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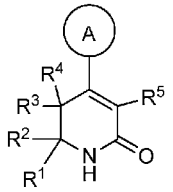
(54) Title: DIHYDROPYRIDINONE MGAT2 INHIBITORS FOR USE IN THE TREATMENT OF METABOLIC DISORDERS



(I)

(57) Abstract: The present invention provides compounds of Formula (I): or a stereoisomer, or a pharmaceutically acceptable salt thereof, wherein all of the variables are as defined herein. These compounds are monoacylglycerol acyltransferase type 2 (MGAT2) inhibitors which may be used as medicaments.

DIHYDROPYRIDINONE MGAT2 INHIBITORS FOR USE IN THE TREATMENT OF METABOLIC DISORDERS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority to U.S. Provisional Application Serial No. 61/949,506, filed March 7, 2014, the entire content of which is incorporated herein by reference.

FIELD OF THE INVENTION

The present invention provides novel heteroaryl dihydropyridinone compounds, and analogues thereof, which are MGAT2 inhibitors, compositions containing them, and methods of using them, for example, for the treatment or prophylaxis of diabetes, obesity, dyslipidemia and related conditions.

BACKGROUND OF THE INVENTION

The prevalence of obesity and diabetes is increasing at an alarming rate. According to WHO, in 2008, 70% of the U.S. adult population was overweight, and among them 33% were obese. Parallel to the explosive number of people becoming overweight and obese, in 2008, it was estimated that 12.3% of the U.S. population had elevated blood glucose [http://www.who.int/diabetes/facts/en/]. The obesity/diabetes epidemic is not unique to the U.S. According to WHO (Fact Sheet No. 312, September 2012), 347 million people worldwide have diabetes. Treating obesity and improving glycemic control effectively and safely remain major challenges for modern medicine.

Monoacylglycerol acyltransferase 2 (MGAT2) has emerged as an attractive target for the treatment of obesity and type II diabetes [Yen, C.L. et al., *Nat. Med.*, 15(4):442-446 (2009)]. MGAT2 is highly and selectively expressed in the small intestine where it exerts a pivotal role in the monoacylglycerol-pathway for the absorption of dietary fat. When dietary fat is ingested, pancreatic lipase digests triglycerides into free fatty acids and 2-monoacylglycerol, which are absorbed by intestinal epithelial enterocytes. Once inside enterocytes, free fatty acids and 2-monoacylglycerol are used as building blocks to resynthesize triglycerides by two sequential acylation steps; first by MGAT and then by DGAT enzyme reactions. Triglycerides are then incorporated into chylomicrons and secreted into lymph to be utilized as an energy supply for the body. MGAT2 knockout

mice exhibit a healthy metabolic phenotype and show resistance to high-fat diet induced obesity, improvement in insulin sensitivity and decreased fat accumulation in liver and adipose tissue. In addition, genetic deletion of MGAT2 produces mice with increased levels of GLP1 [Yen, C.L. et al., *Nat. Med.*, 15(4):442-446 (2009)]. Taken together, these data show that MGAT2 inhibitors hold promise to treat metabolic disorders such as obesity, type II diabetes and dyslipidemia.

SUMMARY OF THE INVENTION

The present invention provides heteroaryl dihydropyridinone compounds, and analogues thereof, which are useful as MGAT2 inhibitors, including stereoisomers, tautomers, pharmaceutically acceptable salts, polymorphs, or solvates thereof.

The present invention also provides processes and intermediates for making the compounds of the present invention or stereoisomers, tautomers, pharmaceutically acceptable salts, polymorphs, or solvates thereof.

The present invention also provides pharmaceutical compositions comprising a pharmaceutically acceptable carrier and at least one of the compounds of the present invention or stereoisomers, tautomers, pharmaceutically acceptable salts, polymorphs, or solvates thereof.

The compounds of the invention may be used in the treatment and/or prophylaxis of multiple diseases or disorders associated with MGAT2, such as diabetes, obesity, dyslipidemia and related conditions, such as microvascular and macrovascular complications associated with diabetes, cardiovascular diseases, Metabolic Syndrome and its component conditions, disorders of glucose and lipid metabolism and other maladies.

The compounds of the invention may be used in therapy.

The compounds of the invention may be used for the manufacture of a medicament for the treatment and/or prophylaxis of multiple diseases or disorders associated with MGAT2.

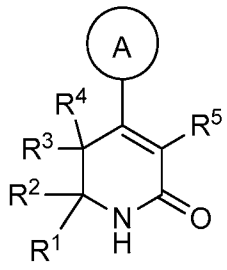
The compounds of the invention can be used alone, in combination with other compounds of the present invention, or in combination with one or more other agent(s).

Other features and advantages of the invention will be apparent from the following detailed description and claims.

DETAILED DESCRIPTION OF THE INVENTION

I. COMPOUNDS OF THE INVENTION

In a first aspect, the present invention provides, *inter alia*, a compound of Formula (I):



(I)

or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, a polymorph, a solvate or a hydrate thereof, wherein:

ring A is independently a 5- to 6-membered heteroaryl comprising carbon atoms and 1-4 heteroatoms selected from N, NR^e, O and S; wherein said heteroaryl is substituted with 0-1 R^6 and 0-2 R^7;

R^1 is independently selected from: $-(CH_2)_m$-(C_{3-6} carbocycle substituted with 0-2 R^b and 0-2 R^g), $-(CH_2)_m$-(5- to 6-membered heteroaryl comprising carbon atoms and 1-4 heteroatoms selected from N, NR^e, O and S; wherein said heteroaryl is substituted with 0-1 R^b and 0-2 R^g), and (a C_{1-12} hydrocarbon chain substituted with 0-3 R^a; wherein said hydrocarbon chain may be straight or branched, saturated or unsaturated);

R^2 is independently selected from: C_{1-4} alkyl, C_{3-4} cycloalkyl, and C_{1-4} haloalkyl;

R^3 is independently selected from: H, F, C_{1-4} alkyl and CN;

R^4 is independently selected from: H, F, and C_{1-4} alkyl;

R^3 and R^4 may be combined with the carbon atom to which they are attached to form a 3- to 6-membered carbocycle;

R^5 is independently selected from: H, halogen, C_{1-6} alkyl, CN, NO_2, R^c, NH_2, $-(CH_2)_n-(X)_t-(CH_2)_mR^c$, $-CONH(C_{1-6}$ alkyl), and $-NHCOX_1SO_2R^i$;

X is independently selected from the group consisting of O, S, NH, CONH, and NHCO;

X_1 is independently C_{1-4} hydrocarbon chain optionally substituted with C_{1-4} alkyl or C_{3-4} cycloalkyl;

R^6 is independently selected from: halogen, C_{1-6} alkyl substituted with 0-2 R^h, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, $CO(C_{1-4}$ alkyl), $-(CH_2)_m-C_{3-6}$ cycloalkyl, $-(CH_2)_m-NR^fR^i$, CN, OR^i, SR^i, and (a 4- to 6-membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, NR^e, O, and S);

R^7 is independently selected from: halogen, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, and C_{1-4} haloalkoxy;

alternatively, R^6 and R^7, together with the carbon atoms to which they are attached, combine to form a 5- to 6-membered carbocyclic ring or a 5- to 6-membered heterocyclic ring comprising carbon atoms and 1-3 heteroatoms selected from N, NR^e, O, and S; wherein said heterocycle is substituted with 0-2 R^g;

R^a is, at each occurrence, independently selected from: halogen, OH, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, $N(C_{1-4}$ alkyl$)_2$, COOH, and $-(CH_2)_n-R^c$;

R^b is, at each occurrence, independently selected from: halogen, OH, C_{1-10} alkyl, C_{1-10} alkoxy, C_{1-10} haloalkyl, C_{1-10} haloalkoxy, C_{1-10} alkylthio, C_{1-10} haloalkylthio, $N(C_{1-4}$ alkyl$)_2$, $-CONH(C_{4-20}$ alkyl), $-CONH(C_{4-20}$ haloalkyl), $-O(CH_2)_sO(C_{1-6}$ alkyl), $-O(CH_2)_sO(C_{1-6}$ haloalkyl), R^c, and $-(CH_2)_n-(O)_t-(CH_2)_mR^c$;

R^c is, at each occurrence, independently selected from: C_{3-6} cycloalkyl substituted with 0-2 R^d, C_{3-6} cycloalkenyl substituted with 0-2 R^d, $-(CH_2)_m-$(phenyl substituted with 0-3 R^d), and a 5- to 6-membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, NR^e, O, and S; wherein said heterocycle is substituted with 0-2 R^d;

R^d is, at each occurrence, independently selected from: halogen, OH, CN, NO_2, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, tetrazolyl, OBn and phenyl;

R^e is, at each occurrence, independently selected from: H, C_{1-8} alkyl, C_{1-8} haloalkyl, $-(CH_2)_n-C_{3-6}$ carbocycle, $CO(C_{1-4}$ alkyl) and COBn;

R^f is, at each occurrence, independently selected from: H and C_{1-4} alkyl;

R^g is, at each occurrence, independently selected from: halogen, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, and C_{1-4} haloalkoxy;

R^h is, at each occurrence, independently selected from: OH, halogen, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, and C_{1-4} haloalkoxy;

R^i is, at each occurrence, independently selected from the group consisting of C_{1-4} alkyl, C_{3-4} cycloalkyl and phenyl;

n, at each occurrence, is independently 0 or 1;

m, at each occurrence, is independently 0, 1, 2, 3, or 4;

s, at each occurrence, is independently 1, 2, or 3; and

t, at each occurrence, is independently 0 or 1.

In a second aspect, the present invention provides a compound of Formula (I) or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, a polymorph, a solvate or a hydrate thereof, within the scope of the first aspect, wherein:

R^1 is independently selected from: (C_{3-6} carbocycle substituted with 0-2 R^b and 0-2 R^g), (a 5- to 6-membered heteroaryl comprising carbon atoms and 1-4 heteroatoms selected from N, NR^e, O and S; wherein said heteroaryl is substituted with 0-1 R^b and 0-2 R^g), and (a C_{1-12} hydrocarbon chain substituted with 0-1 R^a; wherein said hydrocarbon chain may be straight or branched, saturated or unsaturated);

R^3 is independently selected from: H, F, C_{1-4} alkyl and CN;

R^4 is independently selected from: H, F, and C_{1-4} alkyl;

R^b is, at each occurrence, independently selected from: halogen, C_{1-10} alkyl, C_{1-10} alkoxy, C_{1-10} haloalkyl, C_{1-10} haloalkoxy, C_{1-10} alkylthio, C_{1-10} haloalkylthio, $N(C_{1-4}$ alkyl$)_2$, $-CONH(C_{4-20}$ alkyl), $-CONH(C_{4-20}$ haloalkyl), $-O(CH_2)_sO(C_{1-6}$ alkyl), $-O(CH_2)_sO(C_{1-6}$ haloalkyl), R^c, and $-(CH_2)_n-(O)_t-(CH_2)_mR^c$; and

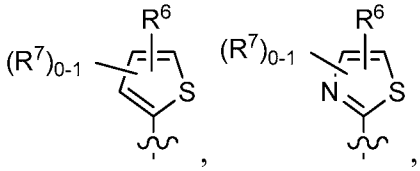
R^d is, at each occurrence, independently selected from: halogen, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, tetrazolyl, OBn and phenyl.

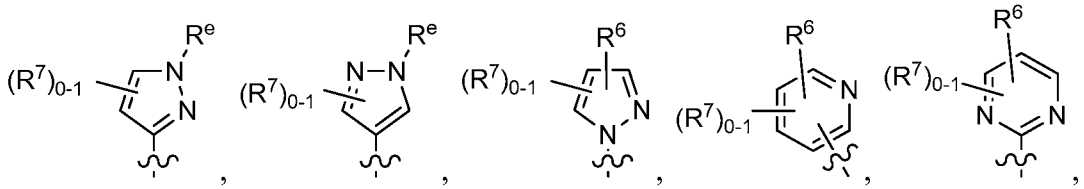
In a third aspect, the present invention provides a compound of Formula (I) or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, a polymorph, a solvate or a hydrate thereof, within the scope of the first or second aspect, wherein:

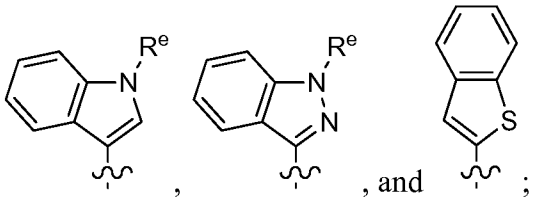
ring A is independently selected from: pyrrolyl, thienyl, thiazolyl, pyrazolyl, pyridyl, and pyrimidinyl; wherein each ring moiety is substituted with 0-1 R^6 and 0-2 R^7; and

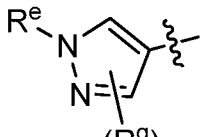
alternatively, R^6 and R^7, together with the carbon atoms to which they are attached, combine to form a 6-membered carbocyclic ring.

In a fourth aspect, the present invention includes a compound of Formula (I), or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, a polymorph, a solvate or a hydrate thereof, within the scope of any of the above aspects, wherein:

ring A is independently selected from:  , ,

 ,

 , and ;

R^1 is independently selected from: (phenyl substituted with 1 R^b and 0-2 R^g),  , and a C_{1-12} hydrocarbon chain substituted with 0-1 R^a; wherein said hydrocarbon chain may be straight or branched, saturated or unsaturated;

R^2 is independently selected from: C_{1-4} alkyl and C_{1-4} haloalkyl;

R^3 is independently selected from: H and F;

R^4 is independently selected from: H and F;

R^5 is independently selected from: CN, NH_2, -CONH(C_{1-6} alkyl), R^c, -CONHSO$_2$(C_{1-4} alkyl), -NHCOCH$_2$SO$_2$(C_{1-4} alkyl), -NHCONH(C_{1-4} alkyl), -OCONH(C_{1-4} alkyl), and -CONH(Ph substituted with 0-1 R^g);

R^6 is independently selected from: halogen, C_{1-4} alkyl substituted with 0-1 N(C_{1-4} alkyl)$_2$, C_{1-4} alkoxy, and C_{3-6} cycloalkyl;

R^7 is independently selected from: halogen, C_{1-4} alkyl and C_{1-4} alkoxy;

R^a is, at each occurrence, independently selected from: halogen, OH, C_{1-4} alkoxy, C_{1-4} haloalkyl, and C_{1-4} haloalkoxy;

R^b is, at each occurrence, independently selected from: halogen, OH, C_{1-8} alkyl, C_{1-8} alkoxy, C_{1-8} haloalkyl, and C_{1-10} haloalkoxy;

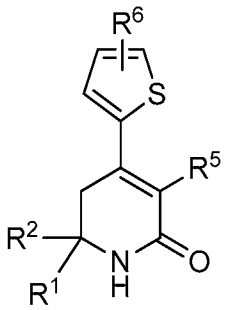
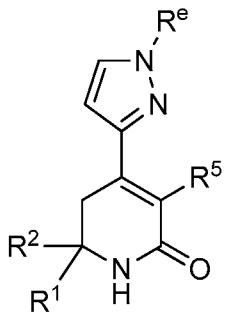
R^c is a 5- to 6-membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, NR^e, O, and S;

R^g is, at each occurrence, independently selected from: halogen, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, and C_{1-4} haloalkoxy;

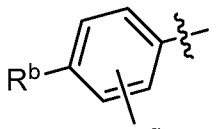
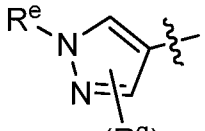
m, at each occurrence, is independently 0, 1, 2 or 3; and

s, at each occurrence, is independently 1, 2, or 3;

In a fifth aspect, the present invention provides a compound of Formula (IIa) or (IIb):


(IIa),

(IIb)

or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, a polymorph, a solvate or a hydrate thereof, within the scope of any of the above aspects, wherein:

R^1 is independently selected from: 
, 
, and (a C_{1-12} hydrocarbon chain; wherein said hydrocarbon chain may be straight or branched, saturated or unsaturated);

R^2 is independently selected from: CF_3 and CH_3;

R^5 is independently selected from: CN, tetrazolyl, $-CONHSO_2(C_{1-4}$ alkyl), $-NHCOCH_2SO_2(C_{1-4}$ alkyl), and $-CONH(4\text{-}C_{1-4}$ alkoxy-Ph);

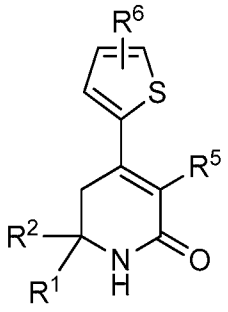
R^6 is independently selected from: halogen, C_{1-4} alkyl substituted with 0-1 $N(C_{1-4}$ alkyl$)_2$, C_{1-4} alkoxy, and C_{3-6} cycloalkyl;

R^b is independently selected from: $-O(CH_2)_{1-6}CF_3$, and $-O(CH_2)_{1-4}CF_2CF_3$;

R^e is independently selected from: $-(CH_2)_{1-6}CF_3$, and $-(CH_2)_{0-1}(C_{3-6}$ cycloalkyl); and

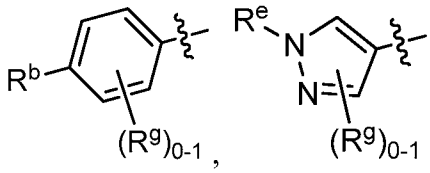
R^g is independently selected from: halogen and C_{1-4} alkoxy.

