50 (m, 1H), 4.80 (s, 1H), 6.77-6.82 (m, 1H), 6.91-6.92 (m, 2H), 7.11-7.20 (m, 1H), 7.81-7.83 (m, 1H), 7.90-7.93 (m, 1H), 8.00-8.03 (m, 1H), 8.36-8.39 (m, 1H); Chiral-HPLC condition, solvent: *n*-hexane (0.1% DEA):EtOH (0.1% DEA) = 10:90, column: OZ-H (250 * 4.6 mm 5 μ m), Rt: 4.64 min.

[000740] Compound **99D**. LC-MS (ESI) m/z : 537 $[M+H]^+$; ^1H -NMR (CD₃OD, 400 MHz) δ (ppm) 1.87-1.88 (m, 1H), 2.03-2.15 (m, 4H), 2.34-2.36 (m, 1H), 3.19-3.30 (m, 2H), 3.32-3.45 (m, 2H), 3.57-3.61 (m, 3H), 3.63-3.85 (m, 4H), 3.98-4.01 (m, 1H), 4.23 (s, 4H), 4.50-4.53 (m, 1H), 4.82-4.83 (m, 1H), 6.80-6.82 (m, 1H), 6.87-6.90 (m, 1H), 6.97 (m, 1H), 7.20-7.22 (m, 1H), 7.77-7.80 (m, 1H), 7.88-7.90 (m, 1H), 7.96-7.97 (m, 1H), 8.29-8.32 (m, 1H); Chiral-HPLC condition, solvent: *n*-hexane (0.1% DEA):EtOH (0.1% DEA) = 10:90, column: OZ-H (250 * 4.6 mm 5 μ m), Rt: 6.26 min.

Example 100

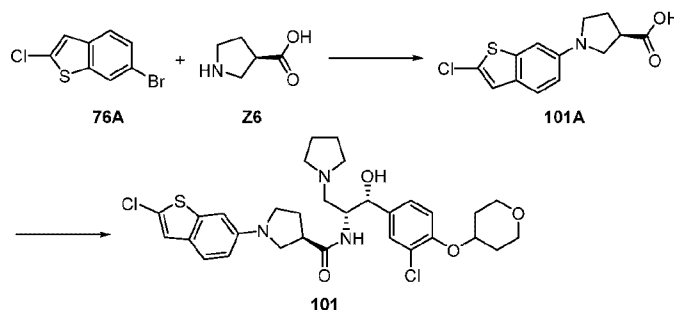


[000741] Compound **100** was synthesized, by employing the procedure described for Compound **1** using Compound **104A** and Intermediate **E** in lieu of Compound **1B** and Intermediate **A**.

[000742] Compound **100**. LC-MS (ESI) m/z : 569 $[M+H]^+$; ^1H -NMR (CD₃OD, 400 MHz) δ (ppm) 0.58-0.76 (m, 4H), 2.04-2.40 (m, 6H), 3.19-3.26 (m, 4H), 3.47-3.50 (m, 1H), 3.60-3.70 (m, 2H), 3.72-3.85 (m, 3H), 3.85-3.89 (m, 2H), 4.55-4.59 (m, 1H), 4.89 (m, 1H), 6.98-7.11 (m, 1H), 7.27-7.33 (m, 2H), 7.52 (s, 1H), 7.80-7.83 (m, 1H), 7.88-7.90 (m, 1H),

8.01-8.02 (m, 1H), 8.35-8.38 (m, 1H); Chiral-HPLC, solvent: MeOH (0.5% DEA) column: AS-H (4.6 * 250 mm 5 um), Rt: 4.48 min.

Example 101

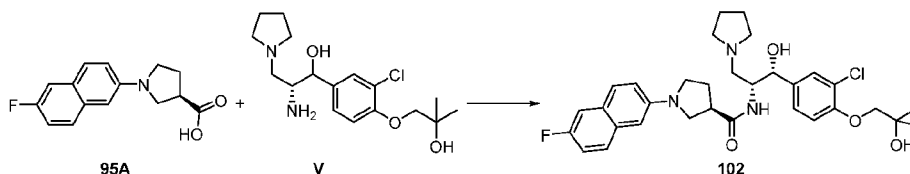


[000743] Compounds **101A** and **101** were synthesized, by employing the procedures described for Compounds **1B** and **1** using Compound **76A**, Intermediate **Z6**, Compound **101A**, and Intermediate **R** in lieu of 1-chloro-4-iodobenzene, Compounds **1A**, **1B**, and Intermediate **A**.

[000744] Compound **101A**. LC-MS (ESI) m/z : 282 $[M+H]^+$; $^1\text{H-NMR}$ (DMSO- d_6 , 400 MHz) δ (ppm) 1.94-1.99 (m, 1H), 2.10-2.15 (m, 1H), 2.64-2.67 (m, 1H), 3.16-3.29 (m, 3H), 3.41-3.44 (m, 1H), 6.62-6.65 (dd, $J = 9.2, 2.4$ Hz, 1H), 6.87 (d, $J = 1.6$ Hz, 1H), 7.22 (s, 1H), 7.49-7.51 (d, $J = 8.8$ Hz, 1H).

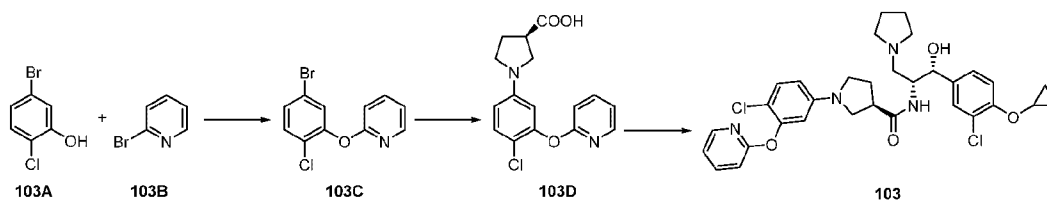
[000745] Compound **101**. LC-MS (ESI) m/z : 618 $[M+H]^+$; $^1\text{H-NMR}$ (CD $_3$ OD, 400 MHz) δ (ppm) 1.58-1.76 (m, 2H), 1.87-1.95 (m, 2H), 2.05-2.21 (m, 6H), 2.49 (m, 1H), 2.99 (m, 1H), 3.21-3.32 (m, 4H), 3.32-3.47 (m, 4H), 3.71-3.93 (m, 5H), 4.42-4.54 (m, 3H), 6.62-6.65 (dd, $J = 9.2, 2.4$ Hz, 1H), 6.77 (d, $J = 2.4$ Hz, 1H), 7.07 (s, 1H), 7.09 (s, 1H), 7.34 (dd, $J = 8.4, 2.4$ Hz, 1H), 7.45 (d, $J = 2.0$ Hz, 1H), 7.50 (d, $J = 8.8$ Hz, 1H).

Example 102



[000746] Compound **102** was synthesized, by employing the procedure described for Compound **1** using Compound **95A** and Intermediate **V** in lieu of Compound **1B** and Intermediate **A**. LC-MS (ESI) m/z : 584 $[M+H]^+$; $^1\text{H-NMR}$ (CD $_3$ OD, 400 MHz) δ (ppm) 1.22 (s, 3H), 1.25 (s, 3H), 2.00-2.03 (m, 2H), 2.12-2.25 (m, 4H), 2.76-2.80 (m, 1H), 3.14-3.24 (m, 3H), 3.32-3.49 (m, 4H), 3.57-3.79 (m, 5H), 4.50-4.53 (m, 1H), 4.88 (s, 1H), 6.78 (d, $J = 1.6$ Hz, 1H), 6.95 (d, $J = 8.8$ Hz, 1H), 7.01 (d, $J = 9.2$ Hz, 1H), 7.10-7.15 (m, 1H), 7.25-7.31 (m, 2H), 7.53 (d, $J = 2.0$ Hz, 1H), 7.64-7.69 (m, 1H).

Example 103



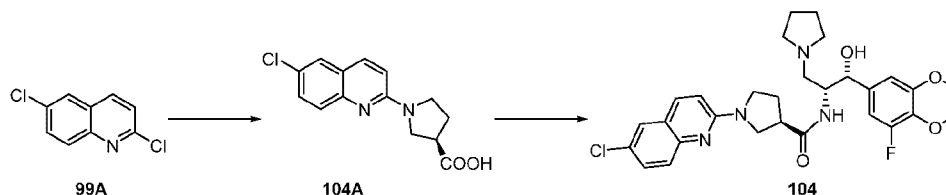
[000747] A mixture of Compound **103A** (4.5 g, 21.8 mmol), Compound **103B** (3.43 g, 21.8 mmol), and K_2CO_3 (7.5 g, 54.4 mmol) in DMF (18 mL) was stirred at 150 °C for 18 h. The reaction mixture was treated with water and extracted with ethyl acetate (150 mL x 3). The extracts were washed with water (50 mL), dried over sodium sulfate, concentrated, and purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, from 5% to 20% v/v) to furnish Compound **103C**. LC-MS (ESI) m/z : 283.0 $[M+H]^+$; ^1H -NMR ($CDCl_3$, 400 MHz) δ (ppm) 6.90-6.97 (m, 2H), 7.08-7.10 (m, 1H), 7.18-7.30 (m, 2H), 7.64-7.68 (m, 1H), 8.07-8.08 (m, 1H).

[000748] Compounds **103D** and **103** were synthesized, by employing the procedures described for Compounds **1B** and **1** using Compound **103C**, Intermediate **Z6**, Compound **103D**, and Intermediate **E** in lieu of 1-chloro-4-iodobenzene, Compound **1A**, **1B**, and Intermediate **A**.

[000749] Compound **103D**. LC-MS (ESI) m/z : 319.1 $[M+H]^+$.

[000750] Compound **103**. LC-MS (ESI) m/z : 611.2 $[M+H]^+$; ^1H -NMR (CD_3OD , 400 MHz) δ (ppm) 0.57-0.76 (m, 4H), 2.04-2.20 (m, 6H), 2.56-2.60 (m, 1H), 3.11-3.30 (m, 6H), 3.50-3.51 (m, 1H), 3.58-3.73 (m, 4H), 4.50-4.55 (m, 1H), 6.36-6.41 (m, 2H), 6.89 (d, $J = 8.4$ Hz, 1H), 7.09-7.12 (m, 1H), 7.25-7.28 (m, 3H), 7.48 (s, 1H), 7.82-7.83 (m, 1H), 8.08-8.11 (m, 2H).

Example 104

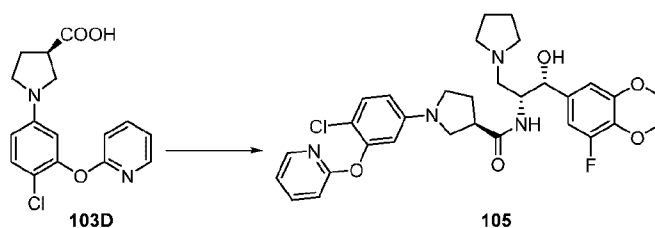


[000751] Compounds **104A** and **104** were synthesized, by employing the procedures described for Compounds **1B** and **1** using Compound **99A**, Intermediate **Z6**, Compound **104A**, and Intermediate **C** in lieu of 1-chloro-4-iodobenzene, Compounds **1A**, **1B**, and Intermediate **A**.

[000752] Compound **104A**. LC-MS m/z : 275 $[M-H]^+$; ^1H -NMR (DMSO- d_6 , 400 MHz) δ (ppm) 1.97-2.13 (m, 2H), 2.68-2.71 (m, 1H), 3.42-3.54 (m, 4H), 3.65-3.67 (m, 1H), 6.85-6.88 (m, 1H), 7.42-7.44 (m, 1H), 7.48-7.50 (m, 1H), 7.73 (m, 1H), 7.91-7.93 (m, 1H).

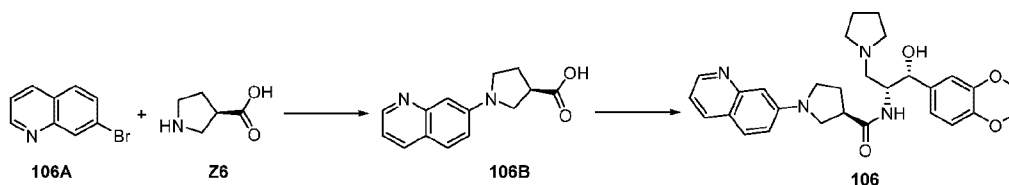
[000753] Compound **104**. LC-MS (ESI) m/z : 555 $[M+H]^+$; ^1H -NMR (CD $_3$ OD, 400 MHz) δ (ppm) 2.02-2.17 (m, 4H), 2.32-2.39 (m, 2H), 3.14-3.30 (m, 2H), 3.31-3.36 (m, 2H), 3.43-3.47 (m, 1H), 3.58-3.64 (m, 1H), 3.70-3.76 (m, 3H), 3.88-3.97 (m, 2H), 4.13-4.30 (m, 4H), 4.48-4.50 (m, 1H), 4.51 (s, 1H), 6.75 (s, 1H), 6.83-6.85 (m, 1H), 7.09-7.18 (m, 1H), 7.80-7.83 (m, 1H), 7.90-7.92 (m, 1H), 8.00 (s, 1H), 8.37-8.39 (m, 1H). Chiral-HPLC condition, solvent: MeOH (0.5% DEA) column: AS-H (4.6 * 250 mm 5 μ m), R_t : 6.15 min.

Example 105



[000754] Compound **105** was synthesized, by employing the procedure described for Compound **1** using Compound **103D** and Intermediate **C** in lieu of Compound **1B** and Intermediate **A**. LC-MS (ESI) m/z : 597.2 $[M+H]^+$; ^1H -NMR (CD $_3$ OD, 400 MHz) δ (ppm) 2.03-2.20 (m, 6H), 2.60-2.67 (m, 1H), 3.14-3.32 (m, 4H), 3.34-3.48 (m, 3H), 3.57-3.81 (m, 3H), 4.11-4.20 (m, 4H), 4.45-4.52 (m, 1H), 4.81 (d, J = 2.0 Hz, 1H), 6.40-6.47 (m, 2H), 6.75-6.79 (m, 2H), 6.90 (d, J = 8.4 Hz, 1H), 7.10-7.13 (m, 1H), 7.27 (d, J = 8.8 Hz, 1H), 7.82-7.84 (m, 1H), 8.11-8.13 (m, 2H).

Example 106

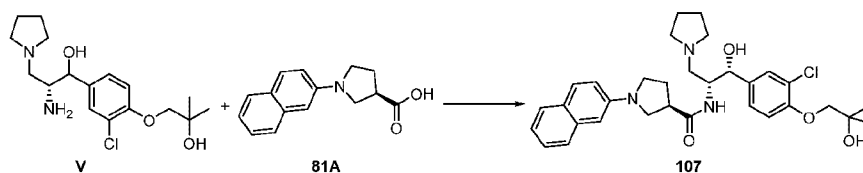


[000755] Compounds **106B** and **106** were synthesized, by employing the procedures described for Compounds **1B** and **1** using Compound **106A**, Interdediate **Z6**, and Compound **106B** in lieu of 1-chloro-4-iodobenzene, Compounds **1A**, and **1B**.

[000756] Compound **106B**. LC-MS (ESI) m/z : 243 $[M+H]^+$; ^1H -NMR (DMSO- d_6 , 400 MHz) δ (ppm) 2.06-2.12 (m, 1H), 2.18-2.23 (m, 1H), 2.83-2.87 (m, 1H), 3.29-3.59 (m, 4H), 6.75 (d, J = 2.0 Hz, 1H), 7.04-7.09 (m, 2H), 7.71 (d, J = 8.8 Hz, 1H), 8.04 (d, J = 7.2 Hz, 1H), 8.61-8.63 (m, 1H).

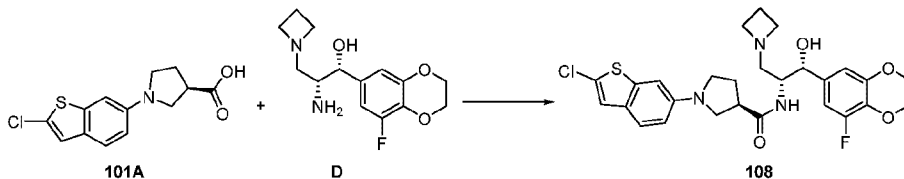
[000757] Compound **106**. LC-MS (ESI) m/z : 503 $[M+H]^+$; $^1\text{H-NMR}$ (CD_3OD , 400 MHz) δ (ppm) 2.06-2.37 (m, 6H), 3.07-3.29 (m, 4H), 3.43-3.79 (m, 7H), 3.98-4.15 (m, 4H), 4.49-4.53 (m, 1H), 4.83 (d, $J = 2.8$ Hz, 1H), 6.76 (d, $J = 1.2$ Hz, 1H), 6.83 (d, $J = 8.0$ Hz, 1H), 6.90-6.94 (m, 2H), 7.33 (d, $J = 9.2$ Hz, 1H), 7.49 (t, $J = 7.2$ Hz, 1H), 8.06 (d, $J = 9.2$ Hz, 1H), 8.69 (d, $J = 5.6$ Hz, 1H), 8.74 (d, $J = 8.0$ Hz, 1H).

Example 107



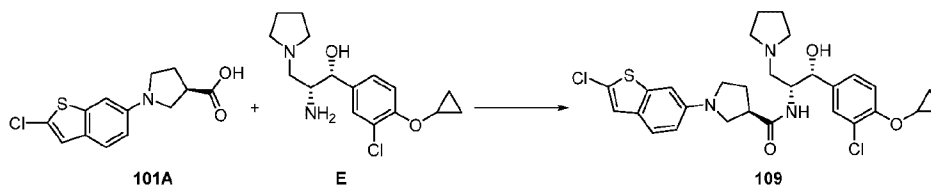
[000758] Compound **107** was synthesized, by employing the procedure described for Compound **1** using Compound **81A** and Intermediate **V** in lieu of Compound **1B** and Intermediate **A**. LC-MS (ESI) m/z : 566 $[M+H]^+$; $^1\text{H-NMR}$ (CD_3OD , 400 MHz) δ (ppm) 1.22 (s, 3H), 1.25 (s, 3H), 2.00-2.05 (m, 2H), 2.10-2.26 (m, 4H), 2.79-2.83 (m, 1H), 3.14-3.25 (m, 3H), 3.32-3.38 (m, 1H), 3.41-3.51 (m, 3H), 3.57-3.62 (m, 1H), 3.66-3.71 (m, 3H), 3.75-3.79 (m, 1H), 4.50-4.55 (m, 1H), 4.87 (s, 1H), 6.94-6.97 (m, 2H), 7.10-7.14 (m, 1H), 7.25-7.31 (m, 2H), 7.52 (d, $J = 1.6$ Hz, 1H), 7.62-7.68 (m, 3H).

Example 108



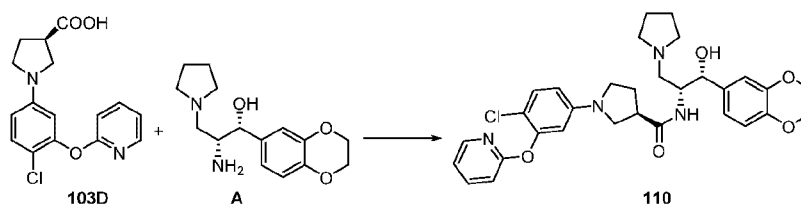
[000759] Compound **108** was synthesized, by employing the procedure described for Compound **1** using Compound **101A** and Intermediate **D** in lieu of Compound **1B** and Intermediate **A**. LC-MS (ESI) m/z : 546 $[M+H]^+$; $^1\text{H-NMR}$ (CD_3OD , 400 MHz) δ (ppm) 2.10-2.13 (m, 1H), 2.23-2.26 (m, 1H), 2.39-2.47 (m, 1H), 2.60-2.68 (m, 2H), 3.13-3.17 (m, 1H), 3.37-3.50 (m, 3H), 3.55-3.59 (m, 1H), 4.16-4.36 (m, 10H), 4.82 (d, $J = 2.0$ Hz, 1H), 6.68 (d, $J = 8.2$ Hz, 1H), 6.75 (s, 1H), 6.82-6.86 (m, 2H), 7.06 (s, 1H), 7.51 (d, $J = 8.8$ Hz, 1H), 8.00 (d, $J = 9.6$ Hz, 1H).

Example 109



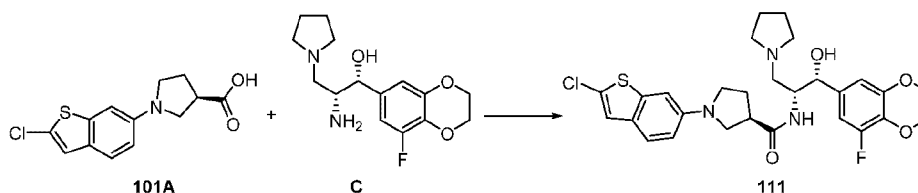
[000760] Compound **109** was synthesized, by employing the procedure described for Compound **1** using Compound **101A** and Intermediate **E** in lieu of Compound **1B** and Intermediate **A**. LC-MS (ESI) m/z : 546 $[M+H]^+$; ^1H -NMR (CD_3OD , 400 MHz) δ (ppm) 0.54-0.55 (m, 1H), 0.68-0.72 (m, 3H), 2.03-2.25 (m, 6H), 2.52-2.56 (m, 1H), 3.11-3.28 (m, 5H), 3.37-3.38 (m, 1H), 3.48-3.52 (m, 1H), 3.60-3.72 (m, 3H), 3.81-3.86 (m, 1H), 4.56-4.61 (m, 1H), 4.94 (d, $J = 2.4$ Hz, 1H), 6.63-6.66 (dd, $J = 8.8, 1.6$ Hz, 1H), 6.79 (s, 1H), 7.06 (s, 1H), 7.26 (s, 2H), 7.50 (d, $J = 8.4$ Hz, 1H), 7.55 (s, 1H), 8.09 (d, $J = 9.6$ Hz, 1H).