In another aspect, the present invention provides a compound of Formula (IIa):



(IIa),

or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, a polymorph, a solvate or a hydrate thereof, within the scope of any of the above aspects, wherein:

R^1 is independently selected from:  , and (a C_{1-12} hydrocarbon chain; wherein said hydrocarbon chain may be straight or branched, saturated or unsaturated);

R^2 is independently selected from: CF_3 and CH_3;

R^5 is independently selected from: CN, tetrazolyl, $-CONHSO_2(C_{1-4}$ alkyl), $-NHCOCH_2SO_2(C_{1-4}$ alkyl), and $-CONH(4\text{-}C_{1-4}$ alkoxy-Ph);

R^6 is independently selected from: halogen, C_{1-4} alkyl substituted with 0-1 $N(C_{1-4}$ alkyl$)_2$, C_{1-4} alkoxy, and C_{3-6} cycloalkyl;

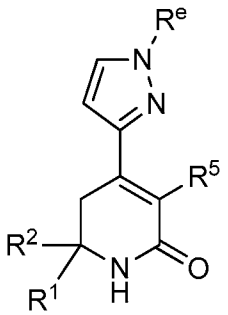
R^b is independently selected from: $-O(CH_2)_{1-6}CF_3$, and $-O(CH_2)_{1-4}CF_2CF_3$;

R^e is independently selected from: $-(CH_2)_{1-6}CF_3$, and $-(CH_2)_{0-1}(C_{3-6}$ cycloalkyl);

and

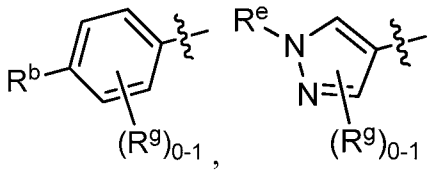
R^g is independently selected from: halogen and C_{1-4} alkoxy.

In another aspect, the present invention provides a compound of Formula (IIb):



(IIb),

or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, a polymorph, a solvate or a hydrate thereof, within the scope of any of the above aspects, wherein:

R^1 is independently selected from:  , and (a C_{1-12} hydrocarbon chain; wherein said hydrocarbon chain may be straight or branched, saturated or unsaturated);

R^2 is independently selected from: CF_3 and CH_3;

R^5 is independently selected from: CN, tetrazolyl, $-CONHSO_2(C_{1-4}$ alkyl), $-NHCOCH_2SO_2(C_{1-4}$ alkyl), and $-CONH(4\text{-}C_{1-4}$ alkoxy-Ph);

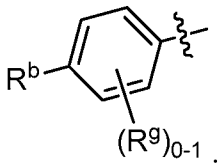
R^6 is independently selected from: halogen, C_{1-4} alkyl substituted with 0-1 $N(C_{1-4}$ alkyl)$_2$, C_{1-4} alkoxy, and C_{3-6} cycloalkyl;

R^b is independently selected from: $-O(CH_2)_{1-6}CF_3$, and $-O(CH_2)_{1-4}CF_2CF_3$;

R^e is independently selected from: $-(CH_2)_{1-6}CF_3$, and $-(CH_2)_{0-1}(C_{3-6}$ cycloalkyl); and

R^g is independently selected from: halogen and C_{1-4} alkoxy.

In a sixth aspect, the present invention includes a compound of Formula (I), (IIa) or (IIb), or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, a polymorph, a solvate or a hydrate thereof, within the scope of any of the above aspects, wherein:

R^1 is  .

In a seventh aspect, the present invention provides a compound selected from the exemplified examples or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, or a solvate thereof.

In another aspect, the present invention provides a compound selected from any subset list of compounds or a single compound from the exemplified examples within the scope of any of the above aspects.

In another embodiment, the compounds of the present invention have hMGAT2 IC_{50} values ≤ 1 μM, using the MGAT2 LCMS assay.

In another embodiment, the compounds of the present invention have hMGAT2 IC_{50} values ≤ 0.5 μM, using the MGAT2 LCMS assay.

In another embodiment, the compounds of the present invention have hMGAT2 IC_{50} values ≤ 0.1 μM, using the MGAT2 LCMS assay.

II. OTHER EMBODIMENTS OF THE INVENTION

In another embodiment, the present invention provides a composition comprising at least one of the compounds of the present invention or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, or a solvate thereof.

In another embodiment, the present invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and at least one of the compounds of the present invention or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, or a solvate thereof.

In another embodiment, the present invention provides a pharmaceutical composition, comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of at least one of the compounds of the present invention or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, or a solvate thereof.

In another embodiment, the present invention provides a process for making a compound of the present invention or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, or a solvate thereof.

In another embodiment, the present invention provides an intermediate for making a compound of the present invention or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, or a solvate thereof.

In another embodiment, the present invention provides a pharmaceutical composition further comprising additional therapeutic agent(s). In a preferred embodiment, the present invention provides pharmaceutical composition, wherein the additional therapeutic agent is, for example, a dipeptidyl peptidase-IV (DPP4) inhibitor (for example a member selected from saxagliptin, sitagliptin, vildagliptin and alogliptin).

In another embodiment, the present invention provides a method for the treatment of multiple diseases or disorders associated with MGAT2, comprising administering to a

patient in need of such treatment a therapeutically effective amount of at least one of the compounds of the present invention, alone, or, optionally, in combination with another compound of the present invention and/or at least one other type of therapeutic agent.

Examples of diseases or disorders associated with the activity of the MGAT2 that can be prevented, modulated, or treated according to the present invention include, but are not limited to, diabetes, hyperglycemia, impaired glucose tolerance, gestational diabetes, insulin resistance, hyperinsulinemia, nonalcoholic fatty liver disease (NAFLD) including nonalcoholic steatohepatitis (NASH), retinopathy, neuropathy, nephropathy, delayed wound healing, atherosclerosis and its sequelae, abnormal heart function, myocardial ischemia, stroke, Metabolic Syndrome, hypertension, obesity, dyslipidemia, dyslipidemia, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, low high-density lipoprotein (HDL), high low-density lipoprotein (LDL), non-cardiac ischemia, lipid disorders, and glaucoma.

In another embodiment, the present invention provides a method for the treatment of diabetes, hyperglycemia, gestational diabetes, obesity, dyslipidemia, and hypertension, comprising administering to a patient in need of such treatment a therapeutically effective amount of at least one of the compounds of the present invention, alone, or, optionally, in combination with another compound of the present invention and/or at least one other type of therapeutic agent.

In another embodiment, the present invention provides a method for the treatment of diabetes, comprising administering to a patient in need of such treatment a therapeutically effective amount of at least one of the compounds of the present invention, alone, or, optionally, in combination with another compound of the present invention and/or at least one other type of therapeutic agent.

In another embodiment, the present invention provides a method for the treatment of hyperglycemia, comprising administering to a patient in need of such treatment a therapeutically effective amount of at least one of the compounds of the present invention, alone, or, optionally, in combination with another compound of the present invention and/or at least one other type of therapeutic agent.

In another embodiment, the present invention provides a method for the treatment of obesity, comprising administering to a patient in need of such treatment a therapeutically effective amount of at least one of the compounds of the present

invention, alone, or, optionally, in combination with another compound of the present invention and/or at least one other type of therapeutic agent.

In another embodiment, the present invention provides a method for the treatment of dyslipidemia, comprising administering to a patient in need of such treatment a therapeutically effective amount of at least one of the compounds of the present invention, alone, or, optionally, in combination with another compound of the present invention and/or at least one other type of therapeutic agent.

In another embodiment, the present invention provides a method for the treatment of hypertension, comprising administering to a patient in need of such treatment a therapeutically effective amount of at least one of the compounds of the present invention, alone, or, optionally, in combination with another compound of the present invention and/or at least one other type of therapeutic agent.

In another embodiment, the present invention provides a compound of the present invention for use in therapy.

In another embodiment, the present invention provides a compound of the present invention for use in therapy for the treatment of multiple diseases or disorders associated with MGAT2.

In another embodiment, the present invention also provides the use of a compound of the present invention for the manufacture of a medicament for the treatment of multiple diseases or disorders associated with MGAT2.

In another embodiment, the present invention provides a method for the treatment of multiple diseases or disorders associated with MGAT2, comprising administering to a patient in need thereof a therapeutically effective amount of a first and second therapeutic agent, wherein the first therapeutic agent is a compound of the present invention. Preferably, the second therapeutic agent, for example, dipeptidyl peptidase-IV (DPP4) inhibitor (for example a member selected from saxagliptin, sitagliptin, vildagliptin, linagliptin and alogliptin).

In another embodiment, the present invention provides a combined preparation of a compound of the present invention and additional therapeutic agent(s) for simultaneous, separate or sequential use in therapy.

In another embodiment, the present invention provides a combined preparation of a compound of the present invention and additional therapeutic agent(s) for simultaneous,

separate or sequential use in the treatment of multiple diseases or disorders associated with MGAT2.

Where desired, the compound of the present invention may be used in combination with one or more other types of anti-diabetic agents and/or one or more other types of therapeutic agents which may be administered orally in the same dosage form, in a separate oral dosage form or by injection. The other type of anti-diabetic agent that may be optionally employed in combination with the MGAT2 inhibitor of the present invention may be one, two, three or more anti-diabetic agents or anti-hyperglycemic agents which may be administered orally in the same dosage form, in a separate oral dosage form, or by injection to produce an additional pharmacological benefit.

The anti-diabetic agents used in the combination with the MGAT2 inhibitor of the present invention include, but are not limited to, insulin secretagogues or insulin sensitizers, other MGAT2 inhibitors, or other anti-diabetic agents. These agents include, but are not limited to, dipeptidyl peptidase IV (DPP4) inhibitors (for example, sitagliptin, saxagliptin, alogliptin, linagliptin and vildagliptin), biguanides (for example, metformin and phenformin), sulfonyl ureas (for example, glyburide, glimepiride and glipizide), glucosidase inhibitors (for example, acarbose, miglitol), PPARγ agonists such as thiazolidinediones (for example, rosiglitazone and pioglitazone), PPAR α/γ dual agonists (for example, muraglitazar, tesaglitazar and aleglitazar), glucokinase activators, GPR40 receptor modulators (*e.g.*, TAK-875), GPR119 receptor modulators (for example, MBX-2952, PSN821, and APD597), sodium-glucose transporter-2 (SGLT2) inhibitors (for example, dapagliflozin, canagliflozin and remagliflozin), 11β-HSD-1 inhibitors (for example MK-0736, BI35585, BMS-823778, and LY2523199), amylin analogs such as pramlintide, leptin signaling modulators (for example, metreleptin), and/or insulin.

The MGAT2 inhibitor of the present invention may also be optionally employed in combination with one or more hypophagic and/or weight-loss agents such as diethylpropion, phendimetrazine, phentermine, orlistat, sibutramine, lorcaserin, pramlintide, topiramate, MCHR1 receptor antagonists, oxyntomodulin, naltrexone, Amylin peptide, NPY Y5 receptor modulators, NPY Y2 receptor modulators, NPY Y4 receptor modulators, cetilistat, 5HT2c receptor modulators, and the like. The compounds of the present invention may also be employed in combination with an agonist of the glucagon-like peptide-1 receptor (GLP-1 R), such as exenatide, liraglutide, GPR-1(1-36)

amide, GLP-1(7-36) amide, GLP-1(7-37), which may be administered via injection, intranasal, or by transdermal or buccal devices.

The MGAT2 inhibitor of the present invention may also be optionally employed in combination with one or more other types of therapeutic agents, such as DGAT inhibitors, LDL lowering drugs such as statins (inhibitors of HMG CoA reductase) or inhibitors of cholesterol absorption, modulators of PCSK9, drugs that increase HDL such as CETP inhibitors.

The present invention may be embodied in other specific forms without departing from the spirit or essential attributes thereof. This invention encompasses all combinations of preferred aspects of the invention noted herein. It is understood that any and all embodiments of the present invention may be taken in conjunction with any other embodiment or embodiments to describe additional embodiments. It is also understood that each individual element of the embodiments is its own independent embodiment. Furthermore, any element of an embodiment is meant to be combined with any and all other elements from any embodiment to describe an additional embodiment.

III. CHEMISTRY

Throughout the specification and the appended claims, a given chemical formula or name shall encompass all stereo and optical isomers and racemates thereof where such isomers exist. The term "stereoisomer(s)" refers to compound(s) which have identical chemical constitution, but differ with regard to the arrangement of the atoms or groups in space. Unless otherwise indicated, all chiral (enantiomeric and diastereomeric) and racemic forms are within the scope of the invention. The term "chiral" refers to molecules which have the property of non-superimposability of the mirror image partner, while the term "achiral" refers to molecules which are superimposable on their mirror image partner. The terms "racemic mixture" and "racemate" refer to an equimolar mixture of two enantiomeric species, devoid of optical activity.

Many geometric isomers of C=C double bonds, C=N double bonds, ring systems, and the like can also be present in the compounds, and all such stable isomers are contemplated in the present invention. *Cis-* and *trans-* (or *E-* and *Z-*) geometric isomers of the compounds of the present invention are described and may be isolated as a mixture of isomers or as separated isomeric forms.

The present compounds can be isolated in optically active or racemic forms. Optically active forms may be prepared by resolution of racemic forms or by synthesis from optically active starting materials. All processes used to prepare compounds of the present invention and intermediates made therein are considered to be part of the present invention. When enantiomeric or diastereomeric products are prepared, they may be separated by conventional methods, for example, by chromatography or fractional crystallization.

Depending on the process conditions the end products of the present invention are obtained either in free (neutral) or salt form. Both the free form and the salts of these end products are within the scope of the invention. If so desired, one form of a compound may be converted into another form. A free base or acid may be converted into a salt; a salt may be converted into the free compound or another salt; a mixture of isomeric compounds of the present invention may be separated into the individual isomers. Compounds of the present invention, free form and salts thereof, may exist in multiple tautomeric forms, in which hydrogen atoms are transposed to other parts of the molecules and the chemical bonds between the atoms of the molecules are consequently rearranged. It should be understood that all tautomeric forms, insofar as they may exist, are included within the invention.

Unless otherwise indicated, any heteroatom with unsatisfied valences is assumed to have hydrogen atoms sufficient to satisfy the valences.

As used herein, the term "alkyl" or "alkylene" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms. For examples, "C_1 to C_{12} alkyl" or "C_{1-12} alkyl" (or alkylene), is intended to include C_1, C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9, C_{10}, C_{11} and C_{12} alkyl groups; "C_4 to C_{18} alkyl" or "C_{4-18} alkyl" (or alkylene), is intended to include C_4, C_5, C_6, C_7, C_8, C_9, C_{10}, C_{11}, C_{12}, C_{13}, C_{14}, C_{15}, C_{16}, C_{17}, and C_{18} alkyl groups. Additionally, for example, "C_1 to C_6 alkyl" or "C_{1-6} alkyl" denotes alkyl having 1 to 6 carbon atoms. Alkyl group can be unsubstituted or substituted with at least one hydrogen being replaced by another chemical group. Example alkyl groups include, but are not limited to, methyl (Me), ethyl (Et), propyl (*e.g.*, n-propyl and isopropyl), butyl (*e.g.*, n-butyl, isobutyl, *t*-butyl), and pentyl (*e.g.*, n-pentyl, isopentyl, neopentyl). When "C_0 alkyl" or "C_0 alkylene" is used, it is intended to denote a direct bond.

"Alkenyl" or "alkenylene" is intended to include hydrocarbon chains of either straight or branched configuration having the specified number of carbon atoms and one or more, preferably one to two, carbon-carbon double bonds that may occur in any stable point along the chain. For example, "C_2 to C_6 alkenyl" or "C_{2-6} alkenyl" (or alkenylene), is intended to include C_2, C_3, C_4, C_5, and C_6 alkenyl groups. Examples of alkenyl include, but are not limited to, ethenyl, 1-propenyl, 2-propenyl, 2-butenyl, 3-butenyl, 2-pentenyl, 3, pentenyl, 4-pentenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexenyl, 2-methyl-2-propenyl, and 4-methyl-3-pentenyl.

"Alkynyl" or "alkynylene" is intended to include hydrocarbon chains of either straight or branched configuration having one or more, preferably one to three, carbon-carbon triple bonds that may occur in any stable point along the chain. For example, "C_2 to C_6 alkynyl" or "C_{2-6} alkynyl" (or alkynylene), is intended to include C_2, C_3, C_4, C_5, and C_6 alkynyl groups; such as ethynyl, propynyl, butynyl, pentynyl, and hexynyl.

When the term "hydrocarbon chain" is used, it is intended to include "alkyl", "alkenyl" and "alkynyl", unless otherwise specified.

The term "alkoxy" or "alkyloxy" refers to an -O-alkyl group. For example, "C_1 to C_6 alkoxy" or "C_{1-6} alkoxy" (or alkyloxy), is intended to include C_1, C_2, C_3, C_4, C_5, and C_6 alkoxy groups. Example alkoxy groups include, but are not limited to, methoxy, ethoxy, propoxy (*e.g.*, n-propoxy and isopropoxy), and *t*-butoxy. Similarly, "alkylthio" or "thioalkoxy" represents an alkyl group as defined above with the indicated number of carbon atoms attached through a sulphur bridge; for example methyl-S- and ethyl-S-.

"Halo" or "halogen" includes fluoro, chloro, bromo, and iodo. "Haloalkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms, substituted with 1 or more halogens. Examples of haloalkyl include, but are not limited to, fluoromethyl, difluoromethyl, trifluoromethyl, trichloromethyl, pentafluoroethyl, pentachloroethyl, 2,2,2-trifluoroethyl, heptafluoropropyl, and heptachloropropyl. Examples of haloalkyl also include "fluoroalkyl" that is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms, substituted with 1 or more fluorine atoms.

"Haloalkoxy" or "haloalkyloxy" represents a haloalkyl group as defined above with the indicated number of carbon atoms attached through an oxygen bridge. For

example, "C_{1-6} haloalkoxy", is intended to include C_1, C_2, C_3, C_4, C_5, and C_6 haloalkoxy groups. Examples of haloalkoxy include, but are not limited to, trifluoromethoxy, 2,2,2-trifluoroethoxy, and pentafluorothoxy. Similarly, "haloalkylthio" or "thiohaloalkoxy" represents a haloalkyl group as defined above with the indicated number of carbon atoms attached through a sulphur bridge; for example trifluoromethyl-S-, and pentafluoroethyl-S-.

The term "cycloalkyl" refers to cyclized alkyl groups, including mono-, bi- or poly-cyclic ring systems. For example, "C_3 to C_6 cycloalkyl" or "C_{3-6} cycloalkyl" is intended to include C_3, C_4, C_5, and C_6 cycloalkyl groups. Example cycloalkyl groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and norbornyl. Branched cycloalkyl groups such as 1-methylcyclopropyl and 2-methylcyclopropyl are included in the definition of "cycloalkyl". The term "cycloalkenyl" refers to cyclized alkenyl groups. C_{4-6} cycloalkenyl is intended to include C_4, C_5, and C_6 cycloalkenyl groups. Example cycloalkenyl groups include, but are not limited to, cyclobutenyl, cyclopentenyl, and cyclohexenyl.

As used herein, "carbocycle", "carbocyclyl", or "carbocyclic residue" is intended to mean any stable 3-, 4-, 5-, 6-, 7-, or 8-membered monocyclic or bicyclic or 7-, 8-, 9-, 10-, 11-, 12-, or 13-membered bicyclic or tricyclic ring, any of which may be saturated, partially unsaturated, unsaturated or aromatic. Examples of such carbocycles include, but are not limited to, cyclopropyl, cyclobutyl, cyclobutenyl, cyclopentyl, cyclopentenyl, cyclohexyl, cycloheptenyl, cycloheptyl, cycloheptenyl, adamantyl, cyclooctyl, cyclooctenyl, cyclooctadienyl, [3.3.0]bicyclooctane, [4.3.0]bicyclononane, [4.4.0]bicyclodecane (decalin), [2.2.2]bicyclooctane, fluorenyl, phenyl, naphthyl, indanyl, adamantyl, anthracenyl, and tetrahydronaphthyl (tetralin). As shown above, bridged rings are also included in the definition of carbocycle (*e.g.*, [2.2.2]bicyclooctane). Preferred carbocycles, unless otherwise specified, are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, indanyl, and tetrahydronaphthyl. When the term "carbocycle" is used, it is intended to include "aryl". A bridged ring occurs when one or more, preferably one to three, carbon atoms link two non-adjacent carbon atoms. Preferred bridges are one or two carbon atoms. It is noted that a bridge always converts a monocyclic ring into a tricyclic ring. When a ring is bridged, the substituents recited for the ring may also be present on the bridge.

As used herein, the term "bicyclic carbocycle" or "bicyclic carbocyclic group" is intended to mean a stable 9- or 10-membered carbocyclic ring system that contains two fused rings and consists of carbon atoms. Of the two fused rings, one ring is a benzo ring fused to a second ring; and the second ring is a 5- or 6-membered carbon ring which is saturated, partially unsaturated, or unsaturated. The bicyclic carbocyclic group may be attached to its pendant group at any carbon atom which results in a stable structure. The bicyclic carbocyclic group described herein may be substituted on any carbon if the resulting compound is stable. Examples of a bicyclic carbocyclic group are, but not limited to, naphthyl, 1,2-dihydronaphthyl, 1,2,3,4-tetrahydronaphthyl, and indanyl.

"Aryl" groups refer to monocyclic or bicyclic aromatic hydrocarbons, including, for example, phenyl, and naphthyl. Aryl moieties are well known and described, for example, in Lewis, R.J., ed., *Hawley's Condensed Chemical Dictionary*, 15th Edition, John Wiley & Sons, Inc., New York (2007). "C_{6-10} aryl" refers to phenyl and naphthyl.

The term "benzyl", as used herein, refers to a methyl group on which one of the hydrogen atoms is replaced by a phenyl group.

As used herein, the term "heterocycle", "heterocyclyl", or "heterocyclic group" is intended to mean a stable 3-, 4-, 5-, 6-, or 7-membered monocyclic or bicyclic or 7-, 8-, 9-, 10-, 11-, 12-, 13-, or 14-membered polycyclic heterocyclic ring that is saturated, partially unsaturated, or fully unsaturated, and that contains carbon atoms and 1, 2, 3 or 4 heteroatoms independently selected from the group consisting of N, O and S; and including any polycyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The nitrogen and sulfur heteroatoms may optionally be oxidized (*i.e.*, N→O and $S(O)_p$, wherein p is 0, 1 or 2). The nitrogen atom may be substituted or unsubstituted (*i.e.*, N or NR wherein R is H or another substituent, if defined). The heterocyclic ring may be attached to its pendant group at any heteroatom or carbon atom that results in a stable structure. The heterocyclic rings described herein may be substituted on carbon or on a nitrogen atom if the resulting compound is stable. A nitrogen in the heterocycle may optionally be quaternized. It is preferred that when the total number of S and O atoms in the heterocycle exceeds 1, then these heteroatoms are not adjacent to one another. It is preferred that the total number of S and O atoms in the heterocycle is not more than 1. When the term "heterocycle" is used, it is intended to include heteroaryl.

Examples of heterocycles include, but are not limited to, acridinyl, azetidinyl, azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzoxazolinyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazolinyl, carbazolyl, 4a*H*-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, 2*H*,6*H*-1,5,2-dithiazinyl, dihydrofuro[2,3-*b*]tetrahydrofuran, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1*H*-indazolyl, imidazolopyridinyl, indolenyl, indolinyl, indolizinyl, indolyl, 3*H*-indolyl, isatinoyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isothiazolopyridinyl, isoxazolyl, isoxazolopyridinyl, methylenedioxyphenyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxazolopyridinyl, oxazolidinylperimidinyl, oxindolyl, pyrimidinyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, piperidonyl, 4-piperidonyl, piperonyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolopyridinyl, pyrazolyl, pyridazinyl, pyridooxazolyl, pyridoimidazolyl, pyridothiazolyl, pyridinyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, 2-pyrrolidonyl, 2*H*-pyrrolyl, pyrrolyl, quinazolinyl, quinolinyl, 4*H*-quinolizinyl, quinoxalinyl, quinuclidinyl, tetrazolyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, 6*H*-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thiazolopyridinyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, and xanthenyl. Also included are fused ring and spiro compounds containing, for example, the above heterocycles.

Examples of 5- to 10-membered heterocycles include, but are not limited to, pyridinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, pyrazinyl, piperazinyl, piperidinyl, imidazolyl, imidazolidinyl, indolyl, tetrazolyl, isoxazolyl, morpholinyl, oxazolyl, oxadiazolyl, oxazolidinyl, tetrahydrofuranyl, thiadiazinyl, thiadiazolyl, thiazolyl, triazinyl, triazolyl, benzimidazolyl, 1*H*-indazolyl, benzofuranyl, benzothiofuranyl, benztetrazolyl, benzotriazolyl, benzisoxazolyl, benzoxazolyl, oxindolyl, benzoxazolinyl, benzthiazolyl, benzisothiazolyl, isatinoyl, isoquinolinyl, octahydroisoquinolinyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, isoxazolopyridinyl, quinazolinyl,

quinolinyl, isothiazolopyridinyl, thiazolopyridinyl, oxazolopyridinyl, imidazolopyridinyl, and pyrazolopyridinyl.

Examples of 5- to 6-membered heterocycles include, but are not limited to, pyridinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, pyrazinyl, piperazinyl, piperidinyl, imidazolyl, imidazolidinyl, indolyl, tetrazolyl, isoxazolyl, morpholinyl, oxazolyl, oxadiazolyl, oxazolidinyl, tetrahydrofuranyl, thiadiazinyl, thiadiazolyl, thiazolyl, triazinyl, and triazolyl. Also included are fused ring and spiro compounds containing, for example, the above heterocycles.

As used herein, the term "bicyclic heterocycle" or "bicyclic heterocyclic group" is intended to mean a stable 9- or 10-membered heterocyclic ring system which contains two fused rings and consists of carbon atoms and 1, 2, 3, or 4 heteroatoms independently selected from the group consisting of N, O and S. Of the two fused rings, one ring is a 5- or 6-membered monocyclic aromatic ring comprising a 5-membered heteroaryl ring, a 6-membered heteroaryl ring or a benzo ring, each fused to a second ring. The second ring is a 5- or 6-membered monocyclic ring which is saturated, partially unsaturated, or unsaturated, and comprises a 5-membered heterocycle, a 6-membered heterocycle or a carbocycle (provided the first ring is not benzo when the second ring is a carbocycle).

The bicyclic heterocyclic group may be attached to its pendant group at any heteroatom or carbon atom which results in a stable structure. The bicyclic heterocyclic group described herein may be substituted on carbon or on a nitrogen atom if the resulting compound is stable. It is preferred that when the total number of S and O atoms in the heterocycle exceeds 1, then these heteroatoms are not adjacent to one another. It is preferred that the total number of S and O atoms in the heterocycle is not more than 1.

Examples of a bicyclic heterocyclic group are, but not limited to, quinolinyl, isoquinolinyl, phthalazinyl, quinazolinyl, indolyl, isoindolyl, indolinyl, 1*H*-indazolyl, benzimidazolyl, 1,2,3,4-tetrahydroquinolinyl, 1,2,3,4-tetrahydroisoquinolinyl, 5,6,7,8-tetrahydro-quinolinyl, 2,3-dihydro-benzofuranyl, chromanyl, 1,2,3,4-tetrahydro-quinoxalinyl, and 1,2,3,4-tetrahydro-quinazolinyl.

As used herein, the term "aromatic heterocyclic group" or "heteroaryl" is intended to mean stable monocyclic and polycyclic aromatic hydrocarbons that include at least one heteroatom ring member such as sulfur, oxygen, or nitrogen. Heteroaryl groups include, without limitation, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, furyl, quinolyl,

isoquinolyl, thienyl, imidazolyl, thiazolyl, indolyl, pyrroyl, oxazolyl, benzofuryl, benzothienyl, benzthiazolyl, isoxazolyl, pyrazolyl, triazolyl, tetrazolyl, indazolyl, 1,2,4-thiadiazolyl, isothiazolyl, purinyl, carbazolyl, benzimidazolyl, indolinyl, benzodioxolanyl, and benzodioxane. Heteroaryl groups are substituted or unsubstituted. The nitrogen atom is substituted or unsubstituted (*i.e.*, N or NR wherein R is H or another substituent, if defined). The nitrogen and sulfur heteroatoms may optionally be oxidized (*i.e.*, N→O and $S(O)_p$, wherein p is 0, 1 or 2).

Examples of 5- to 6-membered heteroaryls include, but are not limited to, pyridinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, pyrazinyl, imidazolyl, imidazolidinyl, tetrazolyl, isoxazolyl, oxazolyl, oxadiazolyl, oxazolidinyl, thiadiazinyl, thiadiazolyl, thiazolyl, triazinyl, and triazolyl.

Bridged rings are also included in the definition of heterocycle. A bridged ring occurs when one or more, preferably one to three, atoms (*i.e.*, C, O, N, or S) link two non-adjacent carbon or nitrogen atoms. Examples of bridged rings include, but are not limited to, one carbon atom, two carbon atoms, one nitrogen atom, two nitrogen atoms, and a carbon-nitrogen group. It is noted that a bridge always converts a monocyclic ring into a tricyclic ring. When a ring is bridged, the substituents recited for the ring may also be present on the bridge.

The term "counter ion" is used to represent a negatively charged species such as chloride, bromide, hydroxide, acetate, and sulfate or a positively charged species such as sodium (Na+), potassium (K+), ammonium (R_nNH_m+ where n = 0-4 and m = 0-4) and the like.

When a dotted ring is used within a ring structure, this indicates that the ring structure may be saturated, partially saturated or unsaturated.

As used herein, the term "amine protecting group" means any group known in the art of organic synthesis for the protection of amine groups which is stable to an ester reducing agent, a disubstituted hydrazine, R4-M and R7-M, a nucleophile, a hydrazine reducing agent, an activator, a strong base, a hindered amine base and a cyclizing agent. Such amine protecting groups fitting these criteria include those listed in Wuts, P.G.M. et al., *Protecting Groups in Organic Synthesis*, Fourth Edition, Wiley (2007) and *The Peptides: Analysis, Synthesis, Biology*, Vol. 3, Academic Press, New York (1981), the disclosure of which is hereby incorporated by reference. Examples of amine protecting

groups include, but are not limited to, the following: (1) acyl types such as formyl, trifluoroacetyl, phthalyl, and p-toluenesulfonyl; (2) aromatic carbamate types such as benzyloxycarbonyl (Cbz) and substituted benzyloxycarbonyls, 1-(p-biphenyl)-1-methylethoxycarbonyl, and 9-fluorenylmethyloxycarbonyl (Fmoc); (3) aliphatic carbamate types such as *tert*-butyloxycarbonyl (Boc), ethoxycarbonyl, diisopropylmethoxycarbonyl, and allyloxycarbonyl; (4) cyclic alkyl carbamate types such as cyclopentyloxycarbonyl and adamantyloxycarbonyl; (5) alkyl types such as triphenylmethyl and benzyl; (6) trialkylsilane such as trimethylsilane; (7) thiol containing types such as phenylthiocarbonyl and dithiasuccinoyl; and (8) alkyl types such as triphenylmethyl, methyl, and benzyl; and substituted alkyl types such as 2,2,2-trichloroethyl, 2-phenylethyl, and *t*-butyl; and trialkylsilane types such as trimethylsilane.

As referred to herein, the term "substituted" means that at least one hydrogen atom is replaced with a non-hydrogen group, provided that normal valencies are maintained and that the substitution results in a stable compound. Ring double bonds, as used herein, are double bonds that are formed between two adjacent ring atoms (*e.g.*, C=C, C=N, or N=N).

In cases wherein there are nitrogen atoms (*e.g.*, amines) on compounds of the present invention, these may be converted to N-oxides by treatment with an oxidizing agent (*e.g.*, mCPBA and/or hydrogen peroxides) to afford other compounds of this invention. Thus, shown and claimed nitrogen atoms are considered to cover both the shown nitrogen and its N-oxide (N→O) derivative.

When any variable occurs more than one time in any constituent or formula for a compound, its definition at each occurrence is independent of its definition at every other occurrence. Thus, for example, if a group is shown to be substituted with 0-3 R, then said group may optionally be substituted with up to three R groups, and at each occurrence R is selected independently from the definition of R.

When a bond to a substituent is shown to cross a bond connecting two atoms in a ring, then such substituent may be bonded to any atom on the ring. When a substituent is listed without indicating the atom in which such substituent is bonded to the rest of the compound of a given formula, then such substituent may be bonded via any atom in such substituent.

Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

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

Compounds of the present invention can form salts which are also within the scope of this invention. Unless otherwise indicated, reference to an inventive compound is understood to include reference to one or more salts thereof. Pharmaceutically acceptable salts are preferred. However, other salts may be useful, *e.g.*, in isolation or purification steps which may be employed during preparation, and thus, are contemplated within the scope of the invention.

As used herein, "pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic groups such as amines; and alkali or organic salts of acidic groups such as carboxylic acids. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, and nitric; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, and isethionic, and the like.

The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound that contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of

suitable salts are found in Allen, L.V., Jr., ed., *Remington: The Science and Practice of Pharmacy*, 22nd Edition, Pharmaceutical Press, London, UK (2012), the disclosure of which is hereby incorporated by reference.

In addition, compounds of formula I may have prodrug forms. Any compound that will be converted *in vivo* to provide the bioactive agent (*i.e.*, a compound of formula I) is a prodrug within the scope and spirit of the invention. Various forms of prodrugs are well known in the art. For examples of such prodrug derivatives, see:

a) Bundgaard, H., ed., *Design of Prodrugs*, Elsevier (1985), and Widder, K. et al., eds., *Methods in Enzymology*, 112:309-396, Academic Press (1985);

b) Bundgaard, H., Chapter 5, "Design and Application of Prodrugs", *A Textbook of Drug Design and Development*, pp. 113-191, Krogsgaard-Larsen, P. et al., eds., Harwood Academic Publishers (1991);

c) Bundgaard, H., *Adv. Drug Deliv. Rev.*, 8:1-38 (1992);

d) Bundgaard, H. et al., *J. Pharm. Sci.*, 77:285 (1988);

e) Kakeya, N. et al., *Chem. Pharm. Bull.*, 32:692 (1984); and

f) Rautio, J., ed., *Prodrugs and Targeted Delivery (Methods and Principles in Medicinal Chemistry)*, Vol. 47, Wiley-VCH (2011).

Compounds containing a carboxy group can form physiologically hydrolyzable esters that serve as prodrugs by being hydrolyzed in the body to yield formula I compounds *per se*. Such prodrugs are preferably administered orally since hydrolysis in many instances occurs principally under the influence of the digestive enzymes. Parenteral administration may be used where the ester *per se* is active, or in those instances where hydrolysis occurs in the blood. Examples of physiologically hydrolyzable esters of compounds of formula I include C_{1-6}alkyl, C_{1-6}alkylbenzyl, 4-methoxybenzyl, indanyl, phthalyl, methoxymethyl, C_{1-6} alkanoyloxy-C_{1-6}alkyl (*e.g.*, acetoxymethyl, pivaloyloxymethyl or propionyloxymethyl), C_{1-6}alkoxycarbonyloxy-C_{1-6}alkyl (*e.g.*, methoxycarbonyl-oxymethyl or ethoxycarbonyloxymethyl, glycyloxymethyl, phenylglycyloxymethyl, (5-methyl-2-oxo-1,3-dioxolen-4-yl)-methyl), and other well known physiologically hydrolyzable esters used, for example, in the penicillin and cephalosporin arts. Such esters may be prepared by conventional techniques known in the art.

Preparation of prodrugs is well known in the art and described in, for example, King, F.D., ed., *Medicinal Chemistry: Principles and Practice*, The Royal Society of Chemistry, Cambridge, UK (Second Edition, reproduced, 2006); Testa, B. et al., *Hydrolysis in Drug and Prodrug Metabolism. Chemistry, Biochemistry and Enzymology*, VCHA and Wiley-VCH, Zurich, Switzerland (2003); Wermuth, C.G., ed., *The Practice of Medicinal Chemistry*, Third Edition, Academic Press, San Diego, CA (2008).