Example 110

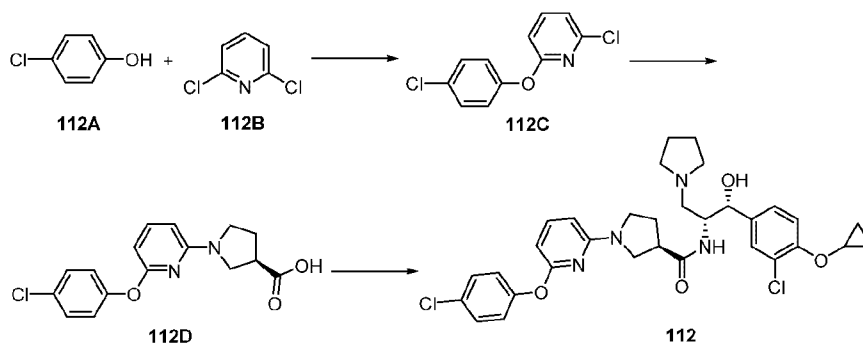


[000761] Compound **110** was synthesized, by employing the procedure described for Compound **1** using Compound **103D** in lieu of Compound **1B**. LC-MS (ESI) m/z : 579.2 $[M+H]^+$; ^1H -NMR (CD_3OD , 400 MHz) δ (ppm) 2.03-2.21 (m, 6H), 2.64-2.69 (m, 1H), 3.12-3.26 (m, 4H), 3.31-3.37 (m, 2H), 3.45-3.49 (m, 1H), 3.57-3.82 (m, 3H), 4.05-4.08 (m, 2H), 4.10-4.20 (m, 2H), 4.45-4.53 (m, 1H), 4.82 (d, $J = 2.4$ Hz, 1H), 6.40 (d, $J = 2.8$ Hz, 1H), 6.44-6.48 (m, 1H), 6.74 (d, $J = 8.4$ Hz, 1H), 6.82-6.85 (m, 1H), 6.90 (d, $J = 8.4$ Hz, 1H), 6.93 (d, $J = 2.0$ Hz, 1H), 7.12-7.14 (m, 1H), 7.28 (d, $J = 8.8$ Hz, 1H), 7.83-7.85 (m, 1H), 8.03-8.14 (m, 2H).

Example 111



[000762] Compound **111** was synthesized, by employing the procedure described for Compound **1** using Compound **101A** and Intermediate **C** in lieu of Compound **1B** and Intermediate **A**. LC-MS (ESI) m/z : 560 $[M+H]^+$; ^1H -NMR (CD_3OD , 400 MHz) δ (ppm) 2.02-2.28 (m, 6H), 2.63-2.67 (m, 1H), 3.14-3.27 (m, 3H), 3.39-3.81 (m, 6H), 4.16-7.27 (m, 4H), 4.49-4.52 (m, 1H), 4.85 (d, $J = 2.0$ Hz, 1H), 6.69 (dd, $J = 8.8, 2.4$ Hz, 1H), 6.77 (s, 1H), 6.82-6.87 (m, 2H), 7.52 (d, $J = 8.8$ Hz, 1H), 8.07 (d, $J = 9.6$ Hz, 1H).

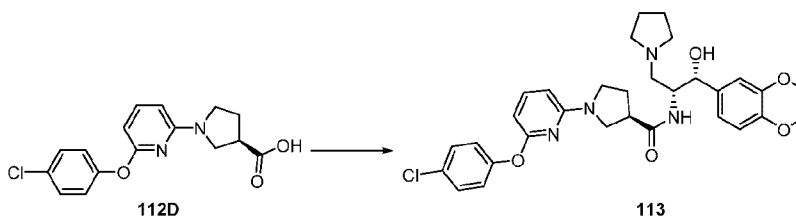
Example 112

[000763] Compound **112C** was synthesized, by employing the procedure described for Compound **103C** using Compound **112A** and **112B** at 120 °C in lieu of Compound **103A** and **103B** at 150 °C. LC-MS (ESI) m/z : 240 $[M+H]^+$.

[000764] Compounds **112D** and **112** were synthesized, by employing the procedures described for Compounds **1B** and **1** using Compound **112C**, Intermediate **Z6**, Compound **112D**, and Intermediate **E** in lieu of 1-chloro-4-iodobenzene, Compounds **1A**, **1B**, and Intermediate **A**.

[000765] Compound **112D**. LC-MS (ESI) m/z : 319 $[M+H]^+$; $^1\text{H-NMR}$ (CD_3OD , 400 MHz) δ (ppm) 1.91-2.08 (m, 1H), 2.18-2.21 (m, 2H), 3.08-3.12 (m, 1H), 3.51-3.57 (m, 3H), 6.00-6.02 (m, 1H), 6.13-6.15 (m, 1H), 7.08-7.11 (m, 2H), 7.34-7.36 (m, 2H), 7.46-7.49 (m, 1H).

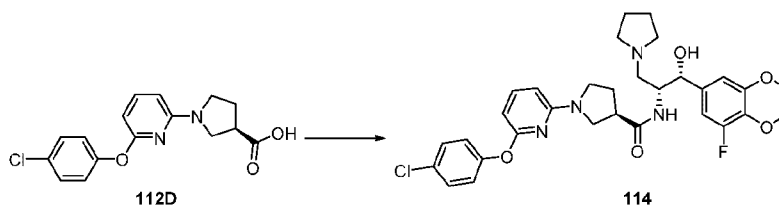
[000766] Compound **112**. LC-MS (ESI) m/z : 611 $[M+H]^+$; $^1\text{H-NMR}$ (CD_3OD , 400 MHz) δ (ppm) 0.65-0.77 (m, 4H), 2.04-2.17 (m, 6H), 2.82-2.86 (m, 1H), 3.08-3.26 (m, 4H), 3.46-3.51 (m, 3H), 3.57-3.75 (m, 4H), 4.50-4.53 (m, 1H), 4.88 (d, $J = 2.4$ Hz, 1H), 6.04-6.12 (m, 2H), 7.12-7.14 (m, 1H), 7.24-7.26 (m, 2H), 7.37-7.39 (m, 2H), 7.45(s, 1H), 7.52-7.54 (m, 1H).

Example 113

[000767] Compound **113** was synthesized, by employing the procedure described for Compound **1** using Compound **112D** in lieu of Compound **1B**. LC-MS (ESI) m/z : 579 $[M+H]^+$; $^1\text{H-NMR}$ (CD_3OD , 400 MHz) δ (ppm) 2.00-2.17 (m, 6H), 2.96-3.22 (m, 5H), 3.47-3.56 (m, 4H), 3.66-3.75 (m, 2H), 4.17-4.20 (m, 4H), 4.44-4.48 (m, 1H), 4.80 (d, $J = 2.8$ Hz,

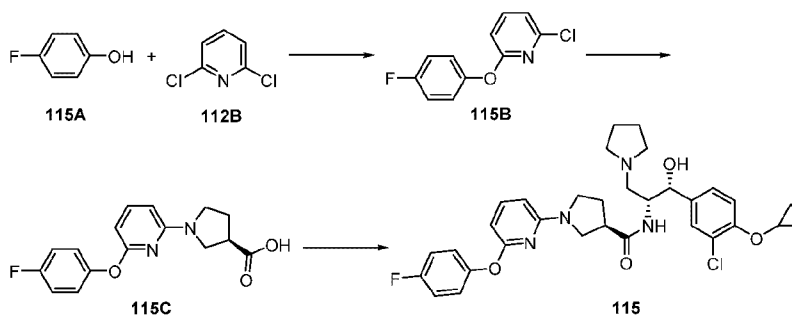
1H), 6.03-6.05 (m, 1H), 6.16-6.18 (m, 1H), 6.73-6.91 (m, 3H), 7.13-7.15 (m, 2H), 7.38-7.40 (m, 2H), 7.54-7.58 (m, 1H).

Example 114



[000768] Compound **114** was synthesized, by employing the procedure described for Compound **1** using Compound **112D** and Intermediate C in lieu of Compound **1B** and Intermediate A. LC-MS (ESI) m/z : 597 $[M+H]^+$; $^1\text{H-NMR}$ (CD_3OD , 400 MHz) δ (ppm) 2.02-2.18 (m, 6H), 2.87-3.23 (m, 5H), 3.45-3.76 (m, 6H), 4.22-4.26 (m, 4H), 4.44-4.49 (m, 1H), 4.80 (d, $J = 2.4$ Hz, 1H), 6.03-6.05 (m, 1H), 6.13-6.15 (m, 1H), 6.75-6.79 (m, 2H), 7.11-7.13 (m, 2H), 7.36-7.39 (m, 2H), 7.50-7.56 (m, 1H).

Example 115



[000769] Compound **115B** was synthesized, by employing the procedure described for Compound **103C** using Compound **115A** at 120 °C in lieu of Compound **103A** at 150 °C. LC-MS (ESI) m/z : 224 $[M+H]^+$; $^1\text{H-NMR}$ (CD_3OD , 400 MHz): δ (ppm) 6.76-6.78 (m, 1H), 7.01-7.05 (m, 5H), 7.65-7.67 (m, 1H).

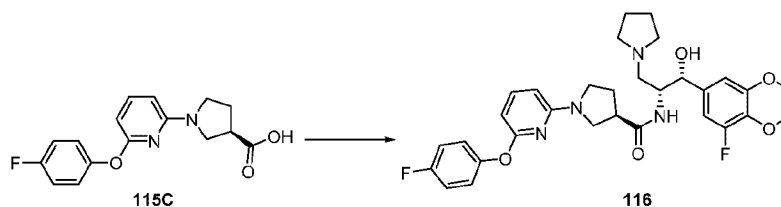
[000770] Compounds **115C** and **115** were synthesized, by employing the procedures described for Compounds **1B** and **1** using Compound **115B**, Intermediate **Z6**, Compound **115C**, and Intermediate **E** in lieu of 1-chloro-4-iodobenzene, Compounds **1A**, **1B**, and Intermediate A.

[000771] Compound **115C**. LC-MS (ESI) m/z : 303 $[M+H]^+$; $^1\text{H-NMR}$ (CD_3OD , 400 MHz): δ (ppm) 1.85-2.16 (m, 3H), 2.90-2.97 (m, 1H), 3.42-3.52 (m, 3H), 5.89-5.91 (m, 1H), 6.06-6.08 (m, 1H), 7.02-7.06 (m, 4H), 7.38-7.40 (m, 1H).

[000772] Compound **115**. LC-MS (ESI) m/z : 595 $[M+H]^+$; $^1\text{H-NMR}$ (CD_3OD , 400 MHz): δ (ppm) 0.62-0.78 (m, 4H), 2.00-2.20 (m, 6H), 2.80-2.84 (m, 1H), 3.06-3.28 (m, 4H),

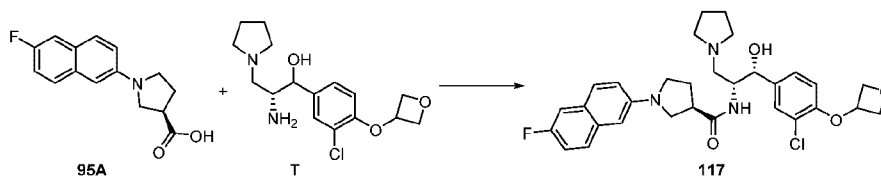
3.43-3.50 (m, 3H), 3.68-3.78 (m, 4H), 4.49-4.55 (m, 1H), 4.88 (d, $J = 2.8$ Hz, 1H), 5.98-5.60 (m, 2H), 6.08-6.10 (m, 1H), 7.13-7.15 (m, 4H), 7.26-7.27 (m, 2H), 7.45-7.52 (m, 2H).

Example 116



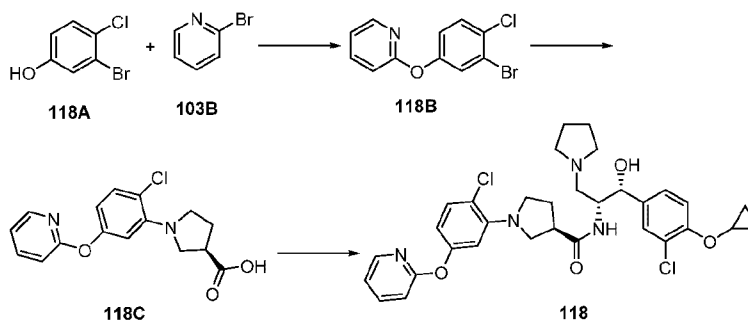
[000773] Compound **116** was synthesized, by employing the procedure described for Compound **1** using Compound **115C** and Intermediate **C** in lieu of Compound **1B** and Intermediate **A**. LC-MS (ESI) m/z : 581 $[M+H]^+$; $^1\text{H-NMR}$ (CD_3OD , 400 MHz): δ (ppm) 2.02-2.19 (m, 6H), 2.94-2.98 (m, 1H), 3.13-3.23 (m, 3H), 3.36-3.76 (m, 7H), 4.22-4.26 (m, 4H), 4.47-4.51 (m, 1H), 4.80 (d, $J = 2.4$ Hz, 1H), 5.95-5.97 (m, 1H), 6.19-6.21 (m, 1H), 6.75-6.81 (m, 2H), 7.15-7.18 (m, 4H), 7.56-7.60 (m, 1H).

Example 117



[000774] Compound **117** was synthesized, by employing the procedure described for Compound **1** using Compound **95A** and Intermediate **T** in lieu of Compound **1B** and Intermediate **A**. LC-MS (ESI) m/z : 568 $[M+H]^+$; $^1\text{H-NMR}$ (CD_3OD , 400 MHz): δ (ppm) 2.04-2.28 (m, 6H), 2.60-2.62 (m, 1H), 3.11-3.25 (m, 3H), 3.34-3.82 (m, 7H), 4.48-4.71 (m, 4H), 4.82-4.86 (m, 1H), 4.94-4.99 (m, 2H), 6.50 (d, $J = 8.0$ Hz, 1H), 7.03 (d, $J = 8.8$ Hz, 1H), 7.16-7.38 (m, 4H), 7.63-7.82 (m, 3H).

Example 118



[000775] Compound **118B** was synthesized, by employing the procedure described for Compound **103C** using Compound **118A** in lieu of Compound **103A**. LC-MS (ESI) m/z : 284

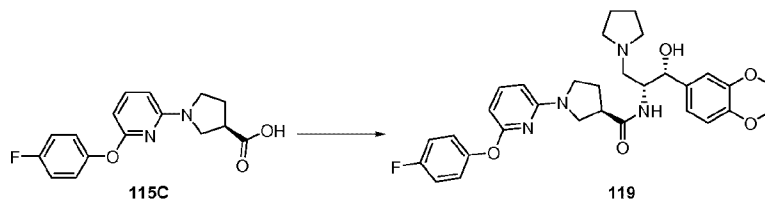
$[M+H]^+$; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ (ppm) 6.88 (d, $J = 8.4$ Hz, 1H), 6.96-7.01 (m, 2H), 7.36-7.40 (m, 2H), 7.63-7.67 (m, 1H), 8.11 (d, $J = 4.8$ Hz, 1H).

[000776] Compounds **118C** and **118** were synthesized, by employing the procedures described for Compounds **1B** and **1** using Compound **118B**, Intermediate **Z6**, Compound **118C**, and Intermediate **E** in lieu of 1-chloro-4-iodobenzene, Compounds **1A**, **1B**, and Intermediate **A**.

[000777] Compound **118C**. LC-MS (ESI) m/z : 319 $[M+H]^+$; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ (ppm) 1.94-2.09 (m, 2H), 2.71-2.79 (m, 1H), 3.25-3.32 (m, 2H), 3.42-3.47 (m, 1H), 3.57-3.61 (m, 1H), 6.46-6.49 (m, 1H), 6.56 (d, $J = 2.4$ Hz, 1H), 6.99-7.01 (m, 1H), 7.11-7.14 (m, 1H), 7.26 (d, $J = 8.4$ Hz, 1H) 7.82-7.86 (m, 1H), 8.15-8.16 (m, 1H).

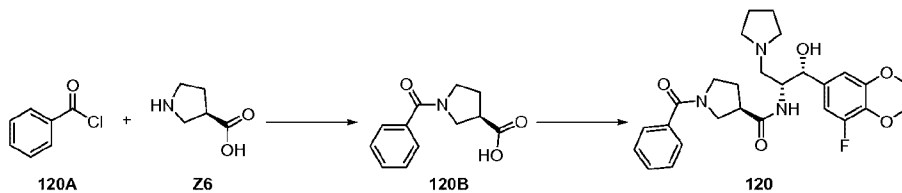
[000778] Compound **118**. LC-MS (ESI) m/z : 611 $[M+H]^+$; $^1\text{H-NMR}$ ($\text{DMSO}-d_6$, 400 MHz): δ (ppm) 0.58-0.61 (m, 2H), 0.72-0.76 (m, 2H), 1.83-2.03 (m, 7H), 2.81-2.85 (m, 1H), 3.01-3.30 (m, 5H), 3.35-3.46 (m, 3H), 3.49-3.56 (m, 2H), 3.77-3.82 (m, 1H), 4.32-4.38 (m, 1H), 4.76 (d, $J = 2.0$ Hz, 1H), 6.56-6.62 (m, 2H), 7.01 (d, $J = 8.4$ Hz, 1H), 7.12-7.15 (m, 1H), 7.22-7.36 (m, 4H), 7.84-7.88 (m, 1H), 7.96-7.98 (m, 1H), 8.15-8.17 (m, 1H), 9.29 (m, 1H).

Example 119



[000779] Compound **119** was synthesized, by employing the procedure described for Compound **1** using Compound **115C** in lieu of Compound **1B**. LC-MS (ESI) m/z : 563 $[M+H]^+$; $^1\text{H-NMR}$ (CD_3OD , 400 MHz): δ (ppm) 2.01-2.20 (m, 6H), 2.96-3.00 (m, 1H), 3.11-3.21 (m, 3H), 3.33-3.76 (m, 7H), 4.18-4.25 (m, 4H), 4.45-4.48 (m, 1H), 4.81 (d, $J = 2.4$ Hz, 1H), 5.97-5.99 (m, 1H), 6.17-6.20 (m, 1H), 6.74-6.91 (m, 3H), 7.15-7.17 (m, 4H), 7.55-7.59 (m, 1H).

Example 120

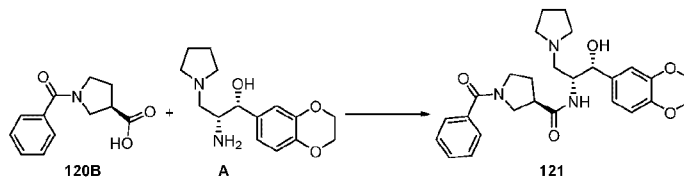


[000780] To a mixture of Intermediate **Z6** (1.00 g, 8.70 mmol) and sodium bicarbonate (1.46 g, 17.39 mmol) in dioxane (10 mL) and water (1 mL) was added benzoyl chloride **120A**

(1.22 g, 8.70 mmol) at room temperature. The mixture was stirred at room temperature for 1 h, and adjusted to pH 1 with aqueous HCl solution (6 N, 1 mL). The mixture was diluted with ice water (50 mL) to form a solid, filtered, and dried to afford Compound **120B**. LC-MS (ESI) m/z : 220 $[M+H]^+$; ^1H -NMR (DMSO- d_6 , 400 MHz): δ (ppm) 1.94-2.20 (m, 2H), 3.03-3.16 (m, 1H), 3.44-3.70 (m, 4H), 7.43-7.52 (m, 5H), 12.59 (s, 1H).

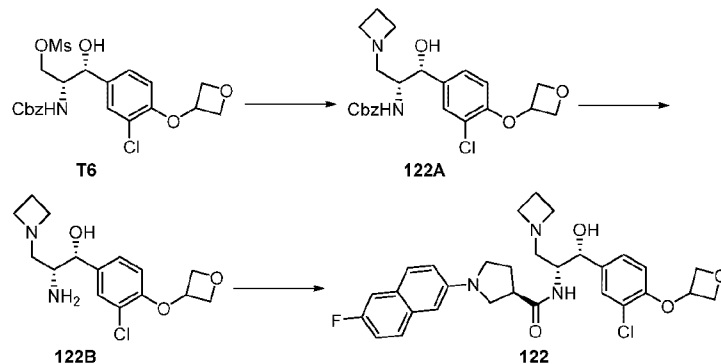
[000781] Compound **120** was synthesized, by employing the procedure described for Compound **1** using Compound **120B** and Intermediate **C** in lieu of Compound **1B** and Intermediate **A**. LC-MS (ESI) m/z : 498 $[M+H]^+$; ^1H -NMR (CD₃OD, 400 MHz): δ (ppm) 1.81 (s, 4H), 2.00-2.17 (m, 2H), 2.60-2.77 (m, 6H), 2.96-3.10 (m, 1H), 3.34-3.77 (m, 4H), 4.04-4.33 (m, 5H), 4.69-4.78 (m, 1H), 6.58-6.74 (m, 2H), 7.44-7.52 (m, 5H).

Example 121



[000782] Compound **121** was synthesized, by employing the procedure described for Compound **1** using Compound **120B** in lieu of Compound **1B**. LC-MS (ESI) m/z : 480 $[M+H]^+$; ^1H -NMR (CD₃OD, 400 MHz): δ (ppm) 1.84 (s, 4H), 2.00-2.17 (m, 2H), 2.63-2.82 (m, 6H), 2.96-3.13 (m, 1H), 3.34-3.79 (m, 4H), 4.00-4.32 (m, 5H), 4.69-4.79 (m, 1H), 6.56-6.90 (m, 3H), 7.43-7.52 (m, 5H).

Example 122



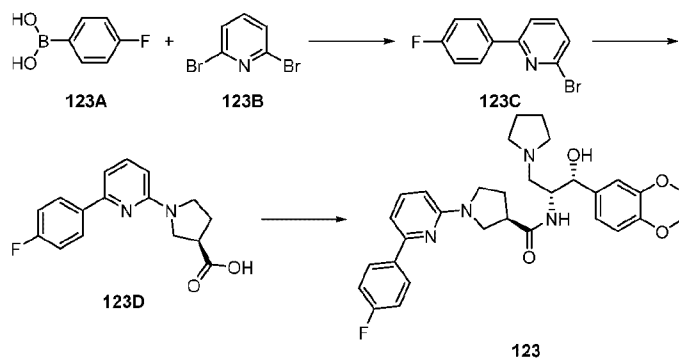
[000783] Compound **122A** was synthesized, by employing the procedure described for Intermediate **A9** using azetidine and Intermediate **T6** in lieu of pyrrolidine and Intermediate **A8**. LC-MS (ESI) m/z : 447 $[M+H]^+$.

[000784] Compound **122B** was synthesized, by employing the procedure described for Intermediate **E** using Intermediate Compound **122A** in lieu of Intermediate **E7**. LC-MS (ESI)

m/z: 313 $[M+H]^+$; ^1H NMR (CD_3OD , 400 MHz): δ (ppm) 2.21-2.59 (m, 2H), 2.45-2.65 (m, 2H), 3.11-3.20 (m, 3H), 3.96-4.03 (m, 2H), 4.69-4.71 (m, 2H), 4.97 (m, 2H), 5.12-5.13 (m, 2H), 6.41-6.43 (m, 1H), 7.14-7.29 (m, 2H).

[000785] Compound **122** was synthesized, by employing the procedure described for Compound **1** using Compounds **122B** and **95A** in lieu of Intermediate **A** and Compound **1B**. LC-MS (ESI) m/z: 554 $[M+H]^+$; ^1H -NMR (CD_3OD , 400 MHz): δ (ppm) 2.13-2.14 (m, 1H), 2.29-2.63 (m, 4H), 3.15-3.21 (m, 1H), 3.41-3.60 (m, 6H), 4.18-4.84 (m, 9H), 4.95-4.98 (m, 1H), 6.50 (d, $J = 8.8$ Hz, 1H), 7.02-7.06 (m, 1H), 7.20-7.83 (m, 7H).

Example 123



[000786] A mixture of 4-fluorophenylboronic acid (**123A**, 3 g, 21.4 mmol), 2,6-dibromopyridine (**123B**, 3 g, 21.4 mmol), $Pd(PPh_3)_4$ (247 mg, 2.14 mmol), and Na_2CO_3 (6.8 g, 64.2 mmol) in toluene (96 mL), ethanol (48 mL) and water (96 mL) was stirred at 50 °C for 18 hours. The reaction mixture was treated with water (50 mL) and extracted with ethyl acetate (150 mL x 3). The extraction was washed with water (50 mL), dried over anhydrous sodium sulfate, concentrated, and purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, from 1% to 5% v/v) to furnish Compound **123C**. LC-MS (ESI) m/z: 252 $[M+H]^+$;

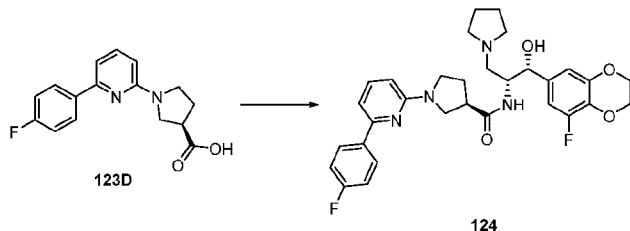
[000787] Compounds **123D** and **123** were synthesized, by employing the procedures described for Compound **1B** and **1** using Compound **123C**, Intermediate **Z6**, and Compound **123D** in lieu of 1-chloro-4-iodobenzene, Compound **1A**, and **1B**.

[000788] Compound **123D**. LC-MS (ESI) m/z: 287 $[M+H]^+$; ^1H -NMR ($CDCl_3$, 400 MHz): δ (ppm) 2.31-2.38 (m, 2H), 3.23-3.29 (m, 1H), 3.56-3.61 (m, 1H), 3.68-3.75 (m, 1H), 3.82-3.89 (m, 2H), 6.32 (d, 1H), 7.00 (d, 1H), 7.08-7.12 (m, 2H), 7.50-7.53 (m, 1H), 7.99-8.03 (m, 2H).

[000789] Compound **123**. LC-MS (ESI) m/z: 547 $[M+H]^+$; ^1H -NMR (CD_3OD , 400 MHz): δ (ppm) 1.82-1.84 (m, 4H), 2.16-2.21 (m, 2H), 2.63-2.78 (m, 6H), 3.11-3.28 (m, 2H),

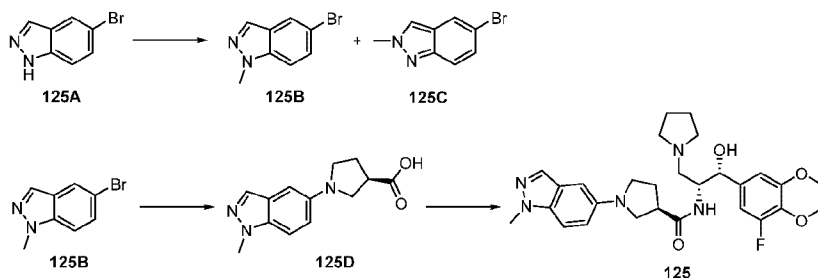
3.45-3.48 (m, 1H), 3.66-3.76 (m, 2H), 4.16-4.27 (m, 5H), 4.80 (d, $J = 3.2$ Hz, 1H), 6.40 (d, $J = 8$ Hz, 1H), 6.77-7.88 (m, 3H), 7.06 (d, $J = 7.2$ Hz, 1H), 7.14-7.18 (m, 2H), 7.54-7.58 (m, 1H), 8.06-8.10 (m, 2H).

Example 124



[000790] Compound **124** was synthesized, by employing the procedure described for Compound **1** using Compound **123D** and Intermediate **C** in lieu of Compound **1B** and Intermediate **A**. LC-MS (ESI) m/z : 565 $[M+H]^+$; $^1\text{H-NMR}$ (CD_3OD , 400 MHz): δ (ppm) 1.82-1.84 (m, 4H), 2.16-2.20 (m, 2H), 2.63-2.79 (m, 6H), 3.13-3.22 (m, 2H), 3.46-3.48 (m, 1H), 3.66-3.76 (m, 2H), 4.20-4.26 (m, 5H), 4.80 (d, $J = 2.4$ Hz, 1H), 6.39 (d, $J = 8$ Hz, 1H), 6.71-6.79 (m, 2H), 7.05 (d, $J = 7.2$ Hz, 1H), 7.13-7.18 (m, 2H), 7.54-7.58 (m, 1H), 8.06-8.10 (m, 2H).

Example 125



[000791] To a solution of Compound **125A** (4.92 g, 25.0 mmol) in THF (300 mL) was added NaH (1.10 g, 27.5 mmol) at 0 °C. The reaction solution was stirred at this temperature for 1 h before methyl iodide (5.32 g, 37.5 mmol) was added at 0 °C. The reaction was allowed to warm to room temperature slowly, stirred for 2 h, and quenched with water and concentrated in *vacuo*. The residue was diluted with water and extracted with dichloromethane (80 mL x 2). The organic layers were combined, dried over anhydrous sodium sulfate, and concentrated. The crude product was purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, 10% v/v) to give Compound **125B** and Compound **125C**. For Compound **125B**: LC-MS (ESI) m/z : 211 $[M+H]^+$; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ (ppm) 4.06 (s, 3H), 7.26-7.28 (m, 1H), 7.44-7.48 (m, 1H), 7.86-7.87 (m, 1H), 7.91 (s, 1H). For Compound **125C**: LC-MS (ESI) m/z : 211 $[M+H]^+$; $^1\text{H-NMR}$

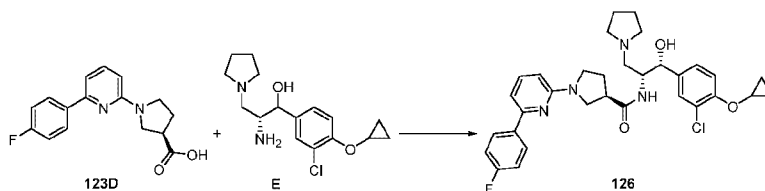
(CDCl₃, 400 MHz) δ (ppm) 4.20 (s, 3H), 7.31-7.34 (m, 1H), 7.56-7.58 (m, 1H), 7.79-7.80 (m, 1H), 7.84 (s, 1H).

[000792] Compounds **125D** and **125** were synthesized, by employing the procedures described for Compounds **1B** and **1** using Compound **125B**, Intermediate **Z6**, Compound **125D**, and Intermediate **C** in lieu of 1-chloro-4-iodobenzene, Compound **1A**, **1B** and Intermediate **A**.

[000793] Compound **125D**. LC-MS (ESI) m/z : 246 [M+H]⁺.

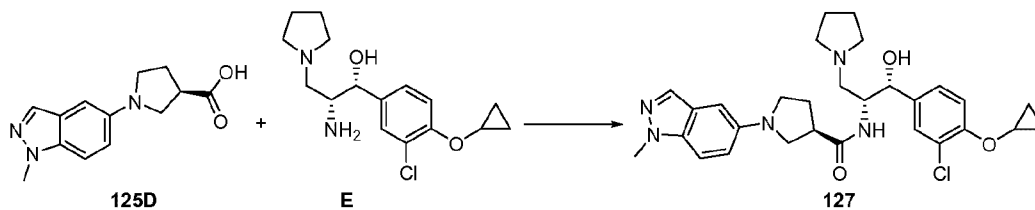
[000794] Compound **125**. LC-MS (m/z) 524 [M+H]⁺; ¹H-NMR (CDCl₃, 400 MHz): δ (ppm) 2.10 (s, 4H), 2.44 (s, 2H), 3.01-3.02 (m, 2H), 3.17-3.21 (m, 1H), 3.41-3.46 (m, 2H), 3.75-3.83 (m, 7 H), 4.02-4.03 (m, 3H), 4.17 (s, 3H), 4.53-4.54 (m, 1H), 4.84 (s, 1H), 6.69 (s, 2H), 7.46-7.59 (m, 2H), 7.83 (s, 1H), 8.03 (s, 1H), 10.58 (brs, 1H).

Example 126



[000795] Compound **126** was synthesized, by employing the procedure described for Compound **1** using Compound **123D** and Intermediate **E** in lieu of Compound **1B** and Intermediate **A**. LC-MS (ESI) m/z : 579 [M+H]⁺; ¹H-NMR (CD₃OD, 400 MHz): δ (ppm) 0.54-0.58 (m, 4H), 1.74-1.76 (m, 4H), 2.04-2.09 (m, 2H), 2.57-2.74 (m, 6H), 3.00-3.12 (m, 2H), 3.34-3.36 (m, 1H), 3.53-3.61 (m, 3H), 4.19-4.20 (m, 1H), 4.77 (d, J = 2.4 Hz, 1H), 6.26 (d, J = 8 Hz, 1H), 6.94 (d, J = 7.2 Hz, 1H), 7.03-7.07 (m, 2H), 7.14 (s, 2H), 7.31 (s, 1H), 7.42-7.45 (m, 1H), 7.95-7.99 (m, 2H); Chiral-HPLC condition, solvent: MeOH (0.1% DEA), column: OJ-H 250 x 4.6 mm, 5 μ m), Rt: 5.65 min.

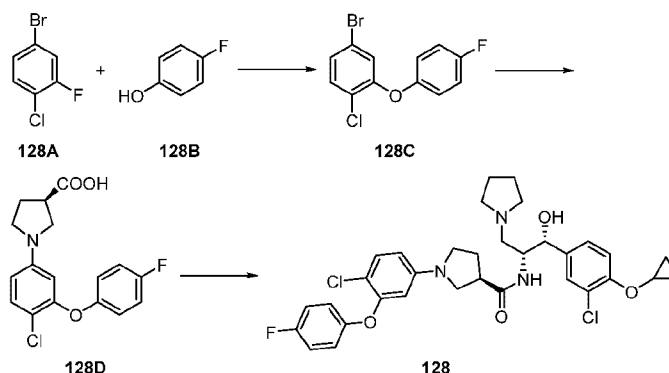
Example 127



[000796] Compound **127** was synthesized, by employing the procedure described for Compound **1** using Compound **125D** and Intermediate **E** in lieu of Compound **1B** and Intermediate **A**. LC-MS (ESI) m/z : 538 [M+H]⁺; ¹H-NMR (CDCl₃, 400 MHz): δ (ppm) 0.73-0.77 (m, 4H), 2.06-2.11 (m, 7H), 3.09-3.37 (m, 10H), 3.66-3.67 (m, 1H), 4.01 (s, 3H), 4.42-4.45 (m, 1H), 5.18-

5.19 (m, 1H), 6.69-6.70 (m, 1H), 6.86-6.89 (m, 1H), 7.05-7.08 (m, 1H), 7.17-7.18 (m, 2H), 7.26-7.28 (m, 1H), 7.43 (s, 1H), 7.82 (s, 1H).

Example 128



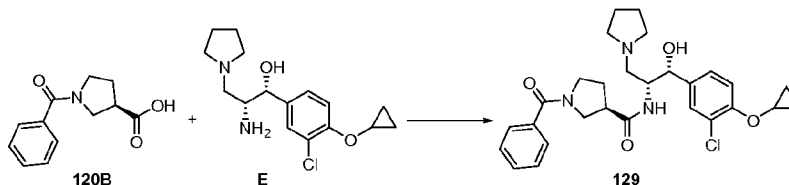
[000797] Compound **128C** was synthesized, by employing the procedure described for Compound **103C** using Compound **128A** and **128B** in lieu of Compound **103A** and **103B**. LC-MS (ESI) m/z : 301.0 $[M+H]^+$.

[000798] Compounds **128D** and **128** were synthesized, by employing the procedures described for Compounds **1B** and **1** using Compound **128C**, Intermediate **Z6**, Compound **128D**, and Intermediate **E** in lieu of 1-chloro-4-iodobenzene, Compound **1A**, **1B** and Intermediate **A**.

[000799] Compound **128D**. LC-MS (ESI) m/z : 334.0 $[M-H]^+$.

[000800] Compound **128**. LC-MS (ESI) m/z : 628.2 $[M+H]^+$; $^1\text{H-NMR}$ (CD_3OD , 400 MHz): δ (ppm) 0.57-0.77 (m, 4H), 2.02-2.19 (m, 6H), 2.56-2.59 (m, 1H), 3.11-3.30 (m, 6H), 3.48-3.51 (m, 1H), 3.58-3.73 (m, 4H), 4.50-4.55 (m, 1H), 4.89 (d, $J = 2.4$ Hz, 1H), 6.18 (d, $J = 2.8$ Hz, 1H), 6.31 (dd, $J = 8.8, 3.2$ Hz, 1H), 6.88-6.91 (m, 2H), 7.03-7.07 (m, 2H), 7.23-7.26 (m, 3H), 7.47 (s, 1H), 8.10 (d, $J = 2.8$ Hz, 1H).

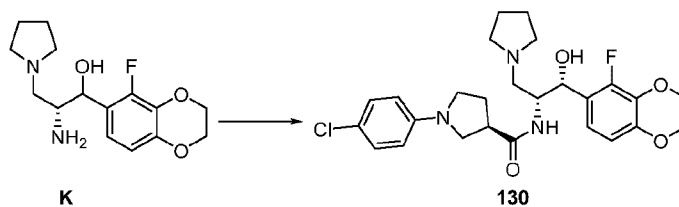
Example 129



[000801] Compound **129** was synthesized, by employing the procedure described for Compound **1** using Compound **120B** and Intermediate **E** in lieu of Compound **1B** and Intermediate **A**. LC-MS (ESI) m/z : 512 $[M+H]^+$; $^1\text{H-NMR}$ (CD_3OD , 400 MHz): δ (ppm) 0.67-0.81 (m, 4H), 1.81 (s, 4H), 2.01-2.17 (m, 2H), 2.59-2.75 (m, 6H), 2.98-3.11 (m, 1H),

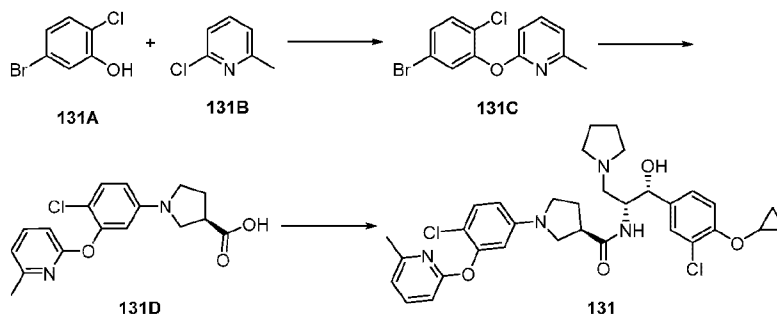
3.38-3.58 (m, 3H), 3.62-3.85 (m, 2H), 4.16-4.28 (m, 1H), 4.80 (d, $J = 30.4$ Hz, 1H), 7.11-7.35 (m, 3H), 7.37-7.51 (m, 5H).

Example 130



[000802] Compound **130** was synthesized, by employing the procedure described for Compound **1** using Intermediate **Z** and **K** in lieu of Compound **1B** and Intermediate **A**. LC-MS (ESI) m/z : 504 $[M+H]^+$; ^1H -NMR (CD_3OD , 400 MHz): δ (ppm) 1.97-2.17 (m, 6H), 2.57-2.61 (m, 1H), 2.93-3.00 (m, 1H), 3.17-3.25 (m, 5H), 3.34-3.40 (m, 1H), 3.65-3.76 (m, 3H), 4.14-4.26 (m, 4H), 4.46-4.75 (m, 1H), 4.76 (d, $J = 9.2$ Hz, 1H), 6.42 (d, $J = 9.2$ Hz, 2H), 6.63 (d, $J = 10.4$ Hz, 1H), 6.88 (t, $J = 8.8$ Hz, 1H), 7.10 (d, $J = 8.8$ Hz, 2H), 8.16 (d, $J = 9.6$ Hz, 1H).

Example 131



[000803] Compound **131C** was synthesized, by employing the procedure described for Compound **103C** using Compound **131A** and **131B** in NMP in lieu of Compound **103A** and **103B** in DMF. LC-MS (ESI) m/z : 298 $[M+H]^+$; ^1H -NMR ($CDCl_3$, 400 MHz): δ (ppm) 2.42 (s, 3H), 6.67 (d, $J = 8.4$ Hz, 1H), 6.90 (d, $J = 7.2$ Hz, 1H), 7.29 (d, $J = 9.2$ Hz, 1H), 7.33 (d, $J = 7.2$ Hz, 2H), 7.60 (t, $J = 8.0$ Hz, 1H).

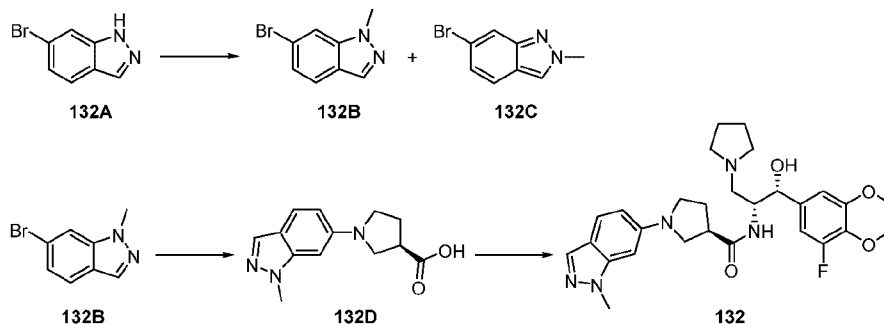
[000804] Compounds **131D** and **131** were synthesized, by employing the procedures described for Compounds **1B** and **1** using Compound **131C**, Intermediate **Z6**, Compound **131D**, and Intermediate **E** in lieu of 1-chloro-4-iodobenzene, Compounds **1A**, **1B** and Intermediate **A**.

[000805] Compound **131D**. LC-MS (ESI) m/z : 333 $[M+H]^+$.

[000806] Compound **131**. LC-MS (ESI) m/z : 625 $[M+H]^+$; ^1H -NMR ($DMSO-d_6$, 400 MHz): δ (ppm) 0.68-0.70 (m, 2H), 0.82-0.83 (m, 2H), 1.65 (d, $J = 7.2$ Hz, 6H), 1.90-1.93 (m,

2H), 2.02-2.05 (m, 2H), 3.14-3.24 (m, 2H), 3.5.-3.59 (m, 4H), 3.93-3.97 (m, 1H), 4.57-4.60 (m, 1H), 4.92 (d, $J = 2.4$ Hz, 1H), 5.02-5.09 (m, 1H), 7.36 (dd, $J = 8.8, 2.0$ Hz, 1H), 7.42 (d, $J = 8.8$ Hz, 1H), 7.45 (d, $J = 1.6$ Hz, 1H), 7.81 (d, $J = 8.4$ Hz, 2H), 7.85 (d, $J = 8.4$ Hz, 2H), 7.93 (dd, $J = 8.8, 1.6$ Hz, 1H), 8.16 (d, $J = 9.2$ Hz, 2H), 9.54 (s, 1H), 9.84 (s, 1H).

Example 132



[000807] To Compound **132A** (10 g, 50.8 mmol) in THF (50 mL) was added sodium hydride (60% in mineral, 2.2 g, 55.8 mmol) with ice bath cooling. The mixture was stirred at room temperature for 30 min. Methyl iodide (4.74 mL, 76.1 mmol) was added at room temperature. The reaction mixture was stirred at room temperature for 1 h, quenched with saturated aqueous ammonium chloride solution (30 mL), and extracted with ethyl acetate (100 mL x 3). The combined organic layers were washed with brine (200 mL), dried over anhydrous sodium sulfate, and concentrated. Purification with flash column chromatography on silica gel (ethyl acetate in petroleum ether, 10% to 30% v/v) gave Compound **132B** and Compound **132C**. For Compound **132B**: LC-MS (ESI) m/z : 211 $[M+H]^+$; ^1H -NMR (DMSO- d_6 , 400 MHz): δ (ppm) 4.04 (s, 3H), 7.26 (dd, $J = 8.8, 2.0$ Hz, 1H), 7.72 (d, $J = 8.4$ Hz, 1H), 7.99 (s, 1H), 8.08 (d, $J = 0.8$ Hz, 1H). For Compound **132C**: LC-MS (ESI) m/z : 211 $[M+H]^+$; ^1H -NMR (DMSO- d_6 , 400 MHz): δ (ppm) 4.17 (s, 3H), 7.13 (dd, $J = 8.8, 2.0$ Hz, 1H), 7.69 (d, $J = 8.8$ Hz, 1H), 7.85 (s, 1H), 8.41 (s, 1H).