The present invention is intended to include all isotopes of atoms occurring in the present compounds. Isotopes include those atoms having the same atomic number but different mass numbers. By way of general example and without limitation, isotopes of hydrogen include deuterium and tritium. Isotopes of carbon include ^{13}C and ^{14}C. Isotopically-labeled compounds of the invention can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described herein, using an appropriate isotopically-labeled reagent in place of the non-labeled reagent otherwise employed.

The term "solvate" means a physical association of a compound of this invention with one or more solvent molecules, whether organic or inorganic. This physical association includes hydrogen bonding. In certain instances the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. The solvent molecules in the solvate may be present in a regular arrangement and/or a non-ordered arrangement. The solvate may comprise either a stoichiometric or nonstoichiometric amount of the solvent molecules. "Solvate" encompasses both solution-phase and isolable solvates. Exemplary solvates include, but are not limited to, hydrates, ethanolates, methanolates, and isopropanolates. Methods of solvation are generally known in the art.

As used herein, "polymorph(s)" refer to crystalline form(s) having the same chemical structure/composition but different spatial arrangements of the molecules and/or ions forming the crystals. Compounds of the present invention can be provided as amorphous solids or crystalline solids. Lyophilization can be employed to provide the compounds of the present invention as a solid.

All measurements are subject to experimental error and are within the contemplation of the invention.

When the invention is described or characterized by any of the disclosed figures or tables, it is understood that all variations within limitations and/or error margins of the experiments and technology are contemplated.

Abbreviations as used herein, are defined as follows: "1 x" for once, "2 x" for twice, "3 x" for thrice, "°C" for degrees Celsius, "eq" for equivalent or equivalents, "g" for gram or grams, "mg" for milligram or milligrams, "L" for liter or liters, "mL" for milliliter or milliliters, "μL" for microliter or microliters, "N" for normal, "M" for molar, "mmol" for millimole or millimoles, "min" for minute or min, "h" for hour or h, "rt" for room temperature, "RT" for retention time, "atm" for atmosphere, "psi" for pounds per square inch, "conc." for concentrate, "aq" for "aqueous", "sat" or "sat'd " for saturated, "MW" for molecular weight, "mp" for melting point, "MS" or "Mass Spec" for mass spectrometry, "ESI" for electrospray ionization mass spectroscopy, "HR" for high resolution, "HRMS" for high resolution mass spectrometry, "LCMS" for liquid chromatography mass spectrometry, "HPLC" for high pressure liquid chromatography, "RP HPLC" for reverse phase HPLC, "TLC" or "tlc" for thin layer chromatography, "NMR" for nuclear magnetic resonance spectroscopy, "nOe" for nuclear Overhauser effect spectroscopy, "^{1}H" for proton, "δ" for delta, "s" for singlet, "d" for doublet, "t" for triplet, "q" for quartet, "m" for multiplet, "br" for broad, "Hz" for hertz, and "α", "β", "R", "S", "E", "Z" and "ee" are stereochemical designations familiar to one skilled in the art.

Me	methyl
Et	ethyl
Pr	propyl
i-Pr	isopropyl
Bu	butyl
i-Bu	isobutyl
t-Bu	*tert*-butyl
Ph	phenyl
Bn	benzyl
Hex	hexanes
MeOH	methanol
EtOH	ethanol

i-PrOH or IPA	isopropanol
AcOH or HOAc	acetic acid
Ag_2CO_3	silver carbonate
AgOAc	silver acetate
$CDCl_3$	deutero-chloroform
$CHCl_3$	chloroform
cDNA	complementary DNA
DCC	*N*,*N*'-dicyclohexylcarbodiimide
DIAD	diisopropyl azodicarboxylate
DMA	dimethylamine
DME	dimethylether
DMF	dimethyl formamide
DMSO	dimethyl sulfoxide
DMAP	4-dimethylaminopyridine
EDTA	ethylenediaminetetraacetic acid
EtOAc	ethyl acetate
Et_2O	diethyl ether
$AlCl_3$	aluminum chloride
Boc	*tert*-butyloxycarbonyl
CH_2Cl_2	dichloromethane
CH_3CN or ACN	acetonitrile
Cs_2CO_3	cesium carbonate
HCl	hydrochloric acid
H_2SO_4	sulfuric acid
K_2CO_3	potassium carbonate
KCN	potassium cyanide
mCPBA or m-CPBA	*meta*-chloroperbenzoic acid
Pd/C	palladium on carbon
$PhSO_2Cl$	benzenesulfonyl chloride
i-Pr_2NEt	diisopropylethylamine
PS	polystyrene
SFC	Supercritical Fluid Chromatography

SiO_2	silica oxide
$SnCl_2$	tin(II) chloride
TBAT	tetrabutylammonium triphenydifluorosilicate
TEA	triethylamine
TFA	trifluoroacetic acid
THF	tetrahydrofuran
KOAc	potassium acetate
$MgSO_4$	magnesium sulfate
NaCl	sodium chloride
NaH	sodium hydride
$NaHCO_3$	sodium bicarbonate
NaOH	sodium hydroxide
Na_2SO_3	sodium sulfite
Na_2SO_4	sodium sulfate
NH_3	ammonia
NH_4Cl	ammonium chloride
NH_4OH	ammonium hydroxide
LG	leaving group
Pd_2dba_3	tris(dibenzylideneacetone)dipalladium(0)
SELECTFLUOR®	*N*-fluoro-*N'*-methyl-triethylenediamine bis(tetrafluoroborate)

The compounds of the present invention can be prepared in a number of ways known to one skilled in the art of organic synthesis. The compounds of the present invention can be synthesized using the methods described below, together with synthetic methods known in the art of synthetic organic chemistry, or by variations thereon as appreciated by those skilled in the art. Preferred methods include, but are not limited to, those described below. The reactions are performed in a solvent or solvent mixture appropriate to the reagents and materials employed and suitable for the transformations being effected. It will be understood by those skilled in the art of organic synthesis that the functionality present on the molecule should be consistent with the transformations proposed. This will sometimes require a judgment to modify the order of the synthetic

steps or to select one particular process scheme over another in order to obtain a desired compound of the invention.

The novel compounds of this invention may be prepared using the reactions and techniques described in this section. Also, in the description of the synthetic methods described below, it is to be understood that all proposed reaction conditions, including choice of solvent, reaction atmosphere, reaction temperature, duration of the experiment and workup procedures, are chosen to be the conditions standard for that reaction, which should be readily recognized by one skilled in the art. Restrictions to the substituents that are compatible with the reaction conditions will be readily apparent to one skilled in the art and alternate methods must then be used.

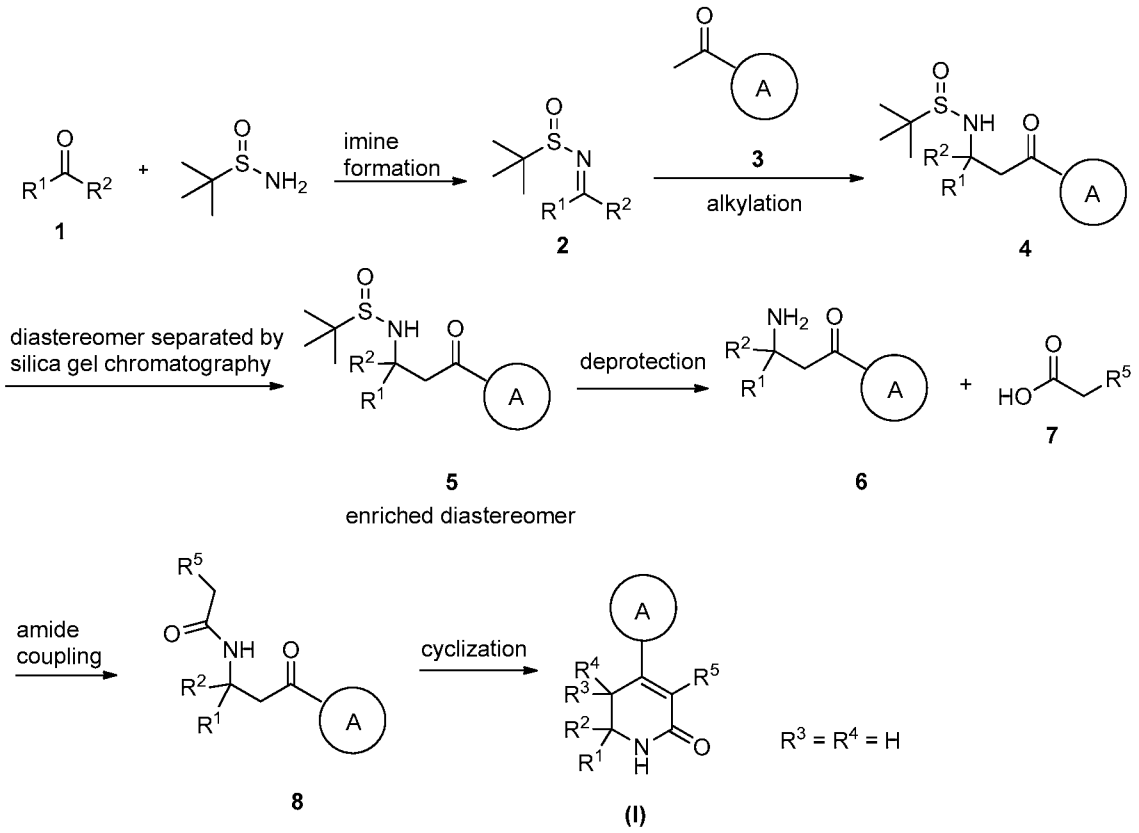
SYNTHESIS

The compounds of Formula (I) may be prepared by the exemplary processes described in the following schemes and working examples, as well as relevant published literature procedures that are used by one skilled in the art. Exemplary reagents and procedures for these reactions appear hereinafter and in the working examples. Protection and de-protection in the processes below may be carried out by procedures generally known in the art (see, for example, Wuts, P.G.M. et al., *Protecting Groups in Organic Synthesis*, Fourth Edition, Wiley (2007)). General methods of organic synthesis and functional group transformations are found in: Trost, B.M. et al., eds., *Comprehensive Organic Synthesis: Selectivity, Strategy & Efficiency in Modern Organic Chemistry*, Pergamon Press, New York, NY (1991); Smith, M.B. et al., *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, Sixth Edition, Wiley & Sons, New York, NY (2007); Katritzky, A.R. et al., eds., *Comprehensive Organic Functional Groups Transformations II*, Second Edition, Elsevier Science Inc., Tarrytown, NY (2004); Larock, R.C., *Comprehensive Organic Transformations*, VCH Publishers, Inc., New York, NY (1999), and references therein.

Compounds of Formula (I), single enantiomer, where $R^3 = R^4 = H$, can be made according to Scheme 1. Ketone **1** is stirred with 2-methylpropane-2-sulfinamide in the presence of a suitable Lewis acid, such as $Ti(OEt)_4$, in a solvent such as THF at reflux temperature to provide imine **2**. Other Lewis acids, solvents and temperatures may be

used as determined by those skilled in the art. Imine **2** is alkylated with ketone **3** in the presence of a base, such as LiHMDS, KHMDS, NaHMDS, or LDA in an aprotic solvent such as THF or ether at a temperature ranging from -78 °C to ambient to provide β-amino ketone **4** as a mixture of two diastereomers, which can be separated by silica gel chromatography to give the desired isomer **5**. Other metal enolates (such as titanium enolate), solvents, and temperatures may be used as determined by those skilled in the art (Tang, T.P. et al., *J. Org. Chem.*, 64:12-13 (1999), *J. Org. Chem.*, 67:7819-7832 (2002)). Preferably, chiral *S*- or *R*-2-methylpropane-2-sulfinamide can be optionally used to generate each of the optically pure enantiomers of imine **2** that can allow for chiral induction to prepare diastereomerically enriched ketone **5**. In these cases, the product mixture can be further purified by silica gel chromatography to obtain desired products with diastereomeric excess of >97%. β-Sulfinamido ketone **5** thus formed is deprotected using HCl in a suitable solvent such as MeOH to provide β-amino ketone **6**. Other conditions to remove the *t*-butylsulfinyl group may be employed as determined by those skilled in the art. β-Amino ketone **6** is acylated with carboxylic acid **7** using conditions described in Scheme 2 to give the β-keto amide **8**. Stirring β-keto amide **8** with a base such as sodium ethoxide in a suitable solvent such as ethanol at room temperature provides compounds having Formula (I).

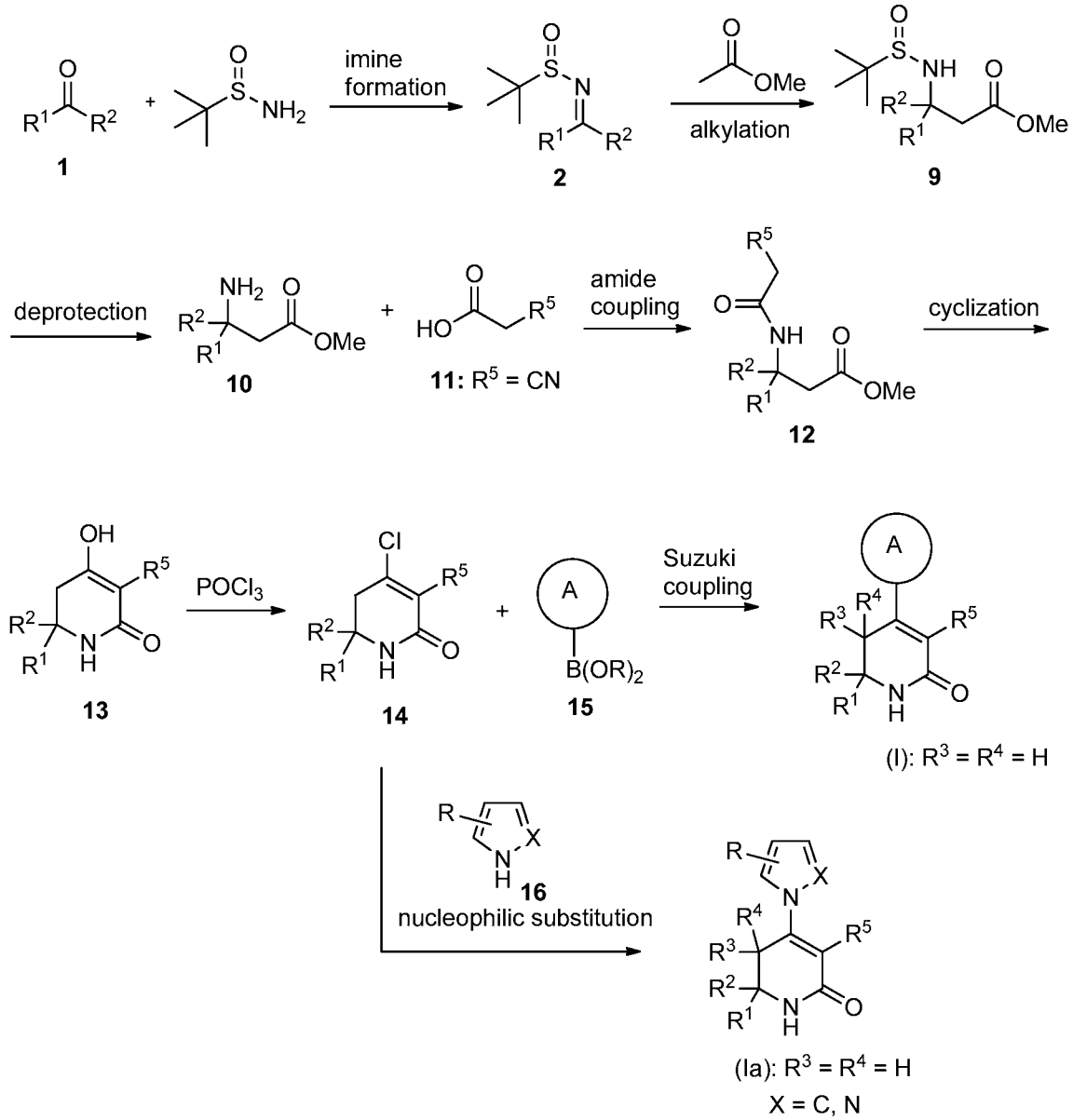
Scheme 1



Alternatively, compounds of Formula (I), where $R^3 = R^4 = H$, may be made according to Scheme 2. Ketone **1** can be reacted with 2-methylpropane-2-sulfinamide in the presence of a suitable Lewis acid, such as $Ti(OEt)_4$, in a solvent such as THF at a temperature ranging from ambient to reflux to provide imine **2**. Other Lewis acids, solvents and temperatures may be used as determined by those skilled in the art. Imine **2** is alkylated with the enolate of an ester in a suitable aprotic solvent such as THF or ether starting at -78 °C then warming to 0 °C or room temperature to provide protected β-sulfinamido ketone **9** as a mixture of two diastereomers, which can be separated by silica gel chromatography to give each individual chiral compound. The generation of the ester enolate is achieved by treating the ester, such as methyl acetate, with a suitable base such as LHMDS, KHMDS, NaHMDS, or LDA in an aprotic solvent such as THF or ether at a temperature ranging from -78 °C to ambient. Other metal enolates (such as titanium enolate), solvents, and temperatures may be used as determined by those skilled in the art (Tang, T.P. et al., *J. Org. Chem.*, 64:12-13 (1999), *J. Org. Chem.*, 67:7819-7832 (2002)). Preferably, chiral *S*- or *R*-2-methylpropane-2-sulfinamide can be optionally used to

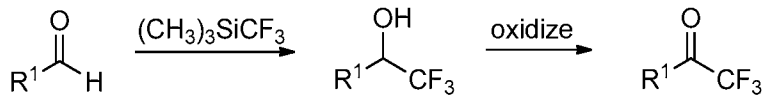
generate each of the optically pure enantiomers of imine **8** that can allow for chiral induction to prepare diastereomerically enriched ester **9**. In these cases, the product mixture can be further purified by silica gel chromatography to obtain desired products with diastereomeric excess of >97%. The *tert*-butyl sulfinyl group of **9** is removed using acids such as HCl and TFA in a suitable solvent such as MeOH or dioxane to generate amino ester **10**. Other conditions to remove the *t*-butylsulfinyl group may be employed as determined by those skilled in the art. β-Amino ketone **10** is acylated with carboxylic acid **11** to give the β-keto amide **12**. Stirring β-keto amide **12** with a base such as sodium ethoxide in a suitable solvent such as ethanol at room temperature to 80 °C provides cyclic enol **13**. Other conditions can also be used to effect the cyclization as determined by those skilled in the art. Compound **13**, when treated with stoichiometric amount of a chlorinating agent, such as $POCl_3$, at elevated temperature in an inert solvent such as toluene, is converted to mono-chloride **14**. Chloride **14** can then react with various boronic reagents through a Suzuki-type of cross coupling reaction to generate compounds of Formula (I). The choices of boronic reagents, catalysts, ligands, bases, solvents and temperatures are well documented in the literature and can be selected appropriately by those skilled in the art. Alternatively, chloride **14** can react with N containing heterocycles **16** through a nucleophilic substitution reaction to generate compounds of Formula (I).