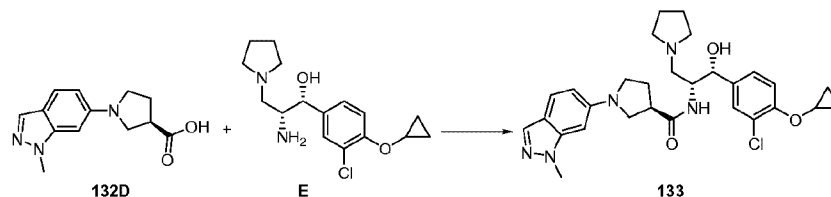
[000808] Compounds **132D** and **132** were synthesized, by employing the procedures described for Compounds **1B** and **1** using Compound **132B**, Intermediate **Z6**, Compound **132D**, and Intermediate **C** in lieu of 1-chloro-4-iodobenzene, Compounds **1A**, **1B** and Intermediate **A**.

[000809] Compound **132D**. LC-MS (ESI) m/z : 246 $[M+H]^+$; ^1H -NMR (DMSO- d_6 , 400 MHz): δ (ppm) 2.18-2.29 (m, 2H), 3.35-3.60 (m, 5H), 3.90 (s, 3H), 6.43 (s, 1H), 6.58 (d, $J = 8.8$ Hz, 1H), 7.50 (d, $J = 8.4$ Hz, 1H), 7.79 (s, 1H), 12.53 (s, 1H).

[000810] Compound **132**. LC-MS (ESI) m/z : 524 $[M+H]^+$; ^1H -NMR (DMSO- d_6 , 400 MHz): δ (ppm) 1.84-2.16 (m, 6H), 2.63-2.67 (m, 1H), 3.08-3.43 (m, 8H), 3.55-3.59 (m, 2H),

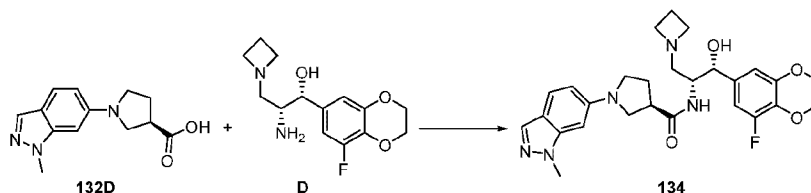
3.92 (m, 3H), 4.14-4.38 (m, 5H), 4.72 (d, $J = 2.0$ Hz, 1H), 6.28 (s, 1H), 6.51 (dd, $J = 8.8, 1.6$ Hz, 1H), 6.73 (s, 1H), 6.85 (dd, $J = 11.6, 1.6$ Hz, 1H), 7.53 (d, $J = 8.8$ Hz, 1H), 7.79 (s, 1H), 8.02 (d, $J = 10.0$ Hz, 1H), 9.24 (brs, 1H).

Example 133



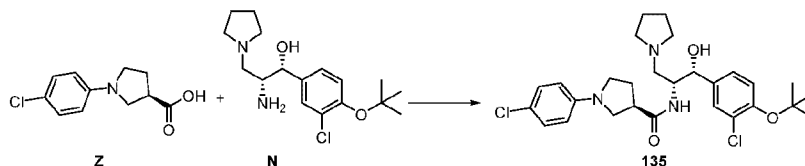
[000811] Compound **133** was synthesized, by employing the procedure described for Compound **1** using Compound **132D** and Intermediate **E** in lieu of Compound **1B** and Intermediate **A**. LC-MS (ESI) m/z : 538 $[M+H]^+$; $^1\text{H-NMR}$ (CD_3OD , 400 MHz): δ (ppm) 0.55-0.73 (m, 4H), 2.03-2.28 (m, 6H), 2.62-2.66 (m, 1H), 3.17-3.31 (m, 3H), 3.40-3.69 (m, 7H), 3.78-3.84 (m, 1H), 4.08 (s, 3H), 4.56-4.58 (m, 1H), 4.96 (d, $J = 2.8$ Hz, 1H), 6.72 (d, $J = 9.2$ Hz, 1H), 7.27 (s, 2H), 7.36 (s, 1H), 7.58 (s, 1H), 7.64 (d, $J = 8.8$ Hz, 1H), 8.10 (s, 1H).

Example 134



[000812] Compound **134** was synthesized, by employing the procedure described for Compound **1** using Compound **132D** and Intermediate **D** in lieu of Compound **1B** and Intermediate **A**. LC-MS (ESI) m/z : 510 $[M+H]^+$; $^1\text{H-NMR}$ (CD_3OD , 400 MHz): δ (ppm) 2.15-2.19 (m, 1H), 2.29-2.34 (m, 1H), 2.42-2.48 (m, 1H), 2.58-2.65 (m, 1H), 2.75-2.79 (m, 1H), 3.19-3.23 (m, 1H), 3.43-3.62 (m, 5H), 3.98-4.34 (m, 12H), 4.84 (d, $J = 2.4$ Hz, 1H), 6.71 (s, 1H), 6.84 (d, $J = 9.2$ Hz, 1H), 6.91 (dd, $J = 11.6, 1.6$ Hz, 1H), 7.35 (s, 1H), 7.71 (d, $J = 8.8$ Hz, 1H), 8.28 (s, 1H).

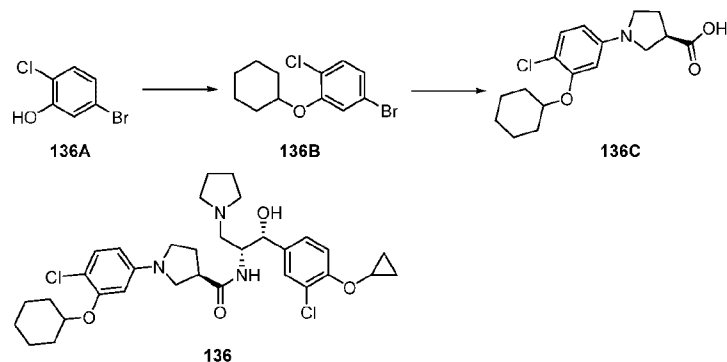
Example 135



[000813] Compound **135** was synthesized, by employing the procedure described for Compound **1** using Intermediates **Z** and **N** in lieu of **1B** and Intermediate **A**. LC-MS (ESI) m/z : 534 $[M+H]^+$; $^1\text{H-NMR}$ (CD_3OD , 400 MHz): δ (ppm) 1.28 (s, 9H), 1.88-2.10 (m, 6H),

2.51 (t, $J = 8.8$ Hz, 1H), 2.98-3.17 (m, 6H), 3.39-3.42 (m, 1H), 3.49-3.59 (m, 2H), 3.66-3.72 (m, 1H), 4.40-4.47 (m, 1H), 4.78 (s, 1H), 6.37 (d, $J = 9.2$ Hz, 2H), 7.01 (d, $J = 9.2$ Hz, 3H), 7.13 (d, $J = 8.8$ Hz, 1H), 7.45 (s, 1H), 8.00 (d, $J = 9.6$ Hz, 1H).

Example 136



[000814] To a solution of Compound **136A** (2.0 g, 9.71 mmol) and bromocyclohexane (4.75 g, 29.1 mmol) in NMP (30 mL) was added cesium carbonate (6.33 mg, 19.4 mmol). The mixture was stirred under nitrogen at 150 °C overnight. After cooling to room temperature the mixture was poured into water (150 mL) and extracted with ethyl acetate (100 mL x 2). The combined organic phases were washed with water (10 mL x 3) and brine (10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to afford a crude compound. The crude product was purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, 5% v/v) to furnish Compound **136B**. LC-MS (ESI) m/z : 289 $[M+H]^+$; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ (ppm) 1.37-1.42 (m, 3H), 1.53-1.56 (m, 1H), 1.63-1.68 (m, 2H), 1.82-1.85 (m, 2H), 1.93-1.96 (m, 2H), 4.27-4.33 (m, 1H), 7.01 (dd, $J = 8.4$, 2.4 Hz, 1H), 7.07 (d, $J = 2.4$ Hz, 1H), 7.21 (d, $J = 8.4$ Hz, 1H).

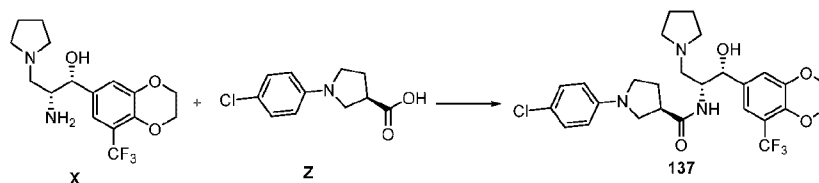
[000815] Compounds **136C** and **136** were synthesized, by employing the procedures described for Compounds **1B** and **1** using Compound **136B**, Intermediate **Z6**, Compound **136C**, and Intermediate **E** in lieu of 1-chloro-4-iodobenzene, Compounds **1A**, **1B** and Intermediate **A**.

[000816] Compound **136C**. LC-MS (ESI) m/z : 324 $[M+H]^+$; $^1\text{H-NMR}$ ($\text{DMSO-}d_6$, 400 MHz): δ (ppm) 1.33-1.38 (m, 3H), 1.47-1.52 (m, 3H), 1.70-1.73 (m, 2H), 1.83-1.87 (m, 2H), 2.10-2.15 (m, 2H), 3.03-3.06 (m, 1H), 3.18-3.25 (m, 2H), 3.36-3.38 (m, 2H), 4.40-4.44 (m, 1H), 6.09 (dd, $J = 8.8$, 2.4 Hz, 1H), 6.21 (d, $J = 2.8$ Hz, 1H), 7.10 (d, $J = 9.2$ Hz, 1H).

[000817] Compound **136**. LC-MS (ESI) m/z : 616 $[M+H]^+$; $^1\text{H-NMR}$ ($\text{DMSO-}d_6$, 400 MHz): δ (ppm) 0.53-0.56 (m, 1H), 0.59-0.74 (m, 3H), 1.34-1.36 (m, 3H), 1.52-1.58 (m, 3H), 1.76-2.13 (m, 10H), 2.56-2.60 (m, 1H), 3.04-3.23 (m, 6H), 3.42-3.74 (m, 5H), 4.31-4.35 (m,

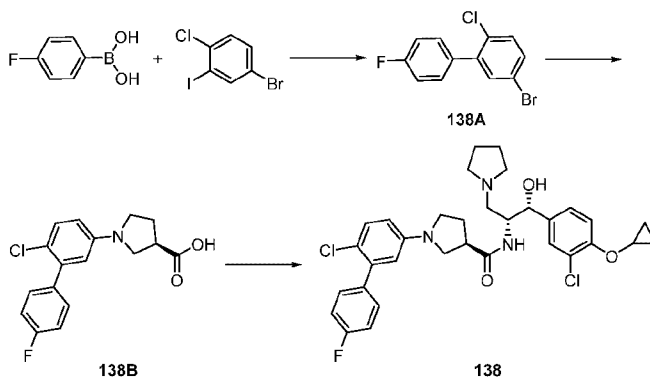
1H), 4.45-4.48 (m, 1H), 4.85 (d, $J = 2.0$ Hz, 1H), 6.01-6.04 (m, 1H), 6.11 (s, 1H), 7.04 (d, $J = 8.4$ Hz, 1H), 7.20 (s, 2H), 7.44 (s, 1H).

Example 137



[000818] Compound **137** was synthesized, by employing the procedure described for Compound **1** using Intermediates **Z** and Compound **X** in lieu of Compound **1B** and Intermediate **A**. LC-MS (ESI) m/z : 554 $[M+H]^+$; ^1H -NMR (CD_3OD , 400 MHz): δ (ppm) 2.02-2.18 (m, 6H), 2.56-2.61 (m, 1H), 3.08-3.25 (m, 4H), 3.35-3.79 (m, 6H), 4.17-4.28 (m, 4H), 4.50-4.55 (m, 1H), 4.89 (d, $J = 2$ Hz, 1H), 6.46-6.48 (m, 2H), 7.12-7.17 (m, 3H), 7.29 (s, 1H), 8.14 (d, $J = 9.6$ Hz, 1H).

Example 138



[000819] A mixture of 4-bromo-1-chloro-2-iodobenzene (1.83 g, 5.79 mmol), (4-fluorophenyl)boronic acid (810 mg, 5.79 mmol), $Pd(PPh_3)_4$ (943 mg, 0.82 mmol), and Na_2CO_3 (3.25 g, 30 mmol) in toluene (85 mL) and H_2O (19 mL) was stirred under nitrogen at 100 °C for 16 h. The reaction mixture was cooled to room temperature, and filtered through celite. The filtrate was treated with water (50 mL), and extracted with ethyl acetate (150 mL x 2). The aqueous layer was acidified to pH 3 with aqueous HCl solution (1 N) and extracted with ethyl acetate (100 mL x 2). The combined organic layers were washed with water (50 mL x 2) and brine (150 mL), dried over anhydrous sodium sulfate, and concentrated to give Compound **138A**. $[M+H]^+$; ^1H -NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.10-7.15 (m, 2H), 7.33 (d, $J = 8.4$ Hz, 1H), 7.37-7.42 (m, 3H), 7.46 (d, $J = 2.4$ Hz, 1H).

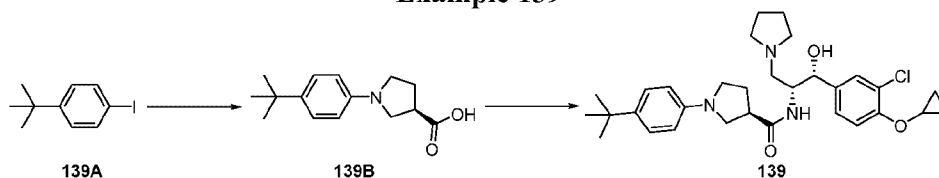
[000820] Compounds **138B** and **138** were synthesized, by employing the procedures described for Compounds **1B** and **1** using Compound **138A**, Intermediate **Z6**, Compound

138B, and Intermediate **E** in lieu of 1-chloro-4-iodobenzene, Intermediate **1A**, **1B** and Intermediate **A**.

[000821] Compound **138C**. LC-MS (ESI) m/z : 320.1 $[M+H]^+$.

[000822] Compound **138**. LC-MS (ESI) m/z : 612.3 $[M+H]^+$; $^1\text{H-NMR}$ (CD_3OD , 400 MHz): δ (ppm) 0.57-0.73 (m, 4H), 2.02-2.23 (m, 6H), 2.62 (dd, $J = 9.6, 7.2$ Hz, 1H), 3.13-3.27 (m, 4H), 3.34-3.37 (m, 2H), 3.48-3.52 (m, 1H), 3.59-3.66 (m, 4H), 4.52-4.55 (m, 1H), 4.90 (d, $J = 2.0$ Hz, 1H), 6.45-6.49 (m, 2H), 7.13-7.18 (m, 2H), 7.24-7.28 (m, 3H), 7.42-7.49 (m, 2H), 7.49 (d, $J = 1.6$ Hz, 1H), 8.11 (d, $J = 9.6$ Hz, 1H).

Example 139

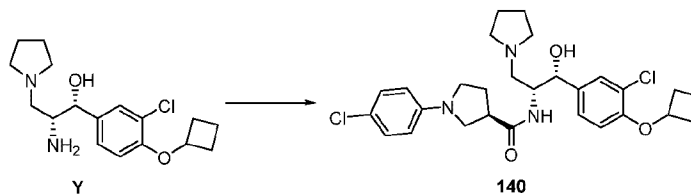


[000823] Compound **139B** and **139** were synthesized, by employing the procedures described for Compounds **1B** and **1** using Compound **139A**, Intermediate **Z6**, Compound **139B**, and Intermediate **E** in lieu of 1-chloro-4-iodobenzene, Intermediates **1A**, **1B** and Intermediate **A**.

[000824] Compound **139B**. LC-MS (ESI) m/z : 248 $[M+H]^+$; $^1\text{H-NMR}$ (CD_3OD , 400 MHz): δ (ppm) 1.28 (s, 9H), 2.25-2.27 (m, 2H), 3.22-3.26 (m, 1H), 3.31-3.35 (m, 2H), 3.36-3.54 (m, 2H), 6.53 (d, $J = 8.8$ Hz, 2H), 7.21 (d, $J = 8.8$ Hz, 2H).

[000825] Compound **139**. LC-MS (ESI) m/z : 540 $[M+H]^+$; $^1\text{H-NMR}$ (CD_3OD , 400 MHz): δ (ppm) 0.62-0.79 (m, 4H), 1.29 (s, 9H), 2.01-2.13 (m, 3H), 2.14-2.28 (m, 3H), 2.54-2.58 (m, 1H), 3.09-3.28 (m, 3H), 3.48-3.82 (m, 8H), 4.53-4.57 (m, 1H), 4.86 (m, 1H), 6.60 (d, $J = 8.4$ Hz, 2H), 7.27-7.35 (m, 4H), 7.52 (s, 1H).

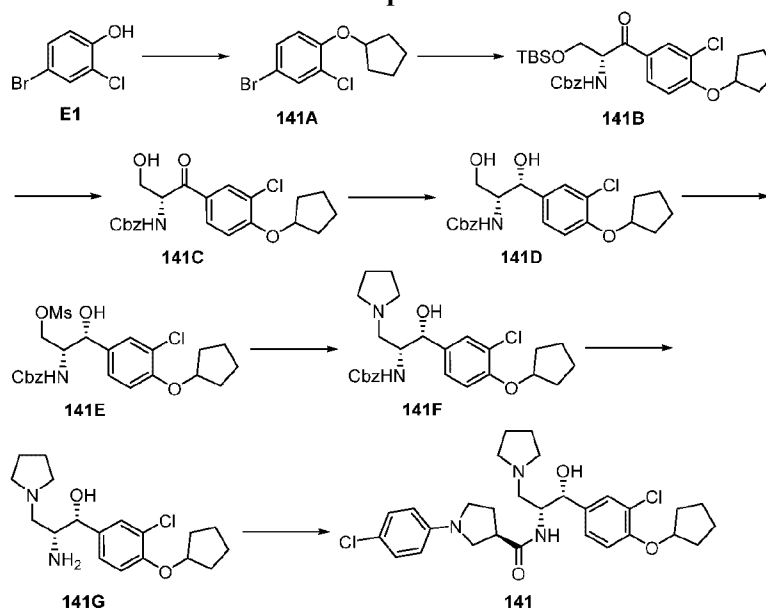
Example 140



[000826] Compound **140** was synthesized, by employing the procedure described for Compound **1** using Intermediates **Z** and **Y** in lieu of Compound **1B** and Intermediate **A**. LC-MS (ESI) m/z : 532 $[M+H]^+$; $^1\text{H-NMR}$ ($\text{DMSO}-d_6$, 400 MHz): δ (ppm) 1.55-1.70 (m, 1H), 1.72-1.78 (m, 1H), 1.96-2.06 (m, 7H), 2.39-2.40 (m, 2H), 2.48-2.50 (m, 1H), 3.10-3.18 (m, 4H), 3.24-3.26 (m, 2H), 3.39-3.44 (m, 1H), 3.54-3.56 (m, 2H), 4.31-4.36 (m, 1H), 4.58-4.65

(m, 1H), 4.79-4.80 (m, 1H), 5.99 (brs, 1H), 6.41-6.43 (m, 2H), 6.83-6.85 (m, 1H), 7.16-7.19 (m, 3H), 7.44-7.45 (m, 1H), 8.01-8.03 (m, 1H).

Example 141



[000827] Compound **141A** was synthesized, by employing the procedure described for Intermediate **E2** using bromocyclopentane in lieu of bromocyclopropane. LC-MS (ESI) m/z : No; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ (ppm) 1.57-1.91 (m, 8H), 4.74-4.78 (m, 1H), 6.78 (d, $J = 12.8$ Hz, 1H), 7.28 (dd, $J = 11.2, 2.4$ Hz, 1H), 7.47 (d, $J = 2.4$ Hz, 1H).

[000828] Compounds **141B**, **141C**, **141D**, **141E**, and **141F** were synthesized, by employing the procedures described correspondingly for Intermediates **A5**, **A6**, **A7**, **A8**, and **A9** using Compounds **141A**, **141B**, **141C**, **141D**, and **141E** in lieu of 6-bromo-2,3-dihydrobenzo[b][1,4]dioxine, Intermediates **A5**, **A6**, **A7**, and **A8**.

[000829] Compound **141B**. LC-MS (ESI) m/z : 532 $[\text{M}+\text{H}]^+$; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ (ppm) -0.12 (d, 6H), 0.74 (s, 9H), 1.59-1.69 (m, 2H), 1.82-2.01 (m, 6H), 3.85-3.97 (m, 2H), 4.88-4.92 (m, 1H), 5.13 (s, 2H), 5.27-5.31 (m, 1H), 5.90 (d, $J = 8.0$ Hz, 1H), 6.95 (d, $J = 8.4$ Hz, 1H), 7.29-7.37 (m, 5H), 7.82-7.85 (dd, $J = 8.8, 2.0$ Hz, 1H), 7.99 (d, $J = 1.6$ Hz, 1H).

[000830] Compound **141C**. LC-MS (ESI) m/z : 418 $[\text{M}+\text{H}]^+$; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ (ppm) 1.65-1.76 (m, 2H), 1.80-1.90 (m, 4H), 1.96-2.06 (m, 2H), 3.80 (dd, $J = 12.0, 5.6$ Hz, 1H), 3.93 (dd, $J = 11.2, 4.8$ Hz, 1H), 5.00-5.03 (m, 1H), 5.11 (s, 2H), 5.23 (t, $J = 5.2$ Hz, 1H), 7.15 (d, $J = 8.8$ Hz, 1H), 7.27-7.36 (m, 5H), 7.97 (dd, $J = 8.4, 2.0$ Hz, 1H), 8.04 (d, $J = 2.0$ Hz, 1H).

[000831] Compound **141D**. LC-MS (ESI) m/z : 402 $[M-OH]^+$; ^1H -NMR (CD_3OD , 400 MHz): δ (ppm) 1.66-1.96 (m, 8H), 3.48-3.55 (m, 1H), 3.67-3.82 (m, 2H), 4.60 (d, $J = 7.2$ Hz, 2H), 5.00 (dd, $J = 30.8, 12.8$ Hz, 2H), 6.82 (d, $J = 4.0$ Hz, 2H), 7.17-7.34 (m, 5H), 7.41 (d, $J = 1.6$ Hz, 1H).

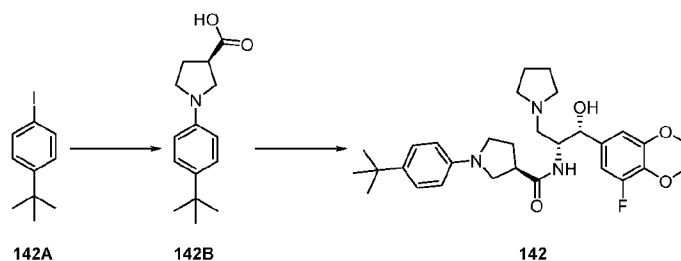
[000832] Compound **141E**, which was directly used for the next step without further purification. LC-MS (ESI) m/z : 480 $[M-OH]^+$.

[000833] Compound **141F**. LC-MS (ESI) m/z : 473 $[M+H]^+$; ^1H -NMR (CD_3OD , 400 MHz): δ (ppm) 2.40-2.68 (m, 12H), 3.15-3.46 (m, 6H), 4.57-4.61 (m, 1H), 5.52 (s, 1H), 5.66-5.71 (m, 2H), 5.78 (t, $J = 12.8$ Hz, 1H), 7.62-7.90 (m, 2H), 7.97-8.03 (m, 2H), 8.07-8.15 (m, 4H).

[000834] Compound **141G** was synthesized, by employing the procedure described for Intermediate **E** using Compound **141F** in lieu of Intermediate **E7**, which was directly used for the next step without further purification. LC-MS (ESI) m/z : 339 $[M+H]^+$; ^1H -NMR (CD_3OD , 400 MHz): δ (ppm) 1.62-2.00 (m, 12H), 2.44-2.75 (m, 6H), 3.02-3.26 (m, 1H), 4.29-4.54 (m, 1H), 4.87-4.90 (m, 1H), 7.03-7.06 (m, 1H), 7.19-7.26 (m, 1H), 7.31-7.37 (m, 1H).

[000835] Compound **141** was synthesized, by employing the procedure described for Compound **1** using Intermediate **Z** and Compound **141G** in lieu of Compound **1B** and Intermediate **A**. LC-MS (ESI) m/z : 546 $[M+H]^+$; ^1H -NMR (CD_3OD , 400 MHz): δ (ppm) 1.58-2.24 (m, 15H), 2.54-2.58 (m, 1H), 3.08-3.29 (m, 6H), 3.48-3.69 (m, 3H), 3.78-3.84 (m, 1H), 4.51-4.60 (m, 1H), 4.77-4.79 (m, 1H), 6.46 (d, 2H), 6.95 (d, 1H), 7.10-7.15 (m, 2H), 7.22-7.25 (m, 1H), 7.51 (d, $J = 2.0$ Hz, 1H), 8.08 (d, $J = 10.0$ Hz, 1H).

Example 142

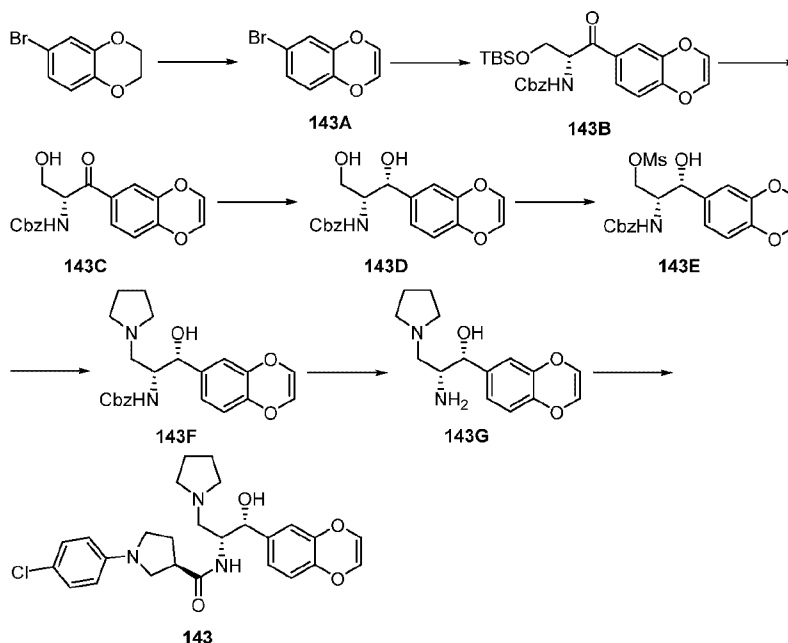


[000836] Compounds **142B** and **142** were synthesized, by employing the procedures described for Compounds **1B** and **1** using Compound **142A**, Intermediate **Z6**, Compound **142B**, and Intermediate **C** in lieu of 1-chloro-4-iodobenzene, Compound **1A**, **1B** and Intermediate **A**.

[000837] Compound **142B**. LC-MS (ESI) m/z : 248 $[M+H]^+$; $^1\text{H-NMR}$ (CD_3OD , 400 MHz): δ (ppm) 1.28 (s, 9H), 2.25-2.27 (m, 2H), 3.22-3.26 (m, 1H), 3.31-3.35 (m, 2H), 3.36-3.54 (m, 2H), 6.53 (d, $J = 8.8$ Hz, 2H), 7.21 (d, $J = 8.8$ Hz, 2H).

[000838] Compound **142**. LC-MS (ESI) m/z : 526 $[M+H]^+$; $^1\text{H-NMR}$ (CD_3OD , 400 MHz): δ (ppm) 1.24 (s, 9H), 1.92-2.01 (m, 4H), 2.02-2.12 (m, 1H), 2.13-2.19 (m, 1H), 2.65-2.70 (m, 1H), 3.06-3.26 (m, 7H), 3.29-3.36 (m, 3H), 4.16-4.21 (m, 4H), 4.35-4.41 (m, 1H), 4.77 (d, $J = 2.8$ Hz, 1H), 6.47 (d, $J = 8.4$ Hz, 2H), 6.70 (s, 1H), 6.74-6.78 (m, 1H), 7.18 (d, $J = 8.4$ Hz, 2H).

Example 143



[000839] A mixture of 6-bromo-2,3-dihydrobenzo[b][1,4]dioxine (1.07 g, 5 mmol), NBS (2.1 g, 12 mmol), and AIBN (20 mg) in CCl_4 (60 mL) was refluxed under nitrogen for 18 h. The mixture was cooled down to room temperature and filtered. The filtrate was washed with water (50 mL x 2) and dried over anhydrous magnesium sulfate. After removal of the solvent, the residue was dissolved in acetone (50 mL) and refluxed under nitrogen for 3 h with NaI (3.75 g, 25 mmol). The mixture was cooled down to room temperature and evaporated. The residue was diluted with water (100 mL) and extracted with dichloromethane (50 mL x 3). The organic layer was washed with aqueous $\text{Na}_2\text{S}_2\text{O}_3$ solution (100 mL x 2) and brine (100 mL), dried over anhydrous sodium sulfate, concentrated, and purified with flash column chromatography on silica gel (petroleum ether, 100% v/v) to yield Compound **143A**. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ (ppm) 5.86 (s, 2H), 6.49 (d, $J = 8.8$ Hz, 1H), 6.76 (d, $J = 2.8$ Hz, 1H), 6.92 (dd, $J = 8.8, 2.8$ Hz, 1H).

[000840] Compounds **143B**, **143C**, **143D**, **143E**, and **143F** were synthesized, by employing the procedures described correspondingly for Intermediates **A5**, **A6**, **A7**, **A8**, and **A9** using Compounds **143A**, **143B**, **143C**, **143D**, and **143E** in lieu of 6-bromo-2,3-dihydrobenzo[b][1,4]dioxine, Intermediates **A5**, **A6**, **A7**, and **A8**.

[000841] Compound **143B**. LC-MS (ESI) m/z: 470 [M+H]⁺; ¹H-NMR (CDCl₃, 400 MHz): δ (ppm) 0.00 (d, *J* = 2.4 Hz, 6H), 0.85 (s, 9H), 3.97 (d, *J* = 9.2 Hz, 2H), 5.15 (d, *J* = 2.8 Hz, 2H), 5.22-5.25 (m, 1H), 6.12 (s, 2H), 6.78 (d, *J* = 8.0 Hz, 1H), 7.29 (d, *J* = 2.0 Hz, 1H), 7.39-7.40 (m, 5H), 7.60-7.63 (m, 1H).

[000842] Compound **143C**. LC-MS (ESI) m/z: 356 [M+H]⁺; ¹H-NMR (CDCl₃, 400 MHz): δ (ppm) 2.59-2.62 (m, 1H), 3.83-3.89 (m, 1H), 3.97-4.02 (m, 1H), 5.14 (s, 2H), 5.22-5.23 (m, 1H), 5.89-5.91 (m, 2H), 6.05-6.06 (m, 1H), 6.67-6.69 (m, 1H), 7.25-7.25 (m, 1H), 7.33-7.37 (m, 5H), 7.50-7.52 (m, 1H).

[000843] Compound **143D**. LC-MS (ESI) m/z: 380 [M+Na]⁺; ¹H-NMR (CDCl₃, 400 MHz): δ (ppm) 2.38 (s, 1H), 3.08 (s, 1H), 3.80-3.84 (m, 3H), 4.86 (s, 1H), 5.05 (s, 2H), 5.43-5.44 (m, 1H), 5.86 (s, 2H), 6.55-6.57 (m, 1H), 6.64 (s, 1H), 6.78-6.80 (m, 1H), 7.30-7.39 (m, 5H).

[000844] Compound **143E**. LC-MS (ESI) m/z: 418 [M-OH]⁺.

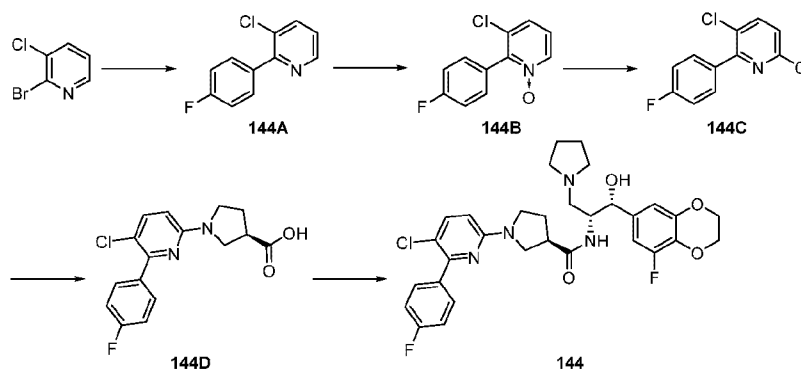
[000845] Compound **143F**. LC-MS (ESI) m/z: 411 [M+H]⁺; ¹H-NMR (CDCl₃, 400 MHz): δ (ppm) 1.77-1.80 (m, 4H), 2.67-2.68 (m, 4H), 2.76-2.80 (m, 1H), 2.86-2.91 (m, 1H), 3.98 (brs, 1H), 4.89-4.90 (m, 1H), 5.01-5.03 (m, 1H), 5.06 (s, 2H), 5.86 (s, 2H), 6.56 (d, *J* = 8.0 Hz, 1H), 6.61 (s, 1H), 6.74-6.76 (m, 1H), 7.29-7.39 (m, 5H).

[000846] Compound **143G** was synthesized, by employing the procedure described for Intermediate **E** using Compound **143F** in lieu of Intermediate **E7**. LC-MS (ESI) m/z: 277 [M+H]⁺.

[000847] Compound **143G**. LC-MS (ESI) m/z: 277 [M+H]⁺.

[000848] Compound **143** was synthesized, by employing the procedure described for Compound **1** using Intermediate **Z** and Compound **143G** in lieu of Compound **1B** and Intermediate **A**. LC-MS (ESI) m/z: 484 [M+H]⁺; ¹H-NMR (CD₃OD, 400 MHz): δ (ppm) 2.01-2.29 (m, 6H), 2.72-2.76 (m, 1H), 3.11-3.29 (m, 4H), 3.35-3.41 (m, 2H), 3.46-3.50 (m, 1H), 3.56-3.62 (m, 1H), 3.65-3.70 (m, 1H), 3.78-3.83 (m, 1H), 4.47-4.50 (m, 1H), 4.82 (d, *J* = 2.4 Hz, 1H), 6.03 (s, 2H), 6.59-6.61 (m, 3H), 6.79 (d, *J* = 1.6 Hz, 1H), 6.87-6.90 (m, 1H), 7.16-7.18 (m, 2H).

Example 144



[000849] A mixture of 2-bromo-3-chloropyridine (5 g, 26 mmol), 4-fluorophenylboronic acid (3.64 g, 26 mmol), Pd(PPh)₂Cl₂ (1.8 g, 2.6 mmol), and K₂CO₃ (5.0 g, 39 mmol) in dioxane (100 mL) and water (10 mL) was stirred at 80 °C for 2 h. The mixture was diluted with ethyl acetate (200 mL), washed with water (100 mL x 2) and brine (100 mL), dried over anhydrous sodium sulfate, concentrated, and purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, 10% v/v) to afford Compound **144A**. LC-MS (ESI) m/z: 208 [M+H]⁺; ¹H-NMR (CDCl₃, 400 MHz): δ (ppm) 7.14-7.14 (m, 2H), 7.24 (dd, *J*₁ = 4.4 Hz, *J*₂ = 8.0 Hz, 1H), 7.71-7.76 (m, 2H), 7.80 (dd, *J*₁ = 1.6 Hz, *J*₂ = 8.4 Hz, 1H), 8.59 (dd, *J*₁ = 1.2 Hz, *J*₂ = 4.4 Hz, 1H).

[000850] To a mixture of Compound **144A** (4.1 g, 19.75 mmol) in dichloromethane (80 mL) was added MCPBA (4.1 g, 23.7 mmol) in portions at room temperature. The mixture was stirred at room temperature for 1 h, diluted with dichloromethane (200 mL), washed with water (200 mL x 2) and brine (100 mL), dried over anhydrous sodium sulfate, concentrated, and purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, 50% v/v) to afford Compound **144B**. LC-MS (ESI) m/z: 224 [M+H]⁺; ¹H-NMR (CDCl₃, 400 MHz): δ (ppm) 7.12-7.16 (m, 3H), 7.33-7.41 (m, 3H), 8.21 (dd, *J*₁ = 1.2 Hz, *J*₂ = 7.2 Hz, 1H).

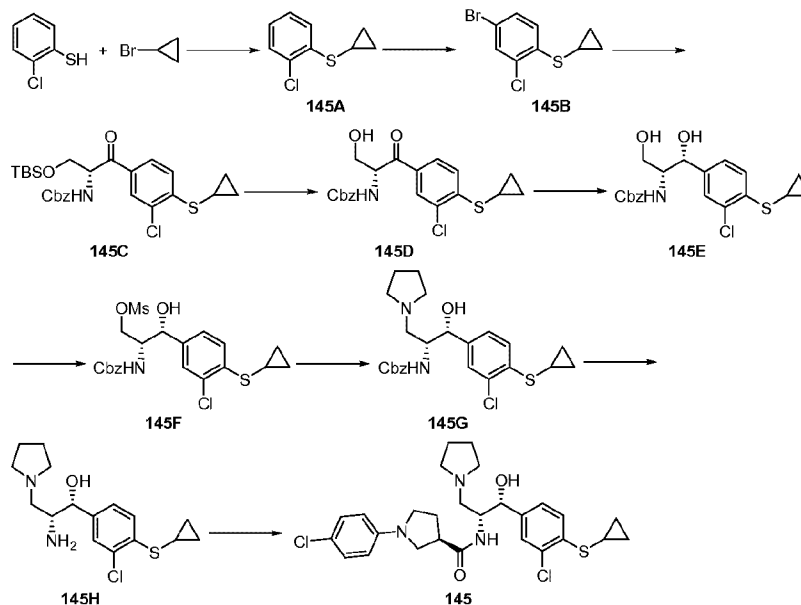
[000851] A mixture of Compound **144B** (3.3 g, 14.76 mmol) in POCl₃ (32 mL) was stirred at 135 °C for 1 h. POCl₃ was removed with evaporation under *vacuo*. The residue was dissolved in dichloromethane (200 mL), washed with water (100 mL x 3) and brine (100 mL), dried over anhydrous sodium sulfate, concentrated, and purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, 20% v/v) to afford Compound **144C**. LC-MS (ESI) m/z: 242 [M+H]⁺; ¹H-NMR (CDCl₃, 400 MHz): δ (ppm) 7.13-7.18 (m, 2H), 7.25 (d, *J* = 8.4 Hz, 1H), 7.74-7.77 (m, 3H).

[000852] Compounds **144D** and **144** were synthesized, by employing the procedures described for Compounds **1B** and **1** using Compound **144C**, Intermediate **Z6**, Compound **144D**, and Intermediate **C** in lieu of 1-chloro-4-iodobenzene, Compound **1A**, **1B** and Intermediate **A**.

[000853] Compound **144D**. LC-MS (ESI) m/z : 321 $[M+H]^+$; $^1\text{H-NMR}$ (DMSO- d_6 , 400 MHz): δ (ppm) 2.12-2.24 (m, 2H), 3.15-3.21 (m, 1H), 3.40-3.48 (m, 2H), 3.55-3.67 (m, 2H), 6.51 (d, $J = 8.4$ Hz, 1H), 7.26-7.31 (m, 2H), 7.64 (d, $J = 8.8$ Hz, 1H), 7.73-7.76 (m, 2H), 12.51 (brs, 1H).

[000854] Compound **144**. LC-MS (ESI) m/z : 599 $[M+H]^+$; $^1\text{H-NMR}$ (DMSO- d_6 , 400 MHz): δ (ppm) 1.82-1.91 (m, 2H), 1.97-2.07 (m, 4H), 2.87-2.92 (m, 1H), 3.08-3.17 (m, 3H), 3.22-3.59 (m, 7H), 4.16-4.17 (m, 4H), 4.27-4.34 (m, 1H), 4.68-4.69 (m, 1H), 5.97 (brs, 1H), 6.39 (d, $J = 8.8$ Hz, 1H), 6.71 (s, 1H), 6.77 (d, $J = 12.8$ Hz, 1H), 7.27-7.32 (m, 2H), 7.68-7.75 (m, 3H), 8.02(d, $J = 9.6$ Hz, 1H), 9.29 (brs, 1H).

Example 145



[000855] To a solution of 2-chlorobenzenethiol (7.2 g, 50 mmol) in DMSO (20 mL) was added potassium *tert*-butoxide (6.7 g, 60 mmol) in portions under nitrogen at 5 °C. The reaction mixture was stirred at 25 °C for 15 min. To the above solution was added bromocyclopropane (12 g, 100 mmol) in DMSO (10 mL) dropwise. The reaction mixture was stirred under nitrogen at 80 °C. After the reaction mixture was cooled to ambient temperature, the dark solution was diluted with water (400 mL) and extracted with ethyl acetate (60 mL x 3). The combined organic phases were washed with brine (50 mL x 2), dried over anhydrous sodium sulfate, filtered, and concentrated to afford the crude product. The crude product was

purified with flash column chromatography on silica gel (petroleum ether) to furnish Compound **145A**. LC-MS (m/z) 185 [M+H]⁺; ¹H-NMR (CDCl₃, 400 MHz): δ (ppm) 0.71-0.75 (m, 2H), 1.11-1.16 (m, 2H), 2.10-2.16 (m, 1H), 7.05-7.10 (m, 1H), 7.23-7.27 (m, 1H), 7.31 (dd, J = 8.0, 1.2 Hz, 1H), 7.55 (dd, J = 8.0, 1.2 Hz, 1H).

[000856] To a solution of Compound **145A** (36 g, 195.6 mmol) in dry dichloromethane (600 mL) was added Br₂ (37.6 g, 235 mmol) at 5 °C dropwise. The reaction mixture was stirred at 25 °C for 22 hours. It was washed with water (200 mL), saturated sodium thiosulfate (200 mL) and brine (200 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to afford a crude product. The crude product was purified with flash column chromatography on silica gel (petroleum ether) to furnish Compound **145B**. LC-MS (m/z) 263 [M+H]⁺; ¹H-NMR (CDCl₃, 400 MHz): δ (ppm) 0.71-0.75 (m, 2H), 1.12-1.16 (m, 2H), 2.08-2.12 (m, 1H), 7.37 (d, J = 2.0 Hz, 1H), 7.40 (s, 1H), 7.47 (d, J = 2.0 Hz, 1H).

[000857] Compounds **145C**, **145D**, **145E**, **145F**, and **145G** were synthesized, by employing the procedures described correspondingly for Intermediates **A5**, **A6**, **A7**, **A8**, and **A9** using Compounds **145B**, **145C**, **145D**, **145E**, and **145F** in lieu of 6-bromo-2,3-dihydrobenzo[b][1,4]dioxine, Intermediates **A5**, **A6**, **A7**, and **A8**.