Scheme 2



Non-commercial α,α,α-trifluoroketones **1**, where $R^2 = CF_3$, may be made from the corresponding aldehyde **17** as shown in Scheme 3. Aldehyde **17** is reacted with trimethyl-(trifluoromethyl)silane in the presence of a fluoride source, for example cesium fluoride, using a suitable solvent such dimethoxyethane at room temperature. Other fluoride sources, such as potassium hydrogen fluoride or tetrabutylammonium difluorotriphenylsilicate, and other solvents, such as THF or acetonitrile and methanol, may also be employed. Trifluoromethyl alcohol **18** is oxidized using, for example, Dess-Martin periodinane in a suitable solvent such as CH_2Cl_2.

Scheme 3



17 18 1

IV. BIOLOGY

In mammals, there are two triglyceride synthesis pathways: glycerol-3-phosphate pathway and monoacylglycerol pathway. The former is mainly responsible for energy storage in the peripheral tissues such as fat, liver, skeletal muscle; the latter is essential for the dietary fat absorption which takes place in the small intestine. When dietary fat is ingested, pancreatic lipase digests triglycerides into free fatty acids and 2-monoacylglycerol, which are absorbed by intestinal epithelial enterocytes. Once inside enterocytes, free fatty acids and 2-monoacylglycerol are used as building blocks to resynthesize triglycerides by two sequential acylation steps; first by MGAT and then by DGAT enzyme reactions. Triglycerides are then incorporated into chylomicrons and secreted into lymph to be utilized as an energy supply for the body.

Monoacylglycerol acyltransferase 2 (MGAT2) is a membrane-bound acyltransferase that belongs to diacylglycerol acyltransferase 2 (DGAT2) gene family. It is highly and selectively expressed in the small intestine. Genetic deletion of MGAT2 in mice decreased the rate of absorption for the orally ingested triglycerides, indicating that MGAT2 plays an important role for the intestinal MGAT/DGAT pathway [Yen, C.L. et al., *Nat. Med.*, 15(4):442-446 (2009); Okawa, M. et al., *Biochem. Biophys. Res. Commun.*, 390(3):377-381 (2009)]. When chronically challenged with a high fat diet, in contrast to wild type mice that became obese, MGAT2 knockout mice resisted the impact of high-fat feeding and had a lower body weight, less adiposity, and less hepatic fat accumulation. In contrast to hyperinsulinemic wild type mice after high-fat challenge, MGAT2 deletion normalizes the insulin level and decreased fasting glucose. In the glucose tolerance test, they also had an improved glucose excursion. Consistent with their improved glycemic profile, MGAT2 knockout mice also had an increased level of GLP1, an incretin gut hormone that profoundly impacts glucose metabolism [Yen, C.L. et al., *Nat. Med.*, 15(4):442-446 (2009)]. Taken together, it is expected that inhibition of

MGAT2 through pharmacological intervention would provide the same benefit as demonstrated in the knock-out mice, *e.g.*, resistance to weight gain, or conversely, reduction in fat body mass. In addition, MGAT2 inhibition would lead to an improved insulin sensitivity and glucose metabolism which either leads to a decrease in the incidence of Type II diabetes, or a treatment of diabetic condition.

It is also desirable and preferable to find compounds with advantageous and improved characteristics compared with known anti-diabetic agents, in one or more of the following categories that are given as examples, and are not intended to be limiting: (a) pharmacokinetic properties, including oral bioavailability, half life, and clearance; (b) pharmaceutical properties; (c) dosage requirements; (d) factors that decrease blood drug concentration peak-to-trough characteristics; (e) factors that increase the concentration of active drug at the receptor; (f) factors that decrease the liability for clinical drug-drug interactions; (g) factors that decrease the potential for adverse side-effects, including selectivity versus other biological targets; and (h) improved therapeutic index with less propensity for hypoglycemia.

As used herein, the term "patient" encompasses all mammalian species.

As used herein, the term "subject" refers to any human or non-human organism that could potentially benefit from treatment with a MGAT2 inhibitor. Exemplary subjects include human beings of any age with risk factors for metabolic disease. Common risk factors include, but are not limited to, age, sex, weight, family history, or signs of insulin resistance such as acanthosis nigricans, hypertension, dyslipidemia, or polycystic ovary syndrome (PCOS).

As used herein, "treating" or "treatment" cover the treatment of a disease-state in a mammal, particularly in a human, and include: (a) inhibiting the disease-state, *i.e.*, arresting it development; (b) relieving the disease-state, *i.e.*, causing regression of the disease state; and/or (c) preventing the disease-state from occurring in a mammal, in particular, when such mammal is predisposed to the disease-state but has not yet been diagnosed as having it.

As used herein, "preventing" or "prevention" cover the preventive treatment (*i.e.*, prophylaxis and/or risk reduction) of a subclinical disease-state in a mammal, particularly in a human, aimed at reducing the probability of the occurrence of a clinical disease-state. Patients are selected for preventative therapy based on factors that are known to increase

risk of suffering a clinical disease state compared to the general population. "Prophylaxis" therapies can be divided into (a) primary prevention and (b) secondary prevention. Primary prevention is defined as treatment in a subject that has not yet presented with a clinical disease state, whereas secondary prevention is defined as preventing a second occurrence of the same or similar clinical disease state.

As used herein, "risk reduction" or "reducing risk" covers therapies that lower the incidence of development of a clinical disease state. As such, primary and secondary prevention therapies are examples of risk reduction.

"Therapeutically effective amount" is intended to include an amount of a compound of the present invention that is effective when administered alone or in combination to inhibit MGAT2 and/or to prevent or treat the disorders listed herein. When applied to a combination, the term refers to combined amounts of the active ingredients that result in the preventive or therapeutic effect, whether administered in combination, serially, or simultaneously.

ASSAY METHODS

MGAT LCMS Assay

The MGAT enzyme reactions were performed in Corning FALCON® 96-well polypropylene plates, in a total volume of 60 µL of 50 mM potassium phosphate buffer pH 7.4, containing a final concentration of 100 µM 2-oleoylglycerol, 15 µM oleoyl-coenzyme A and 0.0013 µg/µL human or mouse MGAT-2 or 0.0026 µg/µL rat recombinant MGAT-2 membranes expressed in Sf9 cells. Assay plates were run through a fully automated robotics system and shaken for 5 seconds every minute for a total 10 minutes. The reactions were then quenched with 120 µL of ice cold methanol containing 1 µg/mL 1,2-distearoyl-*rac*-glycerol as the internal standard. Plates were shaken for 2 minutes and spun down to remove protein precipitation. After the spin, samples were transferred to LC/MS compatible PCR plates. For LC/MS analysis, a ThermoFisher Surveyor pump, utilizing a Waters SYMMETRY® C8, 50 x 2.1 mm column, was used for the chromatography of enzyme products. The buffer system consists of 0.1% formic acid in water with a mobile phase consisting 0.1% formic acid in methanol. The shallow gradient is 90-100% mobile phase in 0.2 min with a total run time of 2.3 min. The first 0.5 minutes of each injection was diverted to waste to eliminate the presence of

phosphate buffer in the enzymatic reaction. The column was run at 0.6 mL/min and a temperature of 65 °C. Mass spectrometry analysis of the samples was performed on a ThermoFisher Quantum Triple quad utilizing APCI (+) as the mode of ionization. Data was acquired in Single Ion Monitoring (SIM) mode analyzing Diolein = *m/z* 603.6 (PRODUCT) and 1,2- distearoyl-*rac*-glycerol (IS) = *m/z* 607.6. The ratio of Diolein to internal standard (Peak Area Ratio) is utilized to calculate IC_{50} values.

The exemplified Examples disclosed below were tested in the MGAT2 *in vitro* assays described above and were found having MGAT2 inhibitory activity. Table 1 below lists human MGAT2 IC_{50} values measured for the following examples. "NT" denotes "Not tested".

Table 1

Example No.	h-MGAT LCMS IC_{50} (nM)
1	2.5
2	41
3	370
4	0.9
5	7.8
6	2.2
7	9
8	1.5
9	32
10	> 2 μM < 10 μM
11	873
12	363
13	19.4
14	72.1
15	14.5
16	34
17	16.6
18	24.5

Example No.	h-MGAT LCMS IC_{50} (nM)
19	31.8
20	74.7
21	135
22	1.2
23	2.1
24	22.9
25	102
26	43.7
27	185
28	17.6
29	52.1
30	2.7
31	61.9
32	12.6
33	950
34	86.9
35	11.5
36	79.2
37	12.5
38	34.3
39	16.6
40	6.7
41	73.6
42	3.0
43	20.2
44	15.2
45	3.5
46	11.4
47	2.7
48	8.8

Example No.	h-MGAT LCMS IC_{50} (nM)
49	4.5
50	9.4
51	97.4
52	3.2
53	44.0
54	1.1
55	7.8
56	0.2
57	1.4
58	2.2
59	1.4
60	137
61	120
62	2.1
63	0.7
64	1.1
65	8.8
66	0.5
67	97.6
68	30.2
69	148
70	32.3
71	31.5
72	10.3
73	135
74	15
75	1.5
76	4.2
77	522

The compounds of the present invention possess activity as inhibitors of MGAT2, and, therefore, may be used in the treatment of diseases associated with MGAT2 activity. Via modulation of MGAT2, the compounds of the present invention may preferably be employed to modulate, either enhance or decrease the production/secretion of insulin and/or gut hormones, such as GLP1, GIP, CCK, PYY, PP, Amylin.

Accordingly, the compounds of the present invention can be administered to mammals, preferably humans, for the treatment of a variety of conditions and disorders, including, but not limited to, treating, preventing, or slowing the progression of diabetes and related conditions, microvascular complications associated with diabetes, macrovascular complications associated with diabetes, cardiovascular diseases, Metabolic Syndrome and its component conditions, inflammatory diseases and other maladies. Consequently, it is believed that the compounds of the present invention may be used in preventing, inhibiting, or treating diabetes, hyperglycemia, impaired glucose tolerance, gestational diabetes, insulin resistance, hyperinsulinemia, retinopathy, neuropathy, nephropathy, wound healing, atherosclerosis and its sequelae (acute coronary syndrome, myocardial infarction, angina pectoris, peripheral vascular disease, intermittent claudication, myocardial ischemia, stroke, heart failure), Metabolic Syndrome, hypertension, obesity, dyslipidemia, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, low HDL, high LDL, lipid disorders, PCOS, and glaucoma.

Metabolic Syndrome or "Syndrome X" is described in Ford et al., *J. Am. Med. Assoc.*, 287:356-359 (2002) and Arbeeny et al., *Curr. Med. Chem. - Imm., Endoc. & Metab. Agents*, 1:1-24 (2001).

V. PHARMACEUTICAL COMPOSITIONS, FORMULATIONS AND COMBINATIONS

The compounds of this invention can be administered for any of the uses described herein by any suitable means, for example, orally, such as tablets, capsules (each of which includes sustained release or timed release formulations), pills, powders, granules, elixirs, tinctures, suspensions (including nanosuspensions, microsuspensions, spray-dried dispersions), syrups, and emulsions; sublingually; buccally; parenterally, such as by subcutaneous, intravenous, intramuscular, or intrasternal injection, or infusion techniques (*e.g.*, as sterile injectable aqueous or non-aqueous solutions or suspensions);

nasally, including administration to the nasal membranes, such as by inhalation spray; topically, such as in the form of a cream or ointment; or rectally such as in the form of suppositories. They can be administered alone, but generally will be administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice.

The term "pharmaceutical composition" means a composition comprising a compound of the invention in combination with at least one additional pharmaceutically acceptable carrier. A "pharmaceutically acceptable carrier" refers to media generally accepted in the art for the delivery of biologically active agents to animals, in particular, mammals, including, *i.e.*, adjuvant, excipient or vehicle, such as diluents, preserving agents, fillers, flow regulating agents, disintegrating agents, wetting agents, emulsifying agents, suspending agents, sweetening agents, flavoring agents, perfuming agents, antibacterial agents, antifungal agents, lubricating agents and dispensing agents, depending on the nature of the mode of administration and dosage forms.

Pharmaceutically acceptable carriers are formulated according to a number of factors well within the purview of those of ordinary skill in the art. These include, without limitation: the type and nature of the active agent being formulated; the subject to which the agent-containing composition is to be administered; the intended route of administration of the composition; and the therapeutic indication being targeted. Pharmaceutically acceptable carriers include both aqueous and non-aqueous liquid media, as well as a variety of solid and semi-solid dosage forms. Such carriers can include a number of different ingredients and additives in addition to the active agent, such additional ingredients being included in the formulation for a variety of reasons, *e.g.*, stabilization of the active agent, binders, etc., well known to those of ordinary skill in the art. Descriptions of suitable pharmaceutically acceptable carriers, and factors involved in their selection, are found in a variety of readily available sources such as, for example, Allen, L.V., Jr. et al., *Remington: The Science and Practice of Pharmacy* (2 Volumes), 22nd Edition, Pharmaceutical Press (2012).

The dosage regimen for the compounds of the present invention will, of course, vary depending upon known factors, such as the pharmacodynamic characteristics of the particular agent and its mode and route of administration; the species, age, sex, health, medical condition, and weight of the recipient; the nature and extent of the symptoms; the

kind of concurrent treatment; the frequency of treatment; the route of administration, the renal and hepatic function of the patient, and the effect desired.

By way of general guidance, the daily oral dosage of each active ingredient, when used for the indicated effects, will range between about 0.001 to about 5000 mg per day, preferably between about 0.01 to about 1000 mg per day, and most preferably between about 0.1 to about 250 mg per day. Intravenously, the most preferred doses will range from about 0.01 to about 10 mg/kg/minute during a constant rate infusion. Compounds of this invention may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three, or four times daily.

The compounds are typically administered in admixture with suitable pharmaceutical diluents, excipients, or carriers (collectively referred to herein as pharmaceutical carriers) suitably selected with respect to the intended form of administration, *e.g.*, oral tablets, capsules, elixirs, and syrups, and consistent with conventional pharmaceutical practices.

Dosage forms (pharmaceutical compositions) suitable for administration may contain from about 1 milligram to about 2000 milligrams of active ingredient per dosage unit. In these pharmaceutical compositions the active ingredient will ordinarily be present in an amount of about 0.1-95% by weight based on the total weight of the composition.

A typical capsule for oral administration contains at least one of the compounds of the present invention (250 mg), lactose (75 mg), and magnesium stearate (15 mg). The mixture is passed through a 60 mesh sieve and packed into a No. l gelatin capsule.

A typical injectable preparation is produced by aseptically placing at least one of the compounds of the present invention (250 mg) into a vial, aseptically freeze-drying and sealing. For use, the contents of the vial are mixed with 2 mL of physiological saline, to produce an injectable preparation.

The present invention includes within its scope pharmaceutical compositions comprising, as an active ingredient, a therapeutically effective amount of at least one of the compounds of the present invention, alone or in combination with a pharmaceutical carrier. Optionally, compounds of the present invention can be used alone, in combination with other compounds of the invention, or in combination with one or more

other therapeutic agent(s), *e.g.*, an anti-diabetic agent or other pharmaceutically active material.

The compounds of the present invention may be employed in combination with other MGAT2 inhibitors or one or more other suitable therapeutic agents useful in the treatment of the aforementioned disorders including: anti-diabetic agents, anti-hyperglycemic agents, anti-hyperinsulinemic agents, anti-retinopathic agents, anti-neuropathic agents, anti-nephropathic agents, anti-atherosclerotic agents, anti-ischemic agents, anti-hypertensive agents, anti-obesity agents, anti-dyslipidemic agents, anti-dyslipidemic agents, anti-hyperlipidemic agents, anti-hypertriglyceridemic agents, anti-hypercholesterolemic agents, anti-restenotic agents, anti-pancreatic agents, lipid lowering agents, anorectic agents, memory enhancing agents, anti-dementia agents, or cognition promoting agents, appetite suppressants, treatments for heart failure, treatments for peripheral arterial disease and anti-inflammatory agents.

Where desired, the compound of the present invention may be used in combination with one or more other types of anti-diabetic agents and/or one or more other types of therapeutic agents which may be administered orally in the same dosage form, in a separate oral dosage form or by injection. The other type of anti-diabetic agent that may be optionally employed in combination with the MGAT2 inhibitor of the present invention may be one, two, three or more anti-diabetic agents or anti-hyperglycemic agents which may be administered orally in the same dosage form, in a separate oral dosage form, or by injection to produce an additional pharmacological benefit.