[000858] Compound **145C**. LC-MS (ESI) m/z: 520 [M+H]⁺; ¹H-NMR (CDCl₃, 400 MHz): δ (ppm) -0.12 (s, 3H), -0.10 (s, 3H), 0.84 (s, 9H), 0.85-0.86 (m, 2H), 1.20-1.26 (m, 2H), 2.14-2.16 (m, 1H), 3.89-3.96 (m, 2H), 5.13 (s, 2H), 5.30-5.31 (m, 1H), 7.32-7.40 (m, 4H), 7.49 (d, J = 8.4 Hz, 1H), 7.64 (d, J = 8.4 Hz, 1H), 7.81-7.84 (m, 1H), 7.89 (d, J = 2.0 Hz, 1H).

[000859] Compound **145D**. LC-MS (ESI) m/z: 406 [M+H]⁺; ¹H-NMR (CDCl₃, 400 MHz): δ (ppm) 0.74-0.78 (m, 2H), 1.19-1.28 (m, 2H), 2.11-2.16 (m, 1H), 2.74 (s, 1H), 3.87-4.03 (m, 2H), 5.14 (s, 2H), 5.30-5.34 (m, 1H), 6.12 (d, J = 6.8 Hz, 1H), 7.34-7.37 (m, 5H), 7.66 (d, J = 8.0 Hz, 1H), 7.87 (d, J = 8.4 Hz, 1H), 7.93 (s, 1H).

[000860] Compound **145E**. LC-MS (ESI) m/z: 408 [M+H]⁺; ¹H-NMR (CDCl₃, 400 MHz): δ (ppm) 0.69-0.73 (m, 2H), 1.10-1.15 (m, 2H), 2.08-2.12 (m, 1H), 2.89 (s, 1H), 3.60 (s, 1H), 3.77-3.85 (m, 3H), 4.97-5.01 (m, 3H), 5.53 (d, J = 8.0 Hz, 1H), 7.20-7.24 (m, 2H), 7.26-7.36 (m, 5H), 7.48 (d, J = 8.4 Hz, 1H).

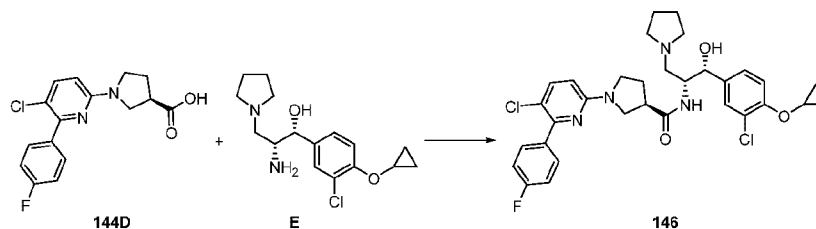
[000861] Compound **145F**, which was directly used for the next step without further purification. LC-MS (ESI) m/z: 468 [M-OH]⁺.

[000862] Compound **145G**. LC-MS (ESI) m/z: 461 [M+H]⁺.

[000863] Compound **145H** was synthesized, by employing the procedure described for Intermediate **E** using Compound **145G** in lieu of Intermediate **E7**, which was directly used for the next step without further purification. LC-MS (ESI) m/z : 327 $[M+H]^+$; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ (ppm) 0.69-0.73 (m, 2H), 1.12-1.15 (m, 2H), 1.84-1.88 (m, 2H), 2.11-2.16 (m, 1H), 2.24-2.26 (m, 2H), 3.15-3.27 (m, 2H), 3.45-3.58 (m, 4H), 4.38-4.49 (m, 1H), 4.71 (s, 1H), 7.25-7.36 (m, 2H), 7.48 (m, 1H).

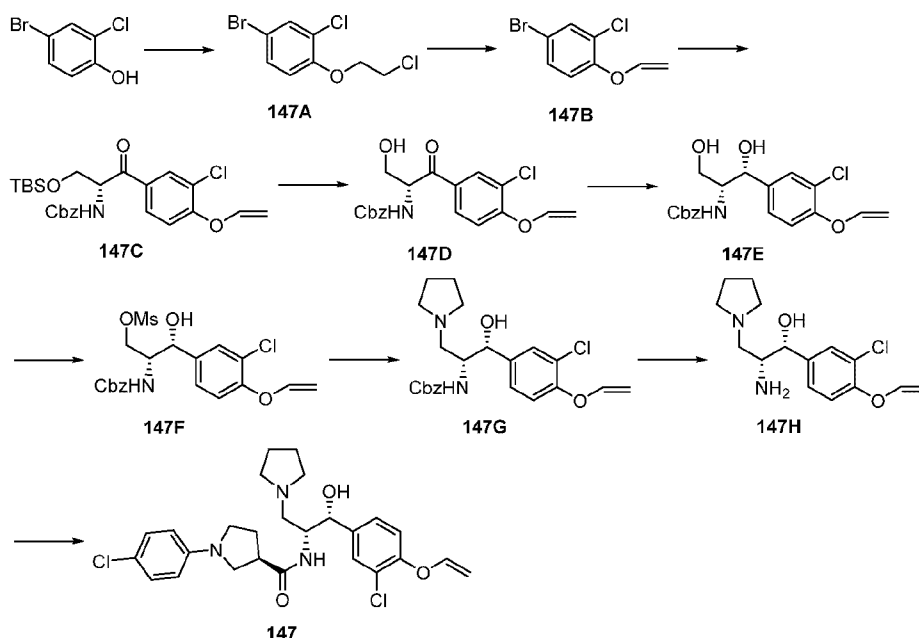
[000864] Compound **145** was synthesized, by employing the procedure described for Compound **1** using Intermediate **Z** and Compound **145H** in lieu of Compound **1B** and Intermediate **A**. LC-MS (m/z) 534 $[M+H]^+$; $^1\text{H-NMR}$ (CD_3OD , 400 MHz): δ (ppm) 0.55-0.57 (m, 2H), 1.08-1.18 (m, 2H), 2.02-2.22 (m, 7H), 2.45-2.50 (m, 1H), 3.07-3.11 (m, 1H), 3.18-3.24 (m, 5H), 3.49-3.53 (m, 1H), 3.60-3.69 (m, 2H), 3.80-3.87 (m, 1H), 4.57-4.62 (m, 1H), 4.95 (d, $J = 2.4$ Hz, 1H), 6.44 (d, $J = 8.8$ Hz, 2H), 7.13 (d, $J = 8.8$ Hz, 2H), 7.31 (dd, $J = 8.0$, 1.6 Hz, 1H), 7.53-7.56 (m, 2H), 8.12 (d, $J = 10.0$ Hz, 1H).

Example 146



[000865] Compound **146** was synthesized, by employing the procedure described for Compound **1** using Compound **144D** and Intermediate **E** in lieu of Compound **1B** and Intermediate **A**. LC-MS (ESI) m/z : 613 $[M+H]^+$; $^1\text{H-NMR}$ ($\text{DMSO}-d_6$, 400 MHz): δ (ppm) 0.57-0.59 (m, 2H), 0.70-0.72 (m, 2H), 1.82-1.91 (m, 2H), 1.98-2.07 (m, 4H), 2.85-2.92 (m, 1H), 3.08-3.17 (m, 3H), 3.22-3.36 (m, 2H), 3.41-3.56 (m, 5H), 3.70-3.76 (m, 1H), 4.33-4.37 (m, 1H), 4.77-4.78 (m, 1H), 5.98 (brs, 1H), 6.38 (d, $J = 8.8$ Hz, 1H), 7.23-7.32 (m, 4H), 7.39 (s, 1H), 7.65 (d, $J = 8.4$ Hz, 1H), 7.73-7.76 (m, 2H), 8.04 (d, $J = 9.6$ Hz, 1H), 9.36 (brs, 1H).

Example 147



[000866] To a solution of 4-bromo-2-chlorophenol (5.04 g, 24.3 mmol) in DMF (30 mL) and was added K_2CO_3 (10.10 g, 72.9 mmol) and 2-chloroethyl-p-toluenesulfonate (4.86 mL, 26.7 mmol). The resulting mixture was heated to 60 °C for 3 hours and cooled to room temperature. The reaction mixture was diluted with ethyl acetate (150 mL) and washed with water (150 mL x 3). The organic phases were dried over anhydrous sodium sulfate and concentrated to furnish Compound **147A**. LC-MS (ESI) m/z : 269 $[M+H]^+$.

[000867] To a solution of Compound **147A** (6.46 g, 24.1 mmol) in DMF (30 mL) was added sodium hydride (1.94 g of 60% dispersion in mineral oil, 48.6 mmol). The resulting mixture was stirred at room temperature for 16 hours. The reaction was diluted with ethyl acetate (150 mL) and washed with water (150 mL x 3). The organic phases were dried over anhydrous sodium sulfate and concentrated to afford Compound **147B**. LC-MS (ESI) m/z : No.

[000868] Compounds **147C**, **147D**, **147E**, **147F**, and **147G** were synthesized, by employing the procedures described correspondingly for Intermediates **A5**, **A6**, **A7**, **A8**, and **A9** using Compounds **147B**, **147C**, **147D**, **147E**, and **147F** in lieu of 6-bromo-2,3-dihydrobenzo[b][1,4]dioxine, Intermediates **A5**, **A6**, **A7**, and **A8**.

[000869] Compound **147C**. LC-MS (ESI) m/z : 490 $[M+H]^+$.

[000870] Compound **147D**. LC-MS (ESI) m/z : 376 $[M+H]^+$.

[000871] Compound **147E**. LC-MS (ESI) m/z : 360 $[M-OH]^+$; ^1H -NMR ($CDCl_3$, 400 MHz): δ (ppm) 1.62 (s, 1H), 2.37-2.38 (m, 1H), 3.27 (s, 1H), 3.83-3.84 (m, 3H), 4.50 (dd, J =

2.0 Hz, 6.0 Hz, 1H), 4.76 (dd, $J = 1.6$ Hz, 13.2 Hz, 1H), 5.02 (s, 2H), 5.46 (s, 1H), 6.54-6.59 (m, 1H), 6.98 (d, $J = 8.8$ Hz, 1H), 7.19-7.22 (m, 1H), 7.27-7.35 (m, 5H), 7.44 (s, 1H).

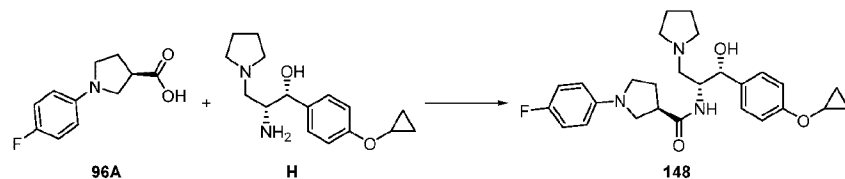
[000872] Compound **147F**, which was directly used for the next step without further purification. LC-MS (ESI) m/z: 438 [M-OH]⁺.

[000873] Compound **147G**. LC-MS (ESI) m/z: 431 [M+H]⁺.

[000874] Compound **147H** was synthesized, by employing the procedure described for Intermediate **E** using Compound **147G** in lieu of Intermediate **E7**, which was directly used for the next step without further purification. LC-MS (ESI) *m/z*: 297 [M+H]⁺.

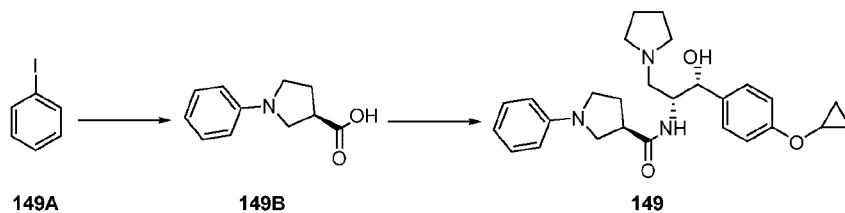
[000875] Compound **147** was synthesized, by employing the procedure described for Compound **1** using Intermediate **Z** and Compound **147H** in lieu of Compound **1B** and Intermediate **A**. LC-MS (ESI) m/z: 504 [M+H]⁺; ¹H-NMR (CD₃OD, 400 MHz): δ (ppm) 2.03-2.21 (m, 6H), 2.56-2.60 (m, 1H), 3.11-3.29 (m, 6H), 3.48-3.51 (m, 1H), 3.60-3.67 (m, 3H), 4.47 (dd, *J* = 6.0 Hz, 2.0 Hz, 1H), 4.50-4.53 (m, 1H), 4.66 (dd, *J* = 14.0 Hz, 2.0 Hz, 1H), 4.93-4.94 (m, 1H), 6.44 (d, *J* = 9.2 Hz, 2H), 6.57-6.62 (m, 1H), 7.04 (d, *J* = 8.4 Hz, 1H), 7.10-7.14 (m, 2H), 7.32 (dd, *J* = 8.4 Hz, 2.0 Hz, 1H), 7.59 (d, *J* = 1.6 Hz, 1H), 8.13 (d, 1H).

Example 148



[000876] Compound **148** was synthesized, by employing the procedure described for Compound **1** using Intermediate **96A** and Intermediate **H** in lieu of Compound **1B** and Intermediate **A**. LC-MS (ESI) m/z : 468 $[M+H]^+$; ^1H -NMR (CD_3OD , 400 MHz): δ (ppm) 0.57-0.67 (m, 2H), 0.71-0.76 (m, 2H), 1.36-1.39 (m, 1H), 2.02-2.10 (m, 3H), 2.11-2.24 (m, 3H), 2.62-2.66 (m, 1H), 3.10-3.30 (m, 6H), 3.46-3.84 (m, 6H), 4.52-4.56 (m, 1H), 6.50-6.53 (m, 2H), 6.95 (d, $J = 8.8$ Hz, 2H), 7.02 (d, $J = 8.8$ Hz, 1H), 7.35 (d, $J = 8.4$ Hz, 2H).

Example 149



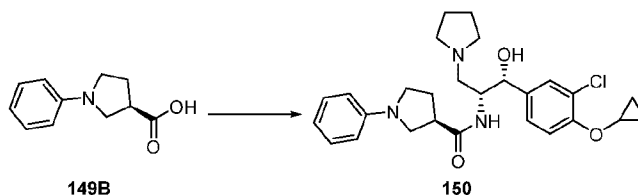
[000877] Compounds **149B** and **149** were synthesized, by employing the procedures described for Compounds **1B** and **1** using Compound **149A**, Intermediate **Z6**, Compound

149B, and Intermediate **H** in lieu of 1-chloro-4-iodobenzene, Compound **1A**, **1B** and Intermediate **A**.

[000878] Compound **149B**. LC-MS (ESI) m/z : 192 $[M+H]^+$; $^1\text{H-NMR}$ (CD_3OD , 400 MHz): δ (ppm) 2.01-2.07 (m, 2H), 2.88-3.17 (m, 3H), 3.23-3.30 (m, 2H), 6.33-6.41 (m, 3H), 6.91-6.95 (m, 2H).

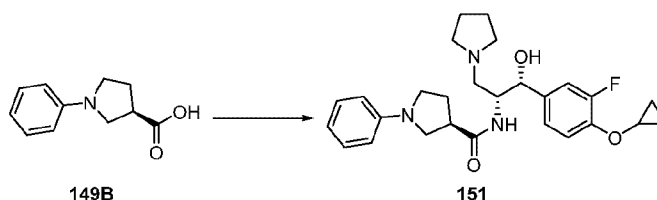
[000879] Compound **149**. LC-MS (ESI) m/z : 450 $[M+H]^+$; $^1\text{H-NMR}$ (CD_3OD , 400 MHz): δ (ppm) 0.49-0.60 (m, 2H), 0.66-0.74 (m, 2H), 1.98-2.09 (m, 2H), 2.18-2.41 (m, 4H), 2.84-2.88 (m, 1H), 3.17-3.32 (m, 3H), 3.46-3.62 (m, 6H), 3.67-3.72 (m, 1H), 3.76-3.84 (m, 1H), 4.51-4.55 (m, 1H), 4.98 (d, $J = 2.4$ Hz, 1H), 6.99-7.04 (m, 4H), 7.14 (t, $J = 7.6$ Hz, 1H), 7.33-7.51 (m, 5H).

Example 150



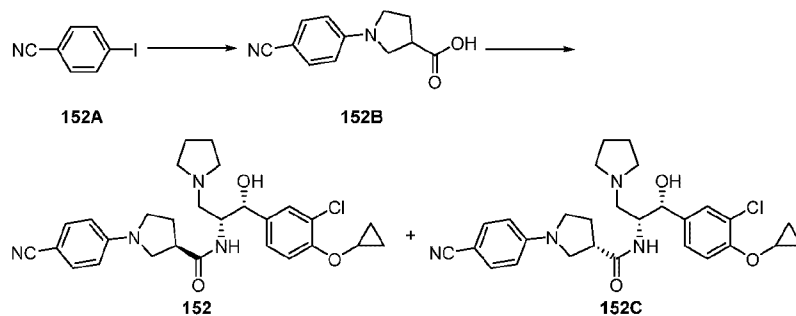
[000880] Compound **150** was synthesized, by employing the procedure described for Compound **1** using Intermediate **149B** and Intermediate **E** in lieu of Compound **1B** and Intermediate **A**. LC-MS (ESI) m/z : 484 $[M+H]^+$; $^1\text{H-NMR}$ (CD_3OD , 400 MHz): δ (ppm) 0.58-0.64 (m, 2H), 0.65-0.78 (m, 2H), 2.01-2.17 (m, 2H), 2.20-2.40 (m, 4H), 2.80-2.87 (m, 1H), 3.19-3.32 (m, 3H), 3.50-3.54 (m, 1H), 3.55-3.65 (m, 4H), 3.68-3.72 (m, 2H), 4.52-4.56 (m, 1H), 4.93 (d, $J = 2.4$ Hz, 1H), 7.06 (d, $J = 8.0$ Hz, 2H), 7.18 (t, $J = 7.6$ Hz, 1H), 7.29-7.37 (m, 2H), 7.42 (t, $J = 8.4$ Hz, 2H), 7.48-7.51 (m, 1H).

Example 151



[000881] Compound **151** was synthesized, by employing the procedure described for Compound **1** using Intermediate **149B** and Intermediate **G** in lieu of Compound **1B** and Intermediate **A**. LC-MS (ESI) m/z : 468 $[M+H]^+$; $^1\text{H-NMR}$ (CD_3OD , 400 MHz): δ (ppm) 0.61-0.78 (m, 4H), 1.98-2.15 (m, 3H), 2.20-2.27 (m, 3H), 2.61-2.65 (m, 1H), 3.09-3.33 (m, 6H), 3.48-3.61 (m, 2H), 3.63-3.70 (m, 1H), 3.74-3.84 (m, 2H), 4.52-4.56 (m, 1H), 4.91 (d, $J = 2.4$ Hz, 1H), 6.49-6.55 (m, 2H), 6.63-6.70 (m, 1H), 7.13-7.36 (m, 5H).

Example 152



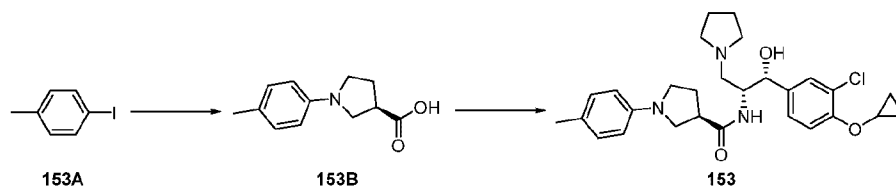
[000882] Compounds **152B**, **152** and **152C** were synthesized, by employing the procedures described for Compounds **1B** and **1** using Compound **152A**, Compound **152B**, and Intermediate **E** in lieu of 1-chloro-4-iodobenzene, Compound **1B** and Intermediate **A**.

[000883] Compound **152B**. LC-MS (ESI) m/z : 217 $[M+H]^+$.

[000884] Compound **152**. LC-MS (ESI) m/z : 509 $[M+H]^+$; $^1\text{H-NMR}$ (CD_3OD , 400 MHz): δ (ppm) 0.61-0.75 (m, 4H), 1.64-1.73 (m, 4H), 1.82-1.87 (m, 3H), 2.09-2.19 (m, 1H), 2.46-2.52 (m, 5H), 2.70-2.74 (m, 1H), 3.20-3.24 (m, 1H), 3.52-3.54 (m, 1H), 3.74-3.77 (m, 1H), 3.97-3.99 (m, 1H), 4.14-4.15 (m, 1H), 4.77 (d, $J = 2.4$ Hz, 1H), 6.35 (d, $J = 8.4$ Hz, 2H), 7.15-7.25 (m, 2H), 7.32 (d, $J = 8.4$ Hz, 2H), 7.38 (s, 1H). Chiral-HPLC condition, solvent: MeOH (0.1% NH_4OH), column: RegisCell (4.6 * 250 mm, 5 μm), R_t : 3.76 min.

[000885] Compound **152C**. LC-MS (ESI) m/z : 509 $[M+H]^+$; $^1\text{H-NMR}$ (CD_3OD , 400 MHz): δ (ppm) 0.58-0.72 (m, 4H), 1.72-1.77 (m, 4H), 2.06-2.12 (m, 2H), 2.55-2.62 (m, 4H), 2.70-2.72 (m, 2H), 2.80-2.82 (m, 1H), 3.03-3.07 (m, 1H), 3.24-3.26 (m, 1H), 3.32-3.37 (m, 1H), 3.67-3.69 (m, 1H), 3.67-3.69 (m, 1H), 4.20-4.21 (m, 1H), 4.84 (d, $J = 2.4$ Hz, 1H), 6.48 (d, $J = 8.4$ Hz, 2H), 7.13-7.20 (m, 2H), 7.36 (s, 1H), 7.39 (d, $J = 8.4$ Hz, 2H). Chiral-HPLC condition, solvent: MeOH (0.1% NH_4OH), column: RegisCell (4.6 * 250 mm, 5 μm), R_t : 4.98 min.

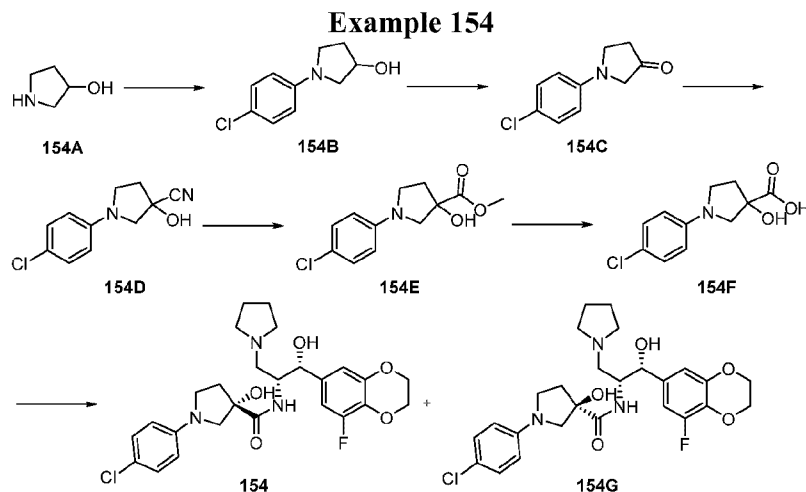
Example 153



[000886] Compounds **153B** and **153** were synthesized, by employing the procedures described for Compounds **1B** and **1** using Compound **153A**, Intermediate **Z6**, Compound **153B**, and Intermediate **E** in lieu of 1-chloro-4-iodobenzene, Compounds **1A**, **1B** and Intermediate **A**.

[000887] Compound **153B**. LC-MS (ESI) m/z : 206 $[M+H]^+$.

[000888] Compound **153**. LC-MS (ESI) m/z : 498 $[M+H]^+$; ^1H -NMR (CD_3OD , 400 MHz): δ (ppm) 0.53-0.68 (m, 4H), 1.73-1.76 (m, 4H), 1.95-2.09 (m, 2H), 2.11 (s, 3H), 2.57-2.74 (m, 7H), 2.93-2.97 (m, 1H), 3.06-3.22 (m, 3H), 3.62-3.66 (m, 1H), 4.17-4.21 (m, 1H), 4.77 (d, $J = 2.2$ Hz, 1H), 6.35 (d, $J = 8.4$ Hz, 2H), 6.87 (d, $J = 8.4$ Hz, 2H), 7.10-7.17 (m, 2H), 7.31 (s, 1H). Chiral-HPLC condition, solvent: *n*-hexane (0.1% NH_4OH) : EtOH (0.1% NH_4OH), column: IA-H (4.6 * 250 mm, 5 μm), R_t : 7.25 min.



[000889] Compound **154B** was synthesized, by employing the procedure described for Compound **1B** using Compound **154A** in lieu of Compound **1A**. LC-MS (ESI) m/z : 198 $[M+H]^+$; ^1H -NMR ($CDCl_3$, 400 MHz): δ (ppm) 1.69-1.7 (m, 1H), 2.04-2.08 (m, 1H), 2.13-2.22 (m, 1H), 3.22-3.24 (m, 1H), 3.29-3.33 (m, 1H), 3.44-3.50 (m, 2H), 4.59-4.61 (m, 1H), 6.46 (d, $J = 8.8$ Hz, 2H), 7.16 (d, $J = 8.8$ Hz, 2H).

[000890] To a solution of oxalyl dichloride (5.7 g, 44.9 mmol) in dichloromethane (30 mL) was added dropwise DMSO (7.2 g, 73.4 mmol) under nitrogen at $-78^\circ C$. The mixture was stirred at $-78^\circ C$ for 30 min and Compound **154B** (4.3 g, 21.8 mmol) was added dropwise. The reaction mixture was stirred at $-78^\circ C$ for 2 h and triethylamine (16 mL) was slowly added to the mixture at $-78^\circ C$. The mixture was allowed to warm to room temperature and stirred for 2 h. The reaction mixture was quenched with water (50 mL) and diluted with dichloromethane (100 mL). The organic layer was washed with water (50 mL) and brine (50 mL), dried over anhydrous sodium sulfate, concentrated, and purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, 10% v/v) to give Compound **154C**. LC-MS (ESI) m/z : 196 $[M+H]^+$; ^1H -NMR ($CDCl_3$, 400 MHz): δ (ppm) 2.74 (m, 2H), 3.65-3.68 (m, 4H), 6.58 (d, $J = 8.8$ Hz, 2H), 7.24 (d, $J = 8.8$ Hz, 2H).

[000891] To a solution of Compound **154C** (415 mg, 2.12 mmol) in methanol (20 mL) was added NaCN (251 mg, 4.5 mmol) and acetic acid (255 mg, 4.5 mmol). The reaction mixture was stirred at room temperature overnight. The mixture was diluted with water (30 mL) and stirred for 30 min and extracted with ethyl acetate (50 mL x 2). The organic layer was washed with water (50 mL) and brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to give Compound **154D**. The crude product was directly used for the next step without further purification. LC-MS (ESI) m/z : 223 $[M+H]^+$.

[000892] A solution of Compound **154D** (1 g, 9.5 mmol) in methanol (20 mL) was stirred at room temperature for 4 h under HCl (gas) atmosphere. The mixture was diluted with water (20 mL) and extracted with ethyl acetate (50 mL x 2). The organic layer was washed with water (20 mL) and brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to give a crude compound. The crude product was purified with reverse flash column chromatography on silica gel using eluent (methanol in water, from 0% to 55% v/v) to furnish Compound **154E**. LC-MS (ESI) m/z : 256 $[M+H]^+$; ^1H -NMR (CD_3OD , 400 MHz): δ (ppm) 1.98-2.03 (m, 1H), 2.23-2.31 (m, 1H), 3.34 (d, $J = 11.2$ Hz, 1H), 3.49-3.63 (m, 2H), 3.84 (d, $J = 12.4$ Hz, 1H), 4.8 (s, 3H), 7.13-7.17 (m, 4H).

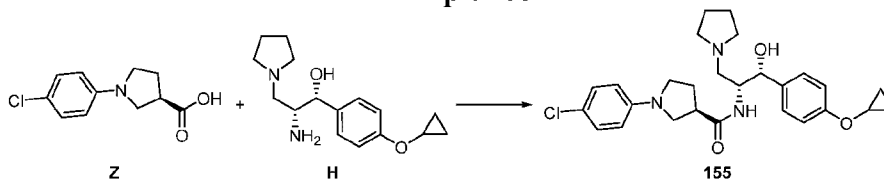
[000893] Compound **154F** was synthesized, by employing the procedure described for Compound **5C** using Compound **154E** in lieu of Compound **5B**. LC-MS (ESI) m/z : 242 $[M+H]^+$.

[000894] Compounds **154** and **154G** were synthesized, by employing the procedures described for Compound **7** using Compound **154F** and Intermediate **C** in lieu of Compound **7B** and Intermediate **A**.

[000895] Compound **154**. LC-MS (ESI) m/z : 520 $[M+H]^+$; ^1H -NMR (CD_3OD , 400 MHz): δ (ppm) 1.93-2.18 (m, 6H), 3.16-3.28 (m, 3H), 3.36-3.51 (m, 3H), 3.66-3.76 (m, 4H), 4.28 (s, 4H), 4.38-4.41 (m, 1H), 4.80-4.81 (m, 1H), 6.49 (d, $J = 8.8$ Hz, 2H), 6.77-6.79 (m, 2H), 7.12 (d, $J = 8.8$ Hz, 2H). Chiral-HPLC, solvent: *n*-hexane (0.1% NH_4OH) : EtOH (0.1% NH_4OH) = 50 : 50, column: IA (4.6 * 250 mm, 5 μm), Rt: 8.01 min.

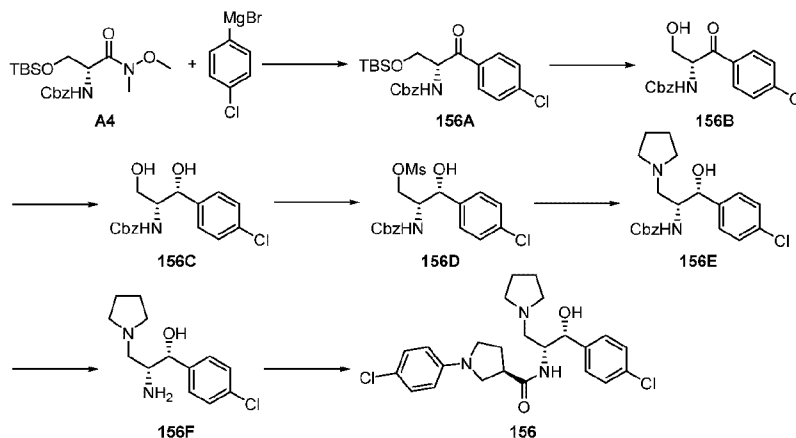
[000896] Compound **154G**. LC-MS (ESI) m/z : 520 $[M+H]^+$; ^1H -NMR (CD_3OD , 400 MHz): δ (ppm) 2.03-2.18 (m, 5H), 2.49-2.57 (m, 1H), 3.02-3.05 (m, 1H), 3.13-3.21 (m, 3H), 3.42-3.53 (m, 3H), 3.67-3.74 (m, 3H), 4.3 (s, 4H), 4.41-4.43 (m, 1H), 4.83-4.84 (m, 1H), 6.48 (d, $J = 8.8$ Hz, 2H), 6.76-6.81 (m, 2H), 7.15 (d, $J = 8.8$ Hz, 2H). Chiral-HPLC condition, solvent: *n*-hexane (0.1% NH_4OH) : EtOH (0.1% NH_4OH) = 50 : 50, column: IA (4.6 * 250 mm, 5 μm), Rt: 10.90 min.

Example 155



[000897] Compound **155** was synthesized, by employing the procedure described for Compound **7** using Intermediates **Z** and **H** in lieu of Compound **7B** and Intermediate **A**. LC-MS (ESI) m/z : 484 $[M+H]^+$; $^1\text{H-NMR}$ (CD_3OD , 400 MHz): δ (ppm) 0.53-0.78 (m, 4H), 1.95-2.24 (m, 6H), 2.64 (dd, $J = 9.3, 6.7$ Hz, 1H), 3.07-3.30 (m, 6H), 3.47-3.69 (m, 4H), 3.76-3.86 (m, 1H), 4.52 (dt, $J = 10.4, 2.9$ Hz, 1H), 4.92 (d, $J = 2.7$ Hz, 1H), 6.48 (d, $J = 8.9$ Hz, 2H), 7.00 (d, $J = 8.7$ Hz, 2H), 7.15 (d, $J = 8.9$ Hz, 2H), 7.34 (d, $J = 8.6$ Hz, 2H).

Example 156



[000898] To a solution of Intermediate **A4** (8.0 g, 20 mmol) in dry THF (200 mL) was added (4-chlorophenyl)magnesium bromide (1 M in 2-methyltetrahydrofuran, 100 mL, 100 mmol) under nitrogen at 0 °C and stirred at room temperature overnight. The mixture was quenched with saturated aqueous ammonium chloride solution (100 mL) and extracted with ethyl acetate (200 mL x 3). The organic layer was washed with brine (200 mL), dried over anhydrous sodium sulfate, concentrated, and purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, 10% v/v) to furnish Compound **156A**. LC-MS (ESI) m/z : 448 $[M+H]^+$; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ (ppm) 0.12 (s, 3H), 0.16 (s, 3H), 0.74 (s, 9H), 3.88-3.98 (m, 2H), 5.13 (s, 2H), 5.30-5.34 (m, 1H), 5.90-5.91 (m, 1H), 7.32-7.37 (m, 5H), 7.45-7.47 (m, 2H), 7.87-7.89 (m, 2H).

[000899] Compounds **156B**, **156C**, **156D**, and **156E** were synthesized, by employing the procedures described correspondingly for Intermediates **A6**, **A7**, **A8**, and **A9** using Compounds **156A**, **156B**, **156C**, and **156D** in lieu of Intermediates **A5**, **A6**, **A7**, and **A8**.

[000900] Compound **156B**. LC-MS (ESI) m/z : 334 $[M+H]^+$; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ (ppm) 2.54 (t, $J = 6.0$ Hz, 1H), 3.88-4.05 (m, 2H), 5.15 (s, 2H), 5.32-5.34 (m, 1H), 6.04-6.05 (m, 1H), 7.34-7.36 (m, 5H), 7.47-7.49 (m, 2H), 7.93-7.95 (m, 2H).

[000901] Compound **156C**. LC-MS (ESI) m/z : 336 $[M+H]^+$; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ (ppm) 2.29 (s, 1H), 3.15 (s, 1H), 3.85-3.86 (m, 3H), 5.02-5.04 (m, 3H), 5.42 (s, 1H), 7.29-7.35 (m, 9H).

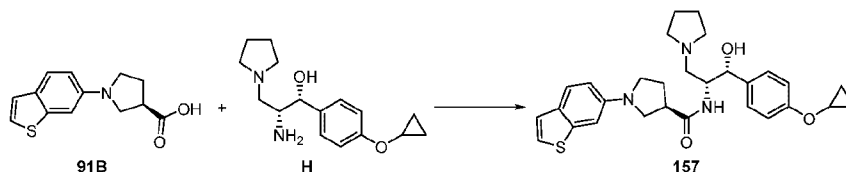
[000902] Compound **156D**. LC-MS (ESI) m/z : 414 $[M+H]^+$.

[000903] Compound **156E**. LC-MS (ESI) m/z : 389 $[M+H]^+$; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ (ppm) 1.77-1.79 (m, 4H), 2.64-2.66 (m, 4H), 2.81-2.87 (m, 2H), 4.01 (s, 1H), 4.98-5.05 (m, 4H), 7.23-7.24 (m, 2H), 7.29-7.37 (m, 7H).

[000904] Compound **156F** was synthesized, by employing the procedure described for Intermediate **E** using Compound **156E** in lieu of Intermediate **E7**. LC-MS (ESI) m/z : 255 $[M+H]^+$.

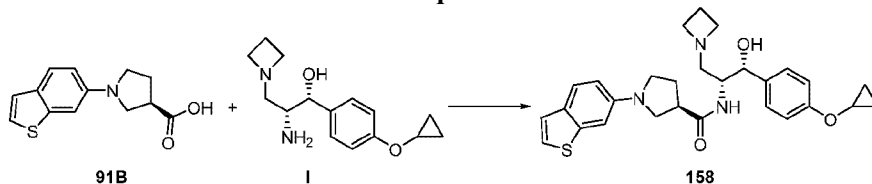
[000905] Compound **156** was synthesized, by employing the procedure described for Compound **7** using Intermediate **Z** and Compound **156F** in lieu of Compound **7B** and Intermediate **A**. LC-MS (ESI) m/z : 462 $[M+H]^+$; $^1\text{H-NMR}$ ($\text{DMSO}-d_6$, 400 MHz): δ (ppm) 1.87-2.04 (m, 6H), 2.41-2.45 (m, 1H), 3.08-3.53 (m, 10H), 4.38-4.42 (m, 1H), 4.85-4.85 (m, 1H), 6.01 (s, 1H), 6.40 (d, $J = 9.2$ Hz, 2H), 7.18 (d, $J = 8.4$ Hz, 2H), 7.38 (s, 4H), 7.98 (d, $J = 9.6$ Hz, 1H), 9.32 (s, 1H).

Example 157



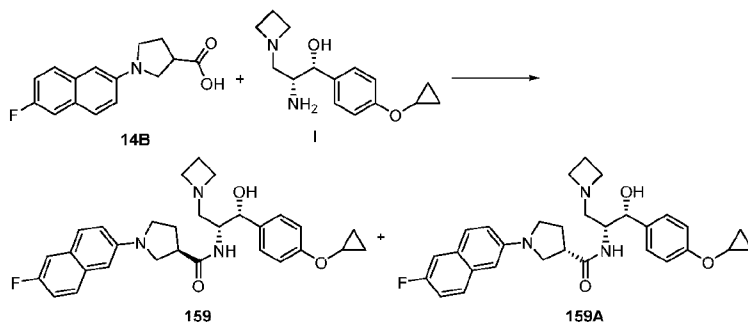
[000906] Compound **157** was synthesized, by employing the procedure described for Compound **7** using Compound **91B** and Intermediate **H** in lieu of Compound **7B** and Intermediate **A**. LC-MS (ESI) m/z : 506 $[M+H]^+$; $^1\text{H-NMR}$ (CD_3OD , 400 MHz): δ (ppm) 0.49-0.69 (m, 4H), 1.95-2.31 (m, 6H), 2.78-2.82 (m, 1H), 3.14-3.28 (m, 3H), 3.34-3.62 (m, 6H), 3.66-3.74 (m, 1H), 3.81-3.87 (m, 1H), 4.53-4.57 (m, 1H), 4.92-4.95 (m, 1H), 6.80 (d, $J = 8.8$ Hz, 1H), 6.98-7.04 (m, 2H), 7.11 (s, 1H), 7.24 (dd, $J = 14.4, 5.2$ Hz, 2H), 7.35 (d, $J = 8.8$ Hz, 2H), 7.70 (d, $J = 8.4$ Hz, 1H).

Example 158



[000907] Compound **158** was synthesized, by employing the procedure described for Compound **7** using Compound **91B** and Intermediate **I** in lieu of Compound **7B** and Intermediate **A**. LC-MS (ESI) m/z : 492 $[M+H]^+$; $^1\text{H-NMR}$ (CD_3OD , 400 MHz): δ (ppm) 0.50-0.69 (m, 4H), 2.13-2.21 (m, 1H), 2.26-2.35 (m, 1H), 2.56-2.68 (m, 1H), 2.78-2.82 (m, 1H), 2.80-2.87 (m, 1H), 3.14-3.21 (m, 1H), 3.37-3.50 (m, 4H), 3.53-3.61 (m, 2H), 4.16-4.37 (m, 5H), 4.86-4.91 (m, 1H), 6.80 (d, $J = 8.8$ Hz, 1H), 6.98-7.04 (m, 2H), 7.11 (s, 1H), 7.24 (dd, $J = 15.6, 5.6$ Hz, 2H), 7.35 (d, $J = 8.4$ Hz, 2H), 7.70 (d, $J = 8.8$ Hz, 1H).

Example 159



[000908] Compound **159** and **159A** were synthesized, by employing the procedures described for Compound **7** using Compound **14B** and Intermediate **I** in lieu of Compound **7B** and Intermediate **A**.

[000909] Compound **159**. LC-MS (ESI) m/z : 504 $[M+H]^+$; $^1\text{H-NMR}$ (CD_3OD , 400 MHz): δ (ppm) 0.46-0.55 (m, 4H), 1.97-2.13 (m, 4H), 2.15-2.26 (m, 2H), 2.92-3.03 (m, 2H), 3.17-3.22 (m, 2H), 3.22-3.34 (m, 5H), 3.46-3.49 (m, 1H), 3.99-4.01 (m, 1H), 4.70 (d, $J = 3.2$ Hz, 1H), 6.63-6.64 (m, 1H), 6.86-6.92 (m, 3H), 7.01-7.06 (m, 1H), 7.16-7.22 (m, 3H), 7.53-7.57 (m, 2H). Chiral-HPLC condition, solvent: MeOH (0.5% NH_4OH), column: AD-H (4.6 * 250 mm, 5 μm), Rt: 3.24 min.

[000910] Compound **159A**. LC-MS (ESI) m/z : 504 $[M+H]^+$; $^1\text{H-NMR}$ (CD_3OD , 400 MHz): δ (ppm) 0.53-0.69 (m, 4H), 1.65-1.70 (m, 1H), 2.01-2.06 (m, 1H), 2.35-2.46 (m, 2H), 3.03-3.07 (m, 1H), 3.19-3.21 (m, 1H), 3.22-3.23 (m, 1H), 3.36-3.47 (m, 4H), 3.61-3.64 (m, 1H), 4.08-4.14 (m, 4H), 4.21-4.24 (m, 1H), 4.76 (d, $J = 3.2$ Hz, 1H), 6.67-6.68 (m, 1H), 6.90-6.95 (m, 3H), 7.00-7.05 (m, 1H), 7.19-7.24 (m, 3H), 7.50-7.55 (m, 2H). Chiral-HPLC

DEMANDES OU BREVETS VOLUMINEUX

**LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVETS
COMPREND PLUS D'UN TOME.**

CECI EST LE TOME __1__ DE __2__

NOTE: Pour les tomes additionels, veuillez contacter le Bureau Canadien des Brevets.

JUMBO APPLICATIONS / PATENTS

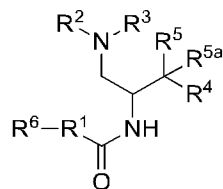
**THIS SECTION OF THE APPLICATION / PATENT CONTAINS MORE
THAN ONE VOLUME.**

THIS IS VOLUME __1__ OF __2__

NOTE: For additional volumes please contact the Canadian Patent Office.