The anti-diabetic agents used in the combination with the compound of the present invention include, but are not limited to, insulin secretagogues or insulin sensitizers, other MGAT2 inhibitors, or other anti-diabetic agents. These agents include, but are not limited to, dipeptidyl peptidase IV (DP4) inhibitors (for example, sitagliptin, saxagliptin, alogliptin, vildagliptin and the like), biguanides (for example, metformin, phenformin and the like), sulfonyl ureas (for example, glyburide, glimepiride, glipizide and the like), glucosidase inhibitors (for example, acarbose, miglitol, and the like), PPARγ agonists such as thiazolidinediones (for example, rosiglitazone, pioglitazone, and the like), PPAR α/γ dual agonists (for example, muraglitazar, tesaglitazar, aleglitazar, and the like), glucokinase activators (as described in Fyfe, M.C.T. et al., *Drugs of the Future*, 34(8):641-653 (2009) and incorporated herein by reference), GPR40 receptor modulators,

GPR119 receptor modulators (MBX-2952, PSN821, APD597 and the like), SGLT2 inhibitors (dapagliflozin, canagliflozin, remagliflozin and the like), amylin analogs such as pramlintide, and/or insulin. Reviews of current and emerging therapies for the treatment of diabetes can be found in: Mohler, M.L. et al., *Medicinal Research Reviews*, 29(1):125-195 (2009), and Mizuno, C.S. et al., *Current Medicinal Chemistry*, 15:61-74 (2008).

The compounds of the present invention may also be optionally employed in combination with agents for treating complication of diabetes. These agents include PKC inhibitors and/or AGE inhibitors.

The compounds of the present invention may also be optionally employed in combination with one or more hypophagic agents such as diethylpropion, phendimetrazine, phentermine, orlistat, sibutramine, lorcaserin, pramlintide, topiramate, MCHR1 receptor antagonists, oxyntomodulin, naltrexone, Amylin peptide, NPY Y5 receptor modulators, NPY Y2 receptor modulators, NPY Y4 receptor modulators, cetilistat, 5HT2c receptor modulators, and the like. The compound of structure I may also be employed in combination with an agonist of the glucagon-like peptide-1 receptor (GLP-1 R), such as exenatide, liraglutide, GPR-1(1-36) amide, GLP-1(7-36) amide, GLP-1(7-37) (as disclosed in U.S. Patent No. 5,614,492 to Habener, the disclosure of which is incorporated herein by reference), which may be administered via injection, intranasal, or by transdermal or buccal devices. Reviews of current and emerging therapies for the treatment of obesity can be found in: Melnikova, I. et al., *Nature Reviews Drug Discovery*, 5:369-370 (2006); Jones, D., *Nature Reviews: Drug Discovery*, 8:833-834 (2009); Obici, S., *Endocrinology*, 150(6):2512-2517 (2009); and Elangbam, C.S., *Vet. Pathol.*, 46(1):10-24 (2009).

The compounds of the present invention may also be optionally employed in combination with one or more other types of therapeutic agents, such as DGAT inhibitors, LDL lowering drugs such as statins (inhibitors of HMG CoA reductase) or inhibitors of cholesterol absorption, modulators of PCSK9, drugs increase HDL such as CETP inhibitors.

The above other therapeutic agents, when employed in combination with the compounds of the present invention may be used, for example, in those amounts

indicated in the *Physicians' Desk Reference*, as in the patents set out above, or as otherwise determined by one of ordinary skill in the art.

Particularly when provided as a single dosage unit, the potential exists for a chemical interaction between the combined active ingredients. For this reason, when the compound of the present invention and a second therapeutic agent are combined in a single dosage unit they are formulated such that although the active ingredients are combined in a single dosage unit, the physical contact between the active ingredients is minimized (that is, reduced). For example, one active ingredient may be enteric coated. By enteric coating one of the active ingredients, it is possible not only to minimize the contact between the combined active ingredients, but also, it is possible to control the release of one of these components in the gastrointestinal tract such that one of these components is not released in the stomach but rather is released in the intestines. One of the active ingredients may also be coated with a material that affects a sustained-release throughout the gastrointestinal tract and also serves to minimize physical contact between the combined active ingredients. Furthermore, the sustained-released component can be additionally enteric coated such that the release of this component occurs only in the intestine. Still another approach would involve the formulation of a combination product in which the one component is coated with a sustained and/or enteric release polymer, and the other component is also coated with a polymer such as a low viscosity grade of hydroxypropyl methylcellulose (HPMC) or other appropriate materials as known in the art, in order to further separate the active components. The polymer coating serves to form an additional barrier to interaction with the other component.

These as well as other ways of minimizing contact between the components of combination products of the present invention, whether administered in a single dosage form or administered in separate forms but at the same time by the same manner, will be readily apparent to those skilled in the art, once armed with the present disclosure.

The compounds of the present invention can be administered alone or in combination with one or more additional therapeutic agents. By "administered in combination" or "combination therapy" it is meant that the compound of the present invention and one or more additional therapeutic agents are administered concurrently to the mammal being treated. When administered in combination, each component may be administered at the same time or sequentially in any order at different points in time.

Thus, each component may be administered separately but sufficiently closely in time so as to provide the desired therapeutic effect.

The compounds of the present invention are also useful as standard or reference compounds, for example as a quality standard or control, in tests or assays involving the MGAT2 enzyme. Such compounds may be provided in a commercial kit, for example, for use in pharmaceutical research involving MGAT2 or anti-diabetic activity. For example, a compound of the present invention could be used as a reference in an assay to compare its known activity to a compound with an unknown activity. This would ensure the experimentor that the assay was being performed properly and provide a basis for comparison, especially if the test compound was a derivative of the reference compound. When developing new assays or protocols, compounds according to the present invention could be used to test their effectiveness.

The compounds of the present invention may also be used in diagnostic assays involving MGAT2.

The present invention also encompasses an article of manufacture. As used herein, article of manufacture is intended to include, but not be limited to, kits and packages. The article of manufacture of the present invention, comprises: (a) a first container; (b) a pharmaceutical composition located within the first container, wherein the composition, comprises: a first therapeutic agent, comprising a compound of the present invention or a pharmaceutically acceptable salt form thereof; and, (c) a package insert stating that the pharmaceutical composition can be used for the treatment and/or prophylaxis of multiple diseases or disorders associated with MGAT2 (as defined previously). In another embodiment, the package insert states that the pharmaceutical composition can be used in combination (as defined previously) with a second therapeutic agent for the treatment and/or prophylaxis of multiple diseases or disorders associated with MGAT2. The article of manufacture can further comprise: (d) a second container, wherein components (a) and (b) are located within the second container and component (c) is located within or outside of the second container. Located within the first and second containers means that the respective container holds the item within its boundaries.

The first container is a receptacle used to hold a pharmaceutical composition. This container can be for manufacturing, storing, shipping, and/or individual/bulk selling.

First container is intended to cover a bottle, jar, vial, flask, syringe, tube (*e.g.*, for a cream preparation), or any other container used to manufacture, hold, store, or distribute a pharmaceutical product.

The second container is one used to hold the first container and, optionally, the package insert. Examples of the second container include, but are not limited to, boxes (*e.g.*, cardboard or plastic), crates, cartons, bags (*e.g.*, paper or plastic bags), pouches, and sacks. The package insert can be physically attached to the outside of the first container via tape, glue, staple, or another method of attachment, or it can rest inside the second container without any physical means of attachment to the first container. Alternatively, the package insert is located on the outside of the second container. When located on the outside of the second container, it is preferable that the package insert is physically attached via tape, glue, staple, or another method of attachment. Alternatively, it can be adjacent to or touching the outside of the second container without being physically attached.

The package insert is a label, tag, marker, etc. that recites information relating to the pharmaceutical composition located within the first container. The information recited will usually be determined by the regulatory agency governing the area in which the article of manufacture is to be sold (*e.g.*, the United States Food and Drug Administration). Preferably, the package insert specifically recites the indications for which the pharmaceutical composition has been approved. The package insert may be made of any material on which a person can read information contained therein or thereon. Preferably, the package insert is a printable material (*e.g.*, paper, plastic, cardboard, foil, adhesive-backed paper or plastic, etc.) on which the desired information has been formed (*e.g.*, printed or applied).

Other features of the invention will become apparent in the course of the following descriptions of exemplary embodiments that are given for illustration of the invention and are not intended to be limiting thereof.

VI. EXAMPLES

The following Examples are offered as illustrative, as a partial scope and particular embodiments of the invention and are not meant to be limiting of the scope of the invention. Abbreviations and chemical symbols have their usual and customary

meanings unless otherwise indicated. Unless otherwise indicated, the compounds described herein have been prepared, isolated and characterized using the schemes and other methods disclosed herein or may be prepared using the same.

HPLC/MS, Preparatory/Analytical HPLC, and Chiral Separation Methods Employed in Characterization or Purification of Examples

Analytical HPLC/MS (unless otherwise noted) was performed on Shimadzu SCL-10A liquid chromatographs and Waters MICROMASS® ZQ Mass Spectrometers (Desolvation Gas: Nitrogen; Desolvation Temp. 250 °C; Ion Source Temp: 120 °C; Positive Electrospray conditions) using the following methods:

Linear Gradient of 0% to100% Solvent B over 2 min, with 1 minute hold at 100% B, or

Linear Gradient of 0% to100% Solvent B over 4 min, with 1 minute hold at 100% B;

UV visualization at 220 nm;

Column: PHENOMENEX® Luna C18 (2) 30mm × 4.6 mm; 5μ particle (heated to Temp. 40 °C);

Flow rate: 1.0 mL/min (2 min gradient) or 0.8 ml/min (4 min gradient);

Solvent A: 10% ACN, 90% water, 0.1% TFA; or, 10% MeOH, 90% water, 0.1% TFA and

Solvent B: 90% ACN, 10% water, 0.1% TFA; or, 90% MeOH, 10% water, 0.1% TFA.

Preparatory HPLC (unless otherwise noted) was performed on a Shimadzu SCL-10A liquid chromatograph with a linear gradient of 20-100% Solvent B over 10 to 30 min, with either a 2 to 5 min hold at 100% Solvent B as determined by on skilled in the art;

UV visualization at 220 nm;

Column: PHENOMENEX® Luna Axia 5μ C18 30 × 100 mm;

Flow rate: 20 mL/min;

Solvent A: 10% ACN, 90% water, 0.1% TFA; or 10% MeOH, 90% water, 0.1% TFA; and

Solvent B: 90% ACN, 10% water, 0.1% TFA; or 90% MeOH, 10% water, 0.1% TFA.

Preparatory chiral SFC chromatography (unless otherwise noted) was performed on a Berger Multigram II SFC chromatograph using one of the following methods:

Preparative Chiral SFC Method A:

Column: CHIRALCEL® OD-H, 30 × 250mm ID, 5 μ

Flow rate: 90 mL/min, 100 bar BP, 40 °C

Mobile Phase: 15% methanol /85% CO_2

Detector Wavelength: 254 nm

Injection Vol and Sample Solution: 0.5 mL of 4.65 g in 35 mL methanol (133 mg/mL)

Preparative Chiral SFC Method B:

Instrument: Berger SFC MGII (HPW-2501)

Column: CHIRALPAK® IA 25 × 3 cm ID, 5 μm

Flow rate: 85.0 mL/min

Mobile Phase: 85/15/0.1,CO_2/IPA/DEA, 150 bar

Detector Wavelength: 225 nm (Lamda max)

Sample Prep and Inj. Volume: 300 μL of ~13 mg / 0.5 mL IPA (~26 mg/mL)

Preparative Chiral SFC Method C:

Column: CHIRALPAK® IA 25 × 3 cm ID, 5 μm

Flow rate: 90 mL/min

Mobile Phase: 85/15/0.1,CO_2/MeOH/DEA, 150 bar

Detector Wavelength: 270 nm (Lambda max)

Sample Prep and Inj. Volume: 300 μL of ~90 mg / 2 mL MeOH (~45 mg/mL)

Preparative Chiral SFC Method D:

Flow rate: 40 mL/min, 100 Bar, 35 °C

Mobile Phase: 20% methanol/80% CO_2

Detector Wavelength: 224 nm (Lambda max)
Injection Volume: 300 μL
Sample Preparation: 10 mg dissolved in 0.5 mL MeCN (20 mg/mL);
17 mg dissolved in 0.5 mL MeCN (34 mg/mL)

Analytical chiral SFC chromatography (unless otherwise noted) was performed on an Aurora Analytical SFC or Berger Analytical SFC using one of the following methods:

Analytical Chiral SFC Method A:
Column: CHIRALCEL® OD-H, 4.6 × 250mm ID, 5 μm
Flow rate: 3.0 mL/min, 100 bar BP, 35 °C.
Mobile Phase: 15% methanol/85% CO_2
Detector Wavelength: 220 nm
Sample Solution: 1 mg/mL in methanol (concentrated/reconstituted)
Injection Volume: 10 μL

Analytical Chiral SFC Method B:
Column: CHIRALPAK® IA 250 × 4.6 mm ID, 5μm
Flow rate: 2.0 mL/min
Mobile Phase: 85/15/0.1, CO_2/IPA/DEA, 150 bar
Detector Wavelength: 225 nm (Lamda max)
Injection Volume: 10 μL

Analytical Chiral SFC Method C:
Column: CHIRALPAK® IA 250 × 4.6 mm ID, 5 μm
Flow rate: 3.0 mL/min
Mobile Phase: 65/35/0.1, CO_2/MeOH/DEA, 150 bar
Detector Wavelength: 270 nm (Lambda max)
Injection Volume: 10 μL

Analytical Chiral SFC Method D:

Column: CHIRALCEL® OD, 250 × 4.6 mm ID, 10 μm

Flow rate: 2.0 mL/min, 100 bar, 35 °C

Mobile Phase: 20% Methanol/80% CO_2

Detector Wavelength: 223 nm

Injection Volume: 10 μL

NMR Employed in Characterization of Examples

^{1}H NMR spectra (unless otherwise noted) were obtained with JEOL® or Bruker FOURIER® transform spectrometers operating at 400 MHz or 500 MHz. ^{1}H-nOe experiments were performed in some cases for regiochemistry elucidation with a 400 MHz Bruker FOURIER® Transform spectrometer.

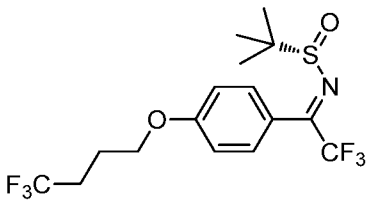
Spectral data are reported as chemical shift (multiplicity, number of hydrogens, coupling constants in Hz) and are reported in ppm (δ units) relative to either an internal standard (tetramethyl silane = 0 ppm) for ^{1}H NMR spectra, or are referenced to the residual solvent peak (2.49 ppm for CD_3SOCD_2H, 3.30 ppm for CD_2HOD, 1.94 for CHD_2CN, 7.26 ppm for $CHCl_3$, 5.32 ppm for $CDHCl_2$).

Microwave instrumentation employed in heating reactions.

BIOTAGE® Initiator 2.5, maximum power 400 W, reaction volume range 0.2 - 10 mL. Reactions are run in sealed pressure vessels specially manufactured for this instrument.

Intermediate 1

(*S*,*E*)-2-Methyl-*N*-(2,2,2-trifluoro-1-(4-(4,4,4-trifluorobutoxy) phenyl)ethylidene)propane-2-sulfinamide



Intermediate 1A. 4-(4,4,4-Trifluorobutoxy)benzaldehyde: To a solution of 4-hydroxybenzaldehyde (20 g, 164 mmol) and 4,4,4-trifluorobutan-1-ol (25 g, 195 mmol) in anhydrous CH_2Cl_2 (500 mL) at 0 °C under argon was added a solution of PPh_3 (51.5 g, 196 mmol) in CH_2Cl_2 (200 mL) over 15 min, and then DIAD (36.4 g, 180 mmol) in

anhydrous CH_2Cl_2 (150 mL) was added dropwise. The mixture was stirred at 0 °C for 0.5 h. The reaction was warmed to rt and stirred for another 3 h. The solvent was removed *in vacuo* and the residue was triturated with CH_2Cl_2 three times to remove insoluble solids. The combined CH_2Cl_2 washings were concentrated and the residue was purified by silica gel chromatography (330 g silica gel, eluted with EtOAc in hexanes) to provide Intermediate 1A (27 g, 71%) as a light brown oil. LCMS Anal. Calc'd for $C_{11}H_{11}F_3O_2$ 232.20, found [M+H] 233.0.

Intermediate 1B. 2,2,2-Trifluoro-1-(4-(4,4,4-trifluorobutoxy)phenyl)ethanol: To the solution of Intermediate 1A (26.7 g, 114 mmol) and trimethyl(trifluoromethyl)silane (16.9 g, 119 mmol) in anhydrous DME (112 mL) was added CsF (500 mg, 3.29 mmol). The reaction was stirred at rt for 16 h. To the mixture was added 4 N aq. HCl (114 mL) and the reaction was stirred at rt for 2.5 h. The reaction was diluted with EtOAc (300 mL) and washed with water, sat'd aq. $NaHCO_3$, sat'd aq. NaCl, dried over anhydrous $MgSO_4$, filtered and concentrated to provide Intermediate 1B (42.5 g, 122%) as an oil. The crude product was used without further purification. LCMS Anal. Calc'd for $C_{12}H_{12}F_6O_2$ 302.21, found [M-H] 301.2.

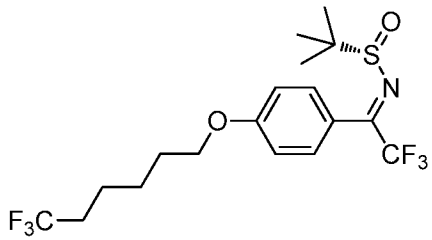
Intermediate 1C. 2,2,2-Trifluoro-1-(4-(4,4,4-trifluorobutoxy)phenyl)ethanone: To a solution of Intermediate 1B (115 mmol) in anhydrous CH_2Cl_2 (320 mL) was added Dess-Martin periodinane (50.2 g, 118 mmol) portionwise at 0 °C. The reaction was stirred at 0 °C for 0.5 h then at rt for 3 h. To the reaction was added 100 mL of sat'd aq. Na_2CO_3 and 250 mL of EtOAc. The reaction was stirred for another 2 h. The insoluble material was removed by filtration. The layers were separated. The organic layer was washed with sat'd aq. Na_2CO_3. Additional solids that formed upon standing overnight were removed. The organic solution was washed with sat'd aq. NaCl, dried over anhydrous $MgSO_4$, filtered and concentrated to provide a dark brown liquid, which was purified by silica gel chromatography (220 g silica gel, elute with EtOAc in hexanes to provide Intermediate 1C (26 g, 76%) as a colorless oil.

Intermediate 1: To a solution of Intermediate 1C (10 g, 33.3 mmol) and (*S*)-2-methylpropane-2-sulfinamide (8.07 g, 66.6 mmol) in THF (125 mL) was added a solution of tetraisopropoxytitanium (37.9 g, 133 mmol) in THF (45 mL) and the reaction mixture was stirred at 65 °C for 4 h. The reaction solvent was removed under vacuum, the residue was dissolved in EtOAc (200 mL) and the solution was washed with sat. aq. $NaHCO_3$

(150 mL). A large amount of solids formed that were filtered through CELITE® and washed with EtOAc (2 x 140 mL). The combined EtOAc solutions were washed with sat. aq. $NaHCO_3$ (100 mL), dried over $MgSO_4$ and concentrated *in vacuo* to a yellow oil that purified by chromatography to give the desired product as a yellow oil (9.64 g, 71.7%).

Intermediate 2

(*S*,*E*)-2-Methyl-*N*-(2,2,2-trifluoro-1-(4-(6,6,6-trifluorohexyloxy) phenyl)ethylidene)propane-2-sulfinamide



Intermediate 2A. 4-(6,6,6-Trifluorohexyloxy)benzaldehyde: To a suspension of 4-hydroxybenzaldehyde (488 mg, 4 mmol) and 6-bromo-1,1,1-trifluorohexane (657 mg, 3 mmol) in MeCN (10 mL) was added K_2CO_3 (829 mg, 6.00 mmol). The resulting mixture was refluxed overnight. Insoluble material was filtered off and rinsed with MeCN. The combined filtrate was concentrated to afford a white solid. This white solid was partitioned between EtOAc and 1 N NaOH solution. The organic layer was separated, washed with sat'd NH_4Cl, dried over $MgSO_4$, filtered and concentrated to afford Intermediate 2A as a clear liquid. LCMS Anal. Calc'd for $C_{13}H_{15}F_3O_2$ 260.10, found [M+H] 261.0.

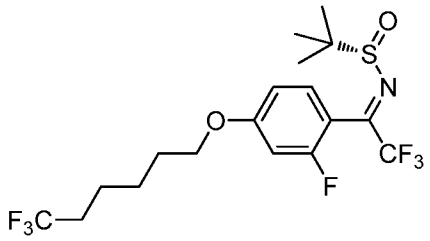
Intermediate 2B. 2,2,2-Trifluoro-1-(4-(6,6,6-trifluorohexyloxy)phenyl)ethanone: Intermediate 2B was prepared using a procedure analogous to Intermediate 1C except that Intermediate 1A was replaced with Intermediate 2A. ^1H NMR (500 MHz, $CDCl_3$) δ 8.06 - 8.02 (m, 2 H), 6.99 - 6.97 (m, 1 H), 4.08 (t, J = 6.2 Hz, 2 H), 2.19 - 2.06 (m, 2 H), 1.92 - 1.82 (m, 2 H), 1.71 - 1.55 (m, 4 H).

Intermediate 2: To a solution of Intermediate 2B (717 mg, 2.184 mmol) and (*S*)-2-methylpropane-2-sulfinamide (529 mg, 4.37 mmol) in THF (10 mL) was added tetraethoxytitanium (1993 mg, 8.74 mmol) in THF (20 mL). The resulting mixture was reflux for 5 h. TLC (20% EtOAc in hexane) indicated the starting ketone was completely consumed. The solvent was evaporated to afford a yellow oil. This yellow oil was

dissolved in EtOAc and then washed with saturated $NaHCO_3$ (25 mL) and a large amount of white precipitation formed which was removed by filtering through a bed of CELITE®. The white precipitate was rinsed with EtOAc. The combined EtOAc solution was washed again with saturated $NaHCO_3$, dried ($MgSO_4$) and concentrated. The crude product was purified by silica gel chromatography (40 g silica gel, eluted with EtOAc in hexanes) to afford Intermediate 2 (620 mg, 66%).

Intermediate 3

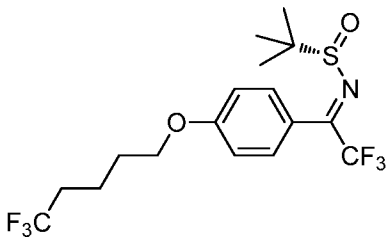
(*S*,*E*)-2-Methyl-*N*-(2,2,2-trifluoro-1-(2-fluoro-4-((6,6,6-trifluorohexyl)oxy) phenyl)ethylidene)propane-2-sulfinamide



Intermediate 3 was prepared using a procedure analogous to Intermediate 1 except that 4-hydroxybenzaldehyde was replaced with 2-fluoro-4-hydroxybenzaldehyde. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 - 7.25 (m, 1H), 6.80 - 6.62 (m, 2H), 4.05 - 3.93 (m, 2H), 2.22 - 2.02 (m, 2H), 1.91 - 1.76 (m, 2H), 1.72 - 1.60 (m, 2H), 1.56 (s, 2H), 1.34 (s, 9H).

Intermediate 4

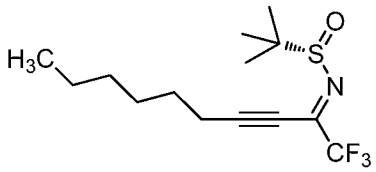
(*S*,*E*)-2-Methyl-*N*-(2,2,2-trifluoro-1-(4-((5,5,5-trifluoropentyl)oxy phenyl)ethylidene)propane-2-sulfinamide



Intermediate 4 was prepared using a procedure analogous to Intermediate 2 except that 6-bromo-1,1,1-trifluorohexane was replaced 5-bromo-1,1,1-trifluoropentane in step 2A. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 (d, J = 8.5 Hz, 2H), 6.95 (d, J = 9.1 Hz, 2H), 4.04 (t, J = 5.9 Hz, 2H), 2.31 - 2.10 (m, 2H), 1.94 - 1.85 (m, 2H), 1.84 - 1.70 (m, 2H).

Intermediate 5

(*S*,*E*)-2-Methyl-*N*-(1,1,1-trifluorodec-3-yn-2-ylidene)propane-2-sulfinamide

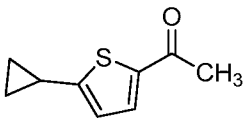


Intermediate 5A 1,1,1-trifluorodec-3-yn-2-one: 2.5 M hexanes solution of N-butyllithium (13.18 ml, 32.9 mmol) was added dropwise to a stirred solution of oct-1-yne (3.3 g, 29.9 mmol) in THF (60 mL) at -50 to -60 °C. The mixture was allowed to come to -5 °C, cooled back to -60 °C followed by the addition of a solution ethyl 2,2,2-trifluoroacetate (4.68 g, 32.9 mmol) in THF (5 mL) at -60 to -55 °C. The mixture was allowed to RT and stirred at RT for 45 min. The reaction mixture was quenched with saturated sodium bicarbonate solution and extracted with DCM. The organic phase was dried ($MgSO_4$) and concentrated at RT *in vacuo* to afford crude yellow oil 5A (6.1 g, 29.6 mmol, 99% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.50 (t, *J* = 7.2 Hz, 2H), 1.70 - 1.62 (m, 2H), 1.48 - 1.39 (m, 2H), 1.36 - 1.26 (m, 4H), 0.90 (t, *J* = 6.9 Hz, 3H).

Intermediate 5 was prepared using a procedure analogous to Intermediate 1 except that Intermediate 1C was replaced with Intermediate 5A. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.55 (t, *J* = 7.2 Hz, 2H), 1.74 - 1.60 (m, 2H), 1.52 - 1.24 (m, 15H), 0.93 (t, *J* = 6.8 Hz, 3H).

Intermediate 6

1-(5-Cyclopropylthiophen-2-yl)ethanone

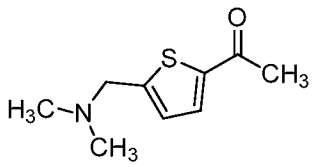


A reaction vial was charged with palladium acetate (6.99 mg, 0.031 mmol), butyl di-1-adamantylphosphine (0.017 g, 0.047 mmol), potassium cyclopropyl trifluoroborate (0.233 g, 1.572 mmol) and Cs_2CO_3 (1.521 g, 4.67 mmol). The vessel was sealed, purged, and back-filled with argon. A solution of 1-(5-chlorothiophen-2-yl)ethanone (0.250 g, 1.556 mmol) in toluene (5.7mL) and water (0.57 mL) was added and the reaction mixture stirred at 100 °C for 16.5 h. The reaction mixture was cooled to rt, diluted with water and extracted with DCM (3x). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The crude product was purified by

prep HPLC, afforded Intermediate 6 (39.2 mg, 0.236 mmol, 15.15% yield) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 (d, *J* = 3.9 Hz, 1H), 6.79 (d, *J* = 3.9 Hz, 1H), 2.52 (s, 3H), 2.19 - 2.09 (m, 1H), 1.18 - 1.08 (m, 2H), 0.88 - 0.74 (m, 2H). LCMS Anal. Calc'd for $C_9H_{10}OS$ 166.0, found [M+H] 166.9.

Intermediate 7

1-(5-((Dimethylamino)methyl)thiophen-2-yl)ethanone



Intermediate 7A. 1-(5-(Hydroxymethyl)thiophen-2-yl)ethanone: To a solution of 5-acetylthiophene-2-carbaldehyde (0.800 g, 5.19 mmol) in THF (10.36 mL) was added sodium triacetoxyborohydride (1.210 g, 5.71 mmol) and the reaction mixture was stirred at 65 °C under argon for 6 h. The reaction mixture was cooled to rt and quenched with sat. NH_4Cl. The aqueous layer was separated and washed with DCM (3x). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The crude product was purified by chromatography to yield Intermediate 7A (0.421 g, 2.70 mmol, 51.9% yield). LCMS Anal. Calc'd for $C_7H_8O_2S$ 156.0, found [M+H] 157.0. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (d, *J* = 3.9 Hz, 1H), 7.03 (d, *J* = 3.6 Hz, 1H), 4.87 (d, *J* = 5.8 Hz, 2H), 2.55 (s, 3H), 2.03 (t, *J* = 6.1 Hz, 1H).

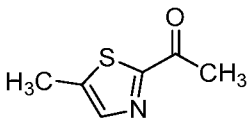
Intermediate 7B. 1-(5-(Chloromethyl)thiophen-2-yl)ethanone: Methanesulfonyl chloride (0.419 mL, 5.38 mmol) was added dropwise to a solution of Intermediate 7A (420 mg, 2.69 mmol) and triethylamine (0.750 mL, 5.38 mmol) in DCM (20.1 mL) and the reaction mixture was stirred at rt under argon for 2 d. The solvent was removed *in vacuo* and the crude product was purified by chromatography to yield Intermediate 7B (488 mg, 2.79 mmol, 104% yield). LCMS Anal. Calc'd for C_7H_7ClOS 174.0, found [M+H] 175.1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (d, *J* = 3.9 Hz, 1H), 7.15 - 7.07 (m, 1H), 4.77 (d, *J* = 0.6 Hz, 2H), 2.55 (s, 3H).

Intermediate 7: Dimethylamine (40 wt% in water) (0.181 mL, 1.431 mmol) was added to a solution of Intermediate 7B (50.00 mg, 0.286 mmol) in ether (0.477 mL) and the reaction mixture stirred at rt for 18 h. The reaction mixture was diluted with ether. The organic layer separated and extracted with 10% aq. citric acid. The aqueous layer

was separated and treated with 1N NaOH (to pH ~10-11). The mixture was extracted with ether (3 x 10 mL) and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. This material was purified by prep. HPLC to yield Intermediate 7 (35.3 mg, 0.119 mmol, 41.5% yield) as a yellow oil. LCMS Anal. Calc'd for $C_9H_{13}NOS$ 183.1, found [M+H] 184.1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (d, J = 3.9 Hz, 1H), 7.34 (d, J = 3.9 Hz, 1H), 4.44 (s, 2H), 2.86 (s, 6H), 2.59 (s, 3H).

Intermediate 8

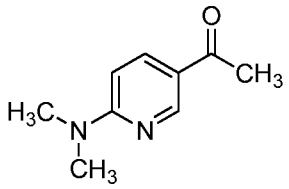
1-(5-Methylthiazol-2-yl)ethanone



Intermediate 8: To a solution of 5-methylthiazole (0.179 mL, 2.017 mmol) in ether (13.63 mL) was added nBuLi (1.387 mL, 2.219 mmol, 1.6 M in hexanes) dropwise at -78 °C and the reaction mixture was stirred at this temperature for 15 min. A solution of N-methoxy-N-methylacetamide (229 mg, 2.219 mmol) in THF (4.0 mL) was added dropwise and the reaction mixture warmed to rt and stirred for 1 h. The reaction mixture was quenched with sat. NH_4Cl. The organic layer was separated and washed with water, brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The crude product was purified by chromatography to yield Intermediate 8 (123 mg, 0.871 mmol, 43.2% yield) as a pale yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (s, 1H), 2.68 (s, 3H), 2.57 (s, 3H). LCMS Anal. Calc'd for C_6H_7NOS 141.0, found [M+H] 141.9.

Intermediate 9

1-(6-(Dimethylamino)pyridin-3-yl)ethanone

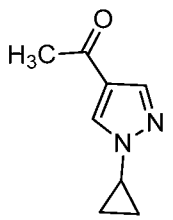


Intermediate 9: A mixture of 1-(6-chloropyridin-3-yl)ethanone (0.100 g, 0.643 mmol) and dimethylamine (40% in water) (0.407 mL, 3.21 mmol) in EtOH (1.071 mL) was stirred at 80 °C under argon for 2 h. The reaction mixture was cooled to rt. The EtOH was removed *in vacuo* and the residue was dissolved in ether and washed with 10%

citric acid. The aqueous layer was separated and adjusted to pH = ~10-11 using 1N NaOH and then extracted with ether (3x). The combined ether layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, concentrated and air dried under vacuum to yield Intermediate 9 (98.1 mg, 0.597 mmol, 93% yield) as a crude light yellow solid which was used in the next step without further purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.78 (d, *J* = 1.9 Hz, 1H), 8.03 (dd, *J* = 8.9, 2.3 Hz, 1H), 6.51 (d, *J* = 9.1 Hz, 1H), 3.19 (s, 6H), 2.51 (s, 3H). LCMS Anal. Calc'd for $C_9H_{12}N_2O$ 164.1, found [M+H] 165.1.

Intermediate 10

1-(1-Cyclopropyl-1*H*-pyrazol-4-yl)ethanone

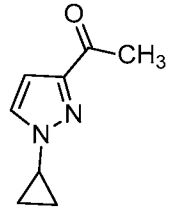


Intermediate 10A. 1-Cyclopropyl-4-iodo-1H-pyrazole: To a mixture of 4-iodo-1*H*-pyrazole (645 mg, 3.33 mmol), cyclopropylboronic acid (571 mg, 6.65 mmol), copper(II) acetate (604 mg, 3.33 mmol) and DMAP (1219 mg, 9.98 mmol) in dioxane (10 mL) was added pyridine (0.323 mL, 3.99 mmol). The resulting mixture was heated to 100 °C for 16h under air. The reaction mixture was concentrated *in vacuo* and diluted with EtOAc. The organic layer was washed with 1M HCl. The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by chromatography to give Intermediate 10A (660 mg, 2.82 mmol, 85% yield) as a light yellow liquid. LCMS Anal. Calc'd for $C_6H_7N_2$ 234.04, found [M+H] 234.9.

Intermediate 10: To a stirred solution of Intermediate 10A (460 mg, 1.965 mmol) in THF (5 mL) at 0 °C was added iPrMgCl (1.081 mL, 2.162 mmol) quickly. After 30 min, additional 0.15 eq of iPrMgCl was added and after 30 min, the mixture was cooled to -78 °C. N-Methoxy-N-methylacetamide (304 mg, 2.95 mmol) was added quickly and the reaction was warmed to RT for 3h. The reaction mixture was concentrated *in vacuo* and diluted with EtOAc. The organic layer was washed with H_2O. The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified to give Intermediate 10 (250mg, 1.665 mmol, 85% yield) as a clear liquid. LCMS Anal. Calc'd for $C_8H_{10}N_2O$ 150.8, found [M+H] 151.0.

Intermediate 11

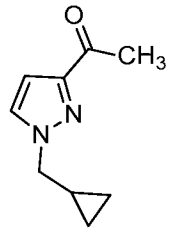
1-(1-Cyclopropyl-1*H*-pyrazol-3-yl)ethanone



Intermediate 11: To a mixture of 1-(1*H*-pyrazol-3-yl)ethanone (160 mg, 1.453 mmol), cyclopropylboronic acid (250 mg, 2.91 mmol), copper(II) acetate (264 mg, 1.453 mmol) and DMAP (533 mg, 4.36 mmol) in dioxane (10 mL) was added pyridine (0.141 mL, 1.744 mmol). The resulting mixture was heated to 100 °C for 16h under air. The reaction mixture was concentrated *in vacuo* and diluted with EtOAc. The organic layer was washed with 1M HCl. The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by chromatography to give Intermediate 11 (80 mg, 0.533 mmol, 36.7% yield) as a colorless liquid. LCMS Anal. Calc'd for $C_8H_{10}N_2O$ 150.8, found [M+H] 151.1.