The embodiments of the present invention for which an exclusive property or privilege is claimed are defined as follows:

1. A compound of Formula I:



Formula I

where

R¹ is cycloalkyl or heterocycloalkyl; wherein the heterocycloalkyl is attached to the C(O) group by a carbon atom and is optionally substituted with hydroxy;

R² is hydrogen, hydroxy, or alkyl; and R³ is alkyl, aminoalkyl, alkylaminoalkyl, or dialkylaminoalkyl; or R² and R³ together with the nitrogen to which they are attached form a 3-10 membered heterocycloalkyl ring which is optionally substituted with 1, 2, 3, or 4 R⁸; and wherein the -NR²R³ heterocycloalkyl is not morpholinyl;

R⁴ is aryl or heteroaryl each of which is optionally substituted with 1, 2, or 3 R⁹ groups;

R⁵ is halo, hydroxy, -N₃, -NH₂, -NHC(O)CH₃, -NH(OCH₃), or -NHC(O)H and R^{5a} is hydrogen, halo, alkyl, or deuterium; or R⁵ and R^{5a} together with the carbon to which they are attached form C(O) or C(NOH);

R⁶ is alkyl, alkoxycarbonyl, aryl, arylalkyl, arylcarbonyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, heteroarylalkyl, or -C(O)NR^{6a}R^{6b}; wherein each aryl and heteroaryl, whether alone or as part of another group, is optionally substituted with 1 or 2 R¹⁰ groups; and wherein each heterocycloalkyl and cycloalkyl, whether alone or as part of another group, is optionally substituted with 1 or 2 groups independently selected from hydroxy, halo, haloalkyl, alkoxy, alkyl, alkylcarbonyl, and alkoxycarbonyl;

R^{6a} is hydrogen or alkyl, and R^{6b} is aryl or heteroaryl each of which is optionally substituted with 1 or 2 halo; or R^{6a} and R^{6b} together with the nitrogen to which they are attached form a heterocycloalkyl optionally substituted with alkyl, hydroxy, alkylcarbonyl, or alkoxycarbonyl;

each R⁸, when present, is independently deuterium, amino, alkylamino, dialkylamino, alkyl, hydroxy, alkoxy, halo, haloalkyl, or cycloalkyl;

each R^9 , when present, is independently cyano, nitro, amino, alkylamino, dialkylamino, halo, haloalkyl, alkyl, $-NR^{11}C(O)NR^{11a}R^{11b}$, hydroxy, alkoxy, haloalkoxy, hydroxyalkoxy, alkenyloxy, cycloalkyloxy, cycloalkylalkyloxy, cycloalkylthio, heterocycloalkyl, heterocycloalkyloxy, heterocycloalkylalkyloxy, or phenyl; where the phenyl is optionally substituted with 1 or 2 R^{9a} ; where each heterocycloalkyl, either alone or as part of another group, is optionally substituted with 1 or 2 groups independently selected from alkyl, hydroxy, alkylcarbonyl, and alkoxycarbonyl;

each R^{9a} , when present, is independently selected from alkyl, hydroxy, alkoxy, halo, haloalkyl, haloalkoxy, alkoxycarbonyl, amino, alkylamino, and dialkylamino;

each R^{10} , when present, is independently cyano, nitro, amino, alkylamino, dialkylamino, halo, haloalkyl, alkyl, alkenyl, alkynyl, $-NR^{11}C(O)NR^{11a}R^{11b}$, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, cycloalkyl, hydroxy, alkoxy, haloalkoxy, hydroxyalkoxy, alkenyloxy, cycloalkyloxy, cycloalkylalkyloxy, cycloalkylthio, aryl, arylalkyl, aryloxy, heteroaryl, heteroarylalkyl, heteroaryloxy, heterocycloalkyl, heterocycloalkyloxy, or heterocycloalkylalkyloxy; where each aryl or heteroaryl either alone or as part of another group, is independently optionally substituted with 1, 2 or 3 R^{10a} ; and each heterocycloalkyl, either alone or as part of another group, is optionally substituted with 1 or 2 groups independently selected from alkyl, hydroxy, alkylcarbonyl, and alkoxycarbonyl groups;

each R^{10a} , when present, is independently selected from cyano, halo, alkyl, alkenyl, haloalkyl, hydroxyalkyl, and cycloalkyl; and

R^{11} , R^{11a} , and R^{11b} are independently hydrogen, alkyl, or cycloalkyl;

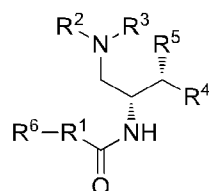
provided that when R^1 is cycloalkyl and R^6 is phenyl then the phenyl is substituted with 1 or 2 groups independently selected from cyano, nitro, amino, alkylamino, dialkylamino, haloalkyl, alkyl, $-NR^{11}C(O)NR^{11a}R^{11b}$, haloalkoxy, cycloalkyloxy, cycloalkylalkyloxy, heterocycloalkyl which is optionally substituted with 1 or 2 alkyl, heterocycloalkyloxy which is optionally substituted with 1 or 2 alkyl, or heterocycloalkylalkyloxy which is optionally substituted with 1 or 2 hydroxy; and

optionally a tautomer, a single stereoisomer or mixture of stereoisomers thereof and additionally optionally a pharmaceutically acceptable salt thereof.

2. The compound of claim 1, wherein R^1 is heterocycloalkyl attached to the $C(O)$ group by a carbon atom and is optionally substituted with hydroxy; and optionally a tautomer, a

single stereoisomer or mixture of stereoisomers thereof and additionally optionally a pharmaceutically acceptable salt thereof.

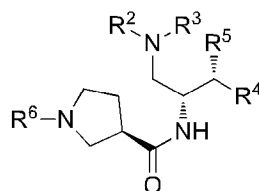
3. The compound of claim 1 or 2, is according to Formula I(a):



Formula I(a)

optionally as a tautomer, a single stereoisomer or mixture of stereoisomers thereof and additionally optionally as a pharmaceutically acceptable salt thereof.

4. The compound of claim 1, 2, or 3, is according to Formula I(d1):



Formula I(d1)

optionally as a tautomer, a single stereoisomer or mixture of stereoisomers thereof and additionally optionally as a pharmaceutically acceptable salt thereof.

5. The compound of claim 1, 2, 3, or 4, wherein R² and R³ together with the nitrogen to which they are attached form a 4-6 membered heterocycloalkyl ring; optionally as a tautomer, a single stereoisomer or mixture of stereoisomers thereof and additionally optionally as a pharmaceutically acceptable salt thereof.

6. The compound of claim 1, 2, 3, 4, or 5, wherein R⁵ is hydroxy and R^{5a} is hydrogen; optionally as a tautomer, a single stereoisomer or mixture of stereoisomers thereof and additionally optionally as a pharmaceutically acceptable salt thereof.

7. The compound of claim 1, 2, 3, 4, 5, or 6, wherein R⁶ is aryl, optionally independently substituted with 1 or 2 R¹⁰ groups; optionally as a tautomer, a single stereoisomer or mixture of stereoisomers thereof and additionally optionally as a pharmaceutically acceptable salt thereof.

8. The compound of claim 1, 2, 3, 4, 5, or 6, wherein R⁶ is heterocycloalkyl or heteroaryl, each optionally independently substituted with 1 or 2 R¹⁰ groups; optionally as a tautomer, a single stereoisomer or mixture of stereoisomers thereof and additionally optionally as a pharmaceutically acceptable salt thereof.

9. The compound of claim 1 or 2, wherein:

R¹ is *N*-(R⁶)-azetidiny, *N*-(R⁶)-pyrrolidiny, or *N*-(R⁶)-piperidiny, each of which is attached to the C(O) by a carbon atom, and is optionally substituted with hydroxy;

R² and R³ together with the nitrogen to which they are attached form a 4-6 membered heterocycloalkyl ring with 1 or 2 nitrogen atoms, which is optionally substituted with 1 or 2 R⁸;

R⁴ is aryl or heteroaryl each of which is optionally substituted with 1 or 2 R⁹ groups;

R⁵ is hydroxy, and R^{5a} is hydrogen;

R⁶ is alkyl, aryl, arylalkyl, arylcarbonyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, or heteroarylalkyl; wherein each aryl and heteroaryl, whether alone or as part of another group, is optionally substituted with 1 or 2 R¹⁰ groups; and wherein each heterocycloalkyl and cycloalkyl, whether alone or as part of another group, is optionally substituted with 1 or 2 groups independently selected from hydroxy, halo, haloalkyl, alkoxy, and alkyl;

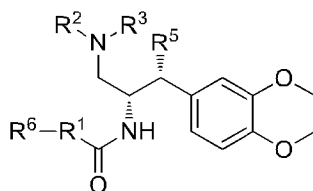
each R⁸, when present, is independently alkyl, hydroxy, alkoxy, halo, or haloalkyl;

each R⁹, when present, is independently cyano, nitro, halo, haloalkyl, alkyl, hydroxy, alkoxy, haloalkoxy, hydroxyalkoxy, alkenyloxy, cycloalkyloxy, cycloalkylalkyloxy, cycloalkylthio, heterocycloalkyl, heterocycloalkyloxy, or heterocycloalkylalkyloxy; where each heterocycloalkyl, whether alone or as part of another group, is optionally substituted with 1 or 2 groups independently selected from alkyl, hydroxy, alkylcarbonyl, and alkoxycarbonyl;

each R¹⁰, when present, is independently is cyano, halo, haloalkyl, alkyl, hydroxy, alkoxy, haloalkoxy, cycloalkyloxy, cycloalkylalkyloxy, aryl, aryloxy, heteroaryloxy, heterocycloalkyl, heterocycloalkyloxy, or heterocycloalkylalkyloxy; where each aryl or heteroaryl either alone or as part of another group, is independently optionally substituted with 1 or 2 halo or alkyl groups; and each heterocycloalkyl, either alone or as part of another group, is optionally substituted with 1 or 2 groups independently selected from alkyl and hydroxy; and

optionally a tautomer, a single stereoisomer or mixture of stereoisomers thereof and additionally optionally a pharmaceutically acceptable salt thereof.

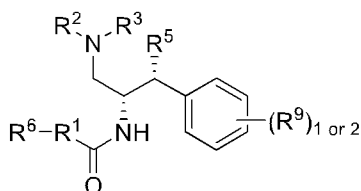
10. The compound of any one of claims 1 to 9, is according to Formula I(c):



Formula I(c)

optionally as a tautomer, a single stereoisomer or mixture of stereoisomers thereof and additionally optionally as a pharmaceutically acceptable salt thereof.

11. The compound of any one of claims 1 to 9, is according to Formula I(d2):



Formula I(d2)

optionally as a tautomer, a single stereoisomer or mixture of stereoisomers thereof and additionally optionally as a pharmaceutically acceptable salt thereof.

12. The compound of any one of claims 1 to 11, wherein:

R¹ is pyrrolidinyl attached to the C(O) by a carbon atom;

R² and R³ together with the nitrogen to which they are attached form azetidiny or pyrrolidinyl;

R⁵ is hydroxy and R^{5a} is hydrogen; and optionally as a tautomer, a single stereoisomer or mixture of stereoisomers thereof and additionally optionally as a pharmaceutically acceptable salt thereof.

13. The compound of any one of claims 1 to 12, wherein R⁶ is aryl or heteroaryl, wherein the aryl is optionally independently substituted with 1 or 2 halo, alkyl, cycloalkyloxy, or heterocycloalkyloxy; and the heteroaryl is optionally independently substituted with 1 or 2

halo, alkyl, or cycloalkyloxy; and optionally as a tautomer, a single stereoisomer or mixture of stereoisomers thereof and additionally optionally as a pharmaceutically acceptable salt thereof.

14. The compound of any one of claims 1 to 12, wherein R⁶ is heterocycloalkyl optionally independently substituted with 1 or 2 halo, hydroxy, or alkyl; and optionally as a tautomer, a single stereoisomer or mixture of stereoisomers thereof and additionally optionally as a pharmaceutically acceptable salt thereof.

15. The compound of claim 1, wherein the compound is selected from the group consisting of the compounds of Examples 1, 1C, 1D, 2, 2A, 2B, 5, 5D, 5E, 8, 8C, 8D, 9, 9D, 9E, 11, 12, 12D, 14, 14C, 14D, 15, 15C, 15D, 17, 17D, 19, 20, 20D, 20E, 21, 21E, 21F, 22, 22C, 22D, 24, 24B, 24C, 25, 25B, 26, 28, 28C, 28D, 30, 35, 35A, 36, 36F, 36G, 43, 43D, 43E, 44, 44C, 46, 46A, 46B, 47, 47A, 47B, 48, 48A, 52, 52A, 53, 53C, 53D, 55, 55A, 55B, 56, 56D, 56E, 58, 58D, 61, 61C, 61D, 63, 63C, 63D, 64, 68, 68C, 70, 70A, 71, 71E, 71F, 72, 72A, 72B, 76, 76D, 76E, 77, 78, 79, 79A, 79B, 80, 80G, 80H, 81, 82, 82E, 83, 83C, 83D, 85, 88, 88C, 88D, 89, 89F, 89G, 90, 90D, 93, 93A, 97, 97C, 99, 99C, 99D, 104, 105, 106, 108, 110, 111, 113, 114, 116, 119, 120, 121, 123, 124, 125, 130, 132, 134, 137, 142, 144, 154, and 154C; and optionally as a tautomer, a single stereoisomer or mixture of stereoisomers thereof and additionally optionally as a pharmaceutically acceptable salt thereof.

16. The compound of claim 1, wherein the compound is selected from the group consisting of the compounds of Examples 3, 3A, 3B, 6, 10, 23, 23B, 32, 32A, 45, 45A, 49, 49A, 50, 50A, 54, 54A, 57, 57A, 59, 60, 60A, 65, 66, 67, 67C, 69, 69A, 73, 74, 74C, 75, 75E, 84, 84A, 86, 87, 91, 92, 94, 95, 96, 98, 98A, 100, 101, 102, 103, 107, 109, 112, 115, 117, 118, 122, 126, 127, 128, 129, 131, 133, 135, 136, 138, 139, 140, 141, 145, 146, 147, 148, 149, 150, 151, 152, 152C, 153, 155, 156, 157, 158, 159, 159A, 160, 161, and 162; and optionally as a tautomer, a single stereoisomer or mixture of stereoisomers thereof and additionally optionally as a pharmaceutically acceptable salt thereof.

17. The compound of claim 1, wherein the compound is selected from the group consisting of the compounds of Examples 1, 1C, 1D, 2, 2A, 2B, 3, 3A, 3B, 6, 8, 8C, 8D, 10, 12, 12D, 13, 13C, 14, 14C, 14D, 19, 20, 20D, 20E, 23, 23B, 24, 24B, 24C, 25, 25B, 27, 27C, 29, 29B, 31, 31B, 32, 32A, 33, 33A, 34, 34A, 35, 35A, 43, 43D, 43E, 44, 44C, 45, 45A, 46, 46A, 46B, 47, 47A, 47B, 49, 49A, 50, 50A, 51, 51A, 52, 52A, 59, 60, 60A, 62, 65, 66, 67,

67C, 69, 69A, 70, 70A, 73, 74, 74C, 75, 75E, 77, 78, 79, 79A, 79B, 81, 84, 84A, 85, 86, 87, 88, 88C, 88D, 89, 89F, 89G, 94, 95, 96, 102, 103, 105, 107, 110, 117, 118, 122, 128, 130, 131, 135, 136, 137, 138, 139, 140, 141, 142, 143, 145, 147, 148, 149, 150, 151, 152, 152C, 153, 154, 154C, 155, 156, 159, 159A, 160, 161, and 162; and optionally as a tautomer, a single stereoisomer or mixture of stereoisomers thereof and additionally optionally as a pharmaceutically acceptable salt thereof.

18. A compound, which is:

(R)-N-((1R,2R)-1-(3-chloro-4-cyclopropoxyphenyl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-1-(6-(4-fluorophenyl)pyridin-2-yl)pyrrolidine-3-carboxamide;

(R)-N-((1R,2R)-3-(azetidin-1-yl)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxypropan-2-yl)-1-(4-chlorophenyl)pyrrolidine-3-carboxamide;

(S)-1-(4-chlorophenyl)-N-((1R,2R)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-3-hydroxypyrrolidine-3-carboxamide; or

(R)-1-(4-chlorophenyl)-N-((1R,2R)-1-(8-fluoro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl)-3-hydroxypyrrolidine-3-carboxamide;

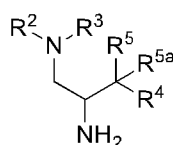
or optionally a tautomer, a single stereoisomer or mixture of stereoisomers thereof, or additionally optionally a pharmaceutically acceptable salt thereof.

19. A pharmaceutical composition comprising a compound of any one of claims 1 to 18, optionally as a tautomer, a single stereoisomer or mixture of stereoisomers thereof and additionally optionally as a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient or carrier.

20. Use of a compound according to any one of claims 1 to 18 or the pharmaceutical composition of claim 19 for treating a disease or disorder.

21. The use of claim 20, wherein the disease or disorder is glycolipid storage diseases; diseases associated with glycolipid accumulation; diseases that cause renal hypertrophy or hyperplasia; diseases that cause hyperglycemia or hyperinsulemia; cancers in which glycolipid synthesis is abnormal; cancer; infectious diseases caused by organisms which use cell surface glycolipids as receptors or in which synthesis of glucosylceramide is essential or important; a metabolic disorder; neuronal disorders; neuronal injury; inflammatory diseases or disorders; diabetes mellitus; and obesity.

22. The use of claim 21, wherein the disease or disorder is diabetic nephropathy, breast cancer, renal adenocarcinoma, brain cancer, neuroblastoma, lung cancer, intestinal cancer, pancreatic cancer, prostate cancer, atherosclerosis, polycystic kidney disease, renal hypertrophy, rheumatoid arthritis, Crohn's disease, asthma, or sepsis.
23. The use of claim 21, wherein the disease or disorder is Tay Sachs, Sandhoffs, GMI gangliosidosis, Niemanns-Pick, Fabry diseases, or Gaucher disease.
24. A method of making a compound according to claim 1 where R⁵ is hydroxy and R^{5a} is hydrogen comprising
- a) treating an intermediate of formula **100**



100

or a salt thereof, where:

R² is hydrogen, hydroxy, or alkyl; and R³ is alkyl, aminoalkyl, alkylaminoalkyl, or dialkylaminoalkyl; or R² and R³ together with the nitrogen to which they are attached form a 3-10 membered heterocycloalkyl ring which is optionally substituted with 1, 2, 3, or 4 R⁸; and wherein the -NR²R³ heterocycloalkyl is not morpholinyl;

R⁴ is aryl or heteroaryl each of which is optionally substituted with 1, 2, or 3 R⁹ groups;

R⁵ is hydroxy and R^{5a} is hydrogen;

each R⁸, when present, is independently deuterium, amino, alkylamino, dialkylamino, alkyl, hydroxy, alkoxy, halo, haloalkyl, or cycloalkyl;

each R⁹, when present, is independently cyano, nitro, amino, alkylamino, dialkylamino, halo, haloalkyl, alkyl, -NR¹¹C(O)NR^{11a}R^{11b}, hydroxy, alkoxy, haloalkoxy, hydroxyalkoxy, alkenyloxy, cycloalkyloxy, cycloalkylalkyloxy, cycloalkylthio, heterocycloalkyl, heterocycloalkyloxy, heterocycloalkylalkyloxy, or phenyl; where the phenyl is optionally substituted with 1 or 2 R^{9a};

where each heterocycloalkyl, either alone or as part of another group, is optionally substituted with 1 or 2 groups independently selected from alkyl, hydroxy, alkylcarbonyl, and alkoxy carbonyl;

each R^{9a} , when present, is independently selected from alkyl, hydroxy, alkoxy, halo, haloalkyl, haloalkoxy, alkoxycarbonyl, amino, alkylamino, and dialkylamino; and

R^{11} , R^{11a} , and R^{11b} are independently hydrogen, alkyl, or cycloalkyl; with an intermediate of formula $R^6-R^1C(O)OH$, using standard amine coupling conditions to yield a compound of Formula I, where:

R^1 is cycloalkyl or heterocycloalkyl; wherein the heterocycloalkyl is attached to the C(O) group by a carbon atom and is optionally substituted with hydroxy;

R^6 is alkyl, alkoxycarbonyl, aryl, arylalkyl, arylcarbonyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, heteroarylalkyl, or $-C(O)NR^{6a}R^{6b}$; wherein each aryl and heteroaryl, whether alone or as part of another group, is optionally substituted with 1 or 2 R^{10} groups; and wherein each heterocycloalkyl and cycloalkyl, whether alone or as part of another group, is optionally substituted with 1 or 2 groups independently selected from hydroxy, halo, haloalkyl, alkoxy, alkyl, alkylcarbonyl, and alkoxycarbonyl;

R^{6a} is hydrogen or alkyl, and R^{6b} is aryl or heteroaryl each of which is optionally substituted with 1 or 2 halo; or R^{6a} and R^{6b} together with the nitrogen to which they are attached form a heterocycloalkyl optionally substituted with alkyl, hydroxy, alkylcarbonyl, or alkoxycarbonyl;

each R^{10} , when present, is independently cyano, nitro, amino, alkylamino, dialkylamino, halo, haloalkyl, alkyl, alkenyl, alkynyl, $-NR^{11}C(O)NR^{11a}R^{11b}$, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, cycloalkyl, hydroxy, alkoxy, haloalkoxy, hydroxyalkoxy, alkenyloxy, cycloalkyloxy, cycloalkylalkyloxy, cycloalkylthio, aryl, arylalkyl, aryloxy, heteroaryl, heteroarylalkyl, heteroaryloxy, heterocycloalkyl, heterocycloalkyloxy, or heterocycloalkylalkyloxy; where each aryl or heteroaryl either alone or as part of another group, is independently optionally substituted with 1, 2 or 3 R^{10a} ; and each heterocycloalkyl, either alone or as part of another group, is optionally substituted with 1 or 2 groups independently selected from alkyl, hydroxy, alkylcarbonyl, and alkoxycarbonyl groups;

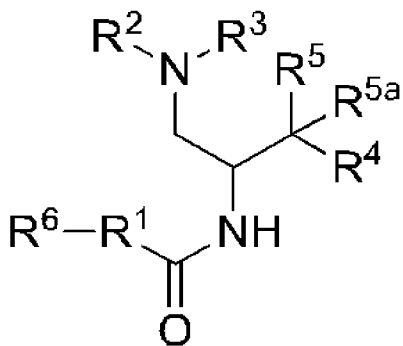
each R^{10a} , when present, is independently selected from cyano, halo, alkyl, alkenyl, haloalkyl, hydroxyalkyl, and cycloalkyl; and

R^{11} , R^{11a} , and R^{11b} are independently hydrogen, alkyl, or cycloalkyl;

provided that when R^1 is cycloalkyl and R^6 is phenyl then the phenyl is substituted with 1 or 2 groups independently selected from cyano, nitro, amino, alkylamino,

dialkylamino, haloalkyl, alkyl, $-\text{NR}^{11}\text{C}(\text{O})\text{NR}^{11\text{a}}\text{R}^{11\text{b}}$, haloalkoxy, cycloalkyloxy, cycloalkylalkyloxy, heterocycloalkyl which is optionally substituted with 1 or 2 alkyl, heterocycloalkyloxy which is optionally substituted with 1 or 2 alkyl, or heterocycloalkylalkyloxy which is optionally substituted with 1 or 2 hydroxy; and

b) optionally separating individual isomers.



Formula I