Intermediate 12

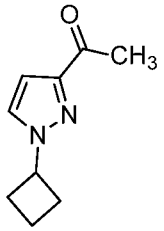
1-(1-(Cyclopropylmethyl)-1*H*-pyrazol-3-yl)ethanone



Intermediate 12: To a stirred solution of 1-(1*H*-pyrazol-3-yl)ethanone (300 mg, 2.72 mmol) and (bromomethyl)cyclopropane (405 mg, 3.00 mmol) in DMF (5 mL) was added K_2CO_3 (565 mg, 4.09 mmol). The reaction was heated to 65 °C for 16h. The reaction mixture was diluted with EtOAc and water. The organic layer was washed with H_2O. The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by chromatography to give Intermediate 12 (338 mg, 2.058 mmol, 76% yield) as a clear liquid. LCMS Anal. Calc'd for $C_9H_{12}N_2O$ 164.09, found [M+H] 165.1.

Intermediate 13

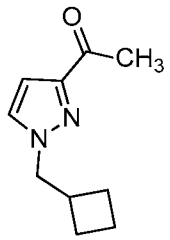
1-(1-Cyclobutyl-1*H*-pyrazol-3-yl)ethanone



Intermediate 13 was prepared using a procedure analogous to Intermediate 12 except that (bromomethyl)cyclopropane was replaced by bromocyclobutane. LCMS Anal. Calc'd for $C_9H_{12}N_2O$ 164.09, found [M+H] 165.1.

Intermediate 14

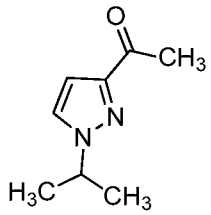
1-(1-(Cyclobutylmethyl)-1*H*-pyrazol-3-yl)ethanone



Intermediate 14 was prepared using a procedure analogous to Intermediate 12 except that (bromomethyl)cyclopropane was replaced by (bromomethyl)cyclobutane. LCMS Anal. Calc'd for $C_{10}H_{14}N_2O$ 178.11, found [M+H] 179.1.

Intermediate 15

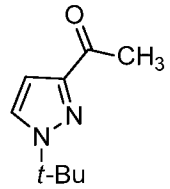
1-(1-Isopropyl-1*H*-pyrazol-3-yl)ethanone



Intermediate 15 was prepared using a procedure analogous to Intermediate 12 except that (bromomethyl)cyclopropane was replaced by 2-iodopropane. LCMS Anal. Calc'd for $C_{10}H_{14}N_2O$ 152.10, found [M+H] 153.1.

Intermediate 16

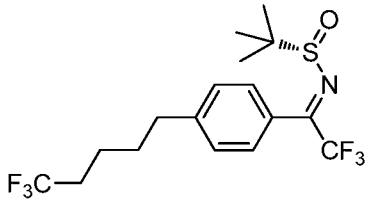
1-(1-(*tert*-Butyl)-1*H*-pyrazol-3-yl)ethanone



Intermediate 16: To a stirred solution of 1-(1*H*-pyrazol-3-yl)ethanone (100 mg, 0.908 mmol) and 2-methylpropan-2-ol (337 mg, 4.54 mmol) was heated to 30 °C. H_2SO_4 (48.4 µl, 0.908 mmol) was added dropwise and the reaction was heated to 100 °C for 4h. The reaction was cooled to RT and diluted with EtOAc. The organic layer was washed with sat. $NaHCO_3$. The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by chromatography to give Intermediate 16 (20 mg, 0.120 mmol, 13.25% yield) as a clear liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (d, *J* = 2.5 Hz, 1H), 6.76 (d, *J* = 2.5 Hz, 1H), 2.58 (s, 3H), 1.62 (s, 9H).

Intermediate 17

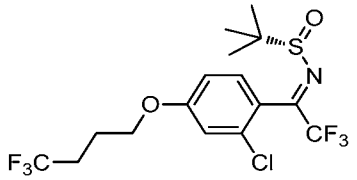
(*S*,*E*)-2-Methyl-*N*-(2,2,2-trifluoro-1-(4-(5,5,5-trifluoropentyl) phenyl)ethylidene)propane-2-sulfinamide



Intermediate 17 was prepared using a procedure similar to Intermediate 1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (d, *J* = 8.0 Hz, 2H), 7.30 - 7.20 (m, 2H), 2.76 - 2.59 (m, 2H), 2.17 - 2.00 (m, 2H), 1.80 - 1.67 (m, 2H), 1.66 - 1.58 (m, 2H), 1.31 (s, 9H).

Intermediate 18

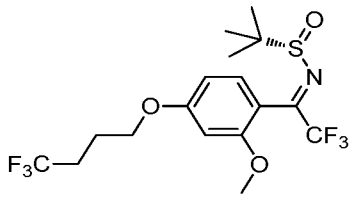
(*S*,*E*)-N-(1-(2-Chloro-4-(4,4,4-trifluorobutoxy)phenyl)-2,2,2-trifluoroethylidene)-2-methylpropane-2-sulfinamide



Intermediate 18 was prepared using a procedure similar to Intermediate 1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17 (d, J = 8.5 Hz, 1H), 6.89 (d, J = 2.5 Hz, 1H), 6.78 - 6.72 (m, 1H), 3.95 (br. s., 2H), 2.31 - 2.16 (m, 2H), 1.99 (d, J = 9.6 Hz, 2H), 1.24 (s, 9H). LCMS Anal. Calc'd for $C_{16}H_{18}ClF_6NO_2S$ 437.1, found [M+H] 438.1.

Intermediate 19

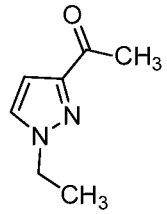
(*S,E*)-2-Methyl-N-(2,2,2-trifluoro-1-(2-methoxy-4-(4,4,4-trifluorobutoxy) phenyl)ethylidene)propane-2-sulfinamide



Intermediate 19 was prepared using a procedure similar to Intermediate 1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 - 7.22 (m, 1H), 6.53 - 6.50 (m, 1H), 6.49 (s, 1H), 4.06 (s, 2H), 3.92 (s, 3H), 2.40 - 2.28 (m, 2H), 2.13 - 2.02 (m, 2H), 1.31 (s, 9H). LCMS Anal. Calc'd for $C_{17}H_{21}F_6NO_3S$ 433.1, found [M+H] 434.1.

Intermediate 20

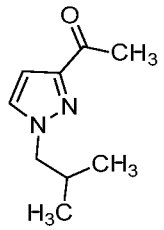
1-(1-Ethyl-1*H*-pyrazol-3-yl)ethanone



Intermediate 20 was prepared using a procedure analogous to Intermediate 12 except that (bromomethyl)cyclopropane was replaced by iodoethane. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (d, J = 2.48 Hz, 1H), 6.77 (d, J = 2.48 Hz, 1H), 4.24 (q, J = 7.43 Hz, 2H), 2.57 (s, 3H), 1.53 (t, J = 7.43 Hz, 3H). LCMS Anal. Calc'd for $C_7H_{10}N_2O$ 138.08, found [M+H] 139.1.

Intermediate 21

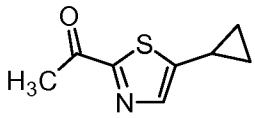
1-(1-Isobutyl-1*H*-pyrazol-3-yl)ethanone



Intermediate 21 was prepared using a procedure analogous to Intermediate 12 except that (bromomethyl)cyclopropane was replaced by 1-bromo-2-methylpropane. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (d, J = 2.48 Hz, 1H), 6.72 (d, J = 2.48 Hz, 1H), 3.93 (d, J = 7.43 Hz, 2H), 2.52 (s, 3H), 2.20 (sept, J = 7.15 Hz, 1H), 0.88 (d, J = 6.60 Hz, 6H). LCMS Anal. Calc'd for $C_9H_{14}N_2O$ 166.11, found [M+H] 167.1.

Intermediate 22

1-(5-Cyclopropylthiazol-2-yl)ethanone



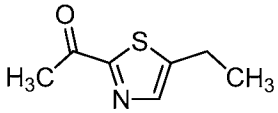
Intermediate 22A. 5-Cyclopropyl-2-(1,1-dimethoxyethyl)thiazole: To a degassed solution of 5-bromo-2-(1,1-dimethoxyethyl)thiazole (0.500 g, 1.983 mmol), prepared using the procedure described in WO 2004/087699, and [1,1′-bis(diphenylphosphino) ferrocene]dichloropalladium (II) complex with dichloromethane (1:1) (0.162 g, 0.198 mmol) in THF (19.83 mL) was added cyclopropylzinc(II) bromide, 0.5 M in THF (19.83 mL, 9.92 mmol) and the reaction mixture was degassed an additional 3 times. The reaction mixture was then heated at 65 °C for 20 h, cooled to rt, diluted with water and extracted with EtOAc (3x). The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (silica gel, hexanes:EtOAc, 100:0 to 70:30) to afford 0.327 g (77%) of Intermediate 22A as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 (d, J = 0.8 Hz, 1H), 3.25 (s, 6H), 2.10 - 1.96 (m, 1H), 1.70 (s, 3H), 1.09 - 0.96 (m, 2H), 0.78 - 0.66 (m, 2H). LCMS Anal. Calc'd for $C_{10}H_{15}NO_2S$ 213.0, found [M+H-MeOH] 182.0.

Intermediate 22: To a solution of Intermediate 22A (327 mg, 1.533 mmol) in DCM (1.821 mL) was added TFA (1.181 mL, 15.33 mmol) and Water (0.091 mL) and the reaction mixture stirred at RT for 2 h. The solvent was removed *in vacuo* and the residue was dissolved in DCM, washed with sat. $NaHCO_3$, water and brine. The organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was

purified by flash chromatography (silica gel, hexanes:EtOAc, 100:0 to 0:100) to afford 0.189 g (74%) of Intermediate 22 as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (s, 1H), 2.66 (s, 3H), 2.24 - 2.06 (m, 1H), 1.24 - 1.13 (m, 2H), 0.93 - 0.80 (m, 2H). LCMS Anal. Calc'd for C_8H_9NOS 167.0, found [M+H] 167.9.

Intermediate 23

1-(5-Ethylthiazol-2-yl)ethanone



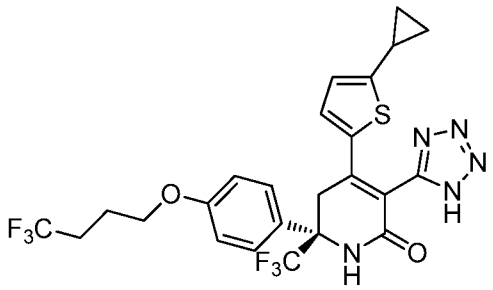
Intermediate 23A. 1-(5-Bromothiazol-2-yl)ethanone: To a solution of 5-bromo-2-(1,1-dimethoxyethyl)thiazole (0.828 g, 3.28 mmol) in DCM (3.90 mL) was added TFA (2.53 mL, 32.8 mmol) and water (0.195 mL) and the reaction mixture stirred at 23 °C under Ar at 1 atm for 2 h. The solvent was removed *in vacuo* (azeotroped with MeOH, 2x) and the residue was dissolved in DCM, washed with sat. $NaHCO_3$, water and brine. The organic layer was dried over anhydrous Na_2SO_4, filtered, concentrated and air-dried under vacuum to give a crude product. The crude product was further purified by ISCO (Hex:EtOAc 0-20%) to give Intermediate 23A (640 mg, 3.11 mmol, 95% yield) as a crude light brown solid. LCMS Anal. Calc'd for C_5H_4BrNOS 204.9, found [M+H] 206.1.

Intermediate 23B. 1-(5-Vinylthiazol-2-yl)ethanone: A solution of potassium vinyltrifluoroborate (0.332 g, 2.475 mmol), palladium (II) chloride (8.78 mg, 0.050 mmol), Ph_3P (0.039 g, 0.149 mmol), Cs_2CO_3 (0.806 g, 2.475 mmol) and Intermediate 23A (0.510g, 2.475 mmol) in a mixture of THF (4.2 ml) and water (0.467 ml) was heated in a sealed reaction vial at 85 °C for 16 h. The reaction mixture was cooled to rt and diluted with water followed by extraction with DCM (3x). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated. The crude product was dissolved in a small amount of dichloromethane and charged to a 40 g silica gel cartridge which was eluted with a gradient from 0 to 30% hexane/ethyl acetate. The desired fractions were concentrated and air-dried under vacuum to yield Intermediate 23B (0.250 g, 1.632 mmol, 65.9% yield) as a yellow oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.81 (s, 1H), 6.83 (dd, J = 17.3, 10.9 Hz, 1H), 5.78 (d, J = 17.4 Hz, 1H), 5.46 (d, J = 11.0 Hz, 1H), 2.68 (s, 3H). LCMS Anal. Calc'd for C_7H_7NOS 153.02, found [M+H] 154.3.

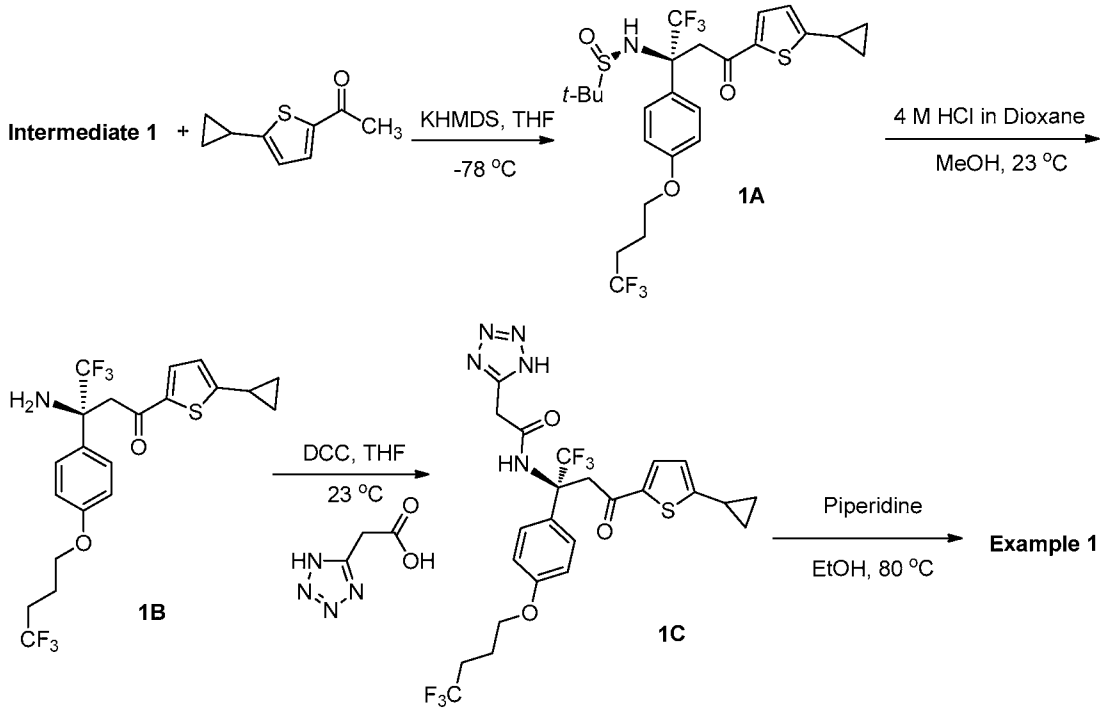
Intermediate 23: A mixture of Intermediate 23B (431 mg, 2.81 mmol), Pd/C (58 mg, 0.055 mmol, ~10% wt) in MeOH (30 mL) was hydrogenated at 1atm for 18 min. Catalyst was filtered off through CELITE®. The filtrate was concentrated to give the crude product which was charged to a 24 g silica gel cartridge which was eluted with a gradient from 0 to 30% hexane/ethyl acetate. Desired fractions were collected and concentrated using a rotary evaporator to give Intermediate 23 as colorless oil (395 mg, 90%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.68 (t, *J* = 1.0 Hz, 1H), 2.93 (qd, *J* = 7.5, 1.0 Hz, 2H), 2.67 (s, 3H), 1.36 (t, *J* = 7.5 Hz, 3H). LCMS Anal. Calc'd for C_7H_9NOS 155.04, found [M+H] 156.3.

Example 1

(*S*)-4-(5-Cyclopropylthiophen-2-yl)-3-(1*H*-tetrazol-5-yl)-6-(4-(4,4,4-trifluorobutoxy) phenyl)-6-(trifluoromethyl)-5,6-dihydropyridin-2(1*H*)-one



Synthetic Scheme 1



1A. (*S*)-N-((*S*)-4-(5-Cyclopropylthiophen-2-yl)-1,1,1-trifluoro-4-oxo-2-(4-(4,4,4-trifluorobutoxy)phenyl)butan-2-yl)-2-methylpropane-2-sulfinamide: To a solution of Intermediate 5 (37.1 mg, 0.223 mmol) in THF (1.195 mL) at -78 °C was added KHMDS (1.0 M in THF) (0.223 mL, 0.223 mmol). The resulting mixture was stirred at -78 °C for 20 min and Intermediate 1 (60 mg, 0.149 mmol) in THF (0.598 mL), was added. Stirring was continued at -78 °C for an additional 1 h. The reaction mixture was quenched with sat. aq. NH_4Cl and was diluted with EtOAc (5 mL) and water (5 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. Purification by chromatography to yield 1A (41.5 mg, 0.073 mmol, 49.0% yield) as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (d, *J* = 8.8 Hz, 2H), 7.54 (d, *J* = 3.9 Hz, 1H), 6.92 (d, *J* = 8.8 Hz, 2H), 6.80 (d, *J* = 3.9 Hz, 1H), 6.67 (s, 1H), 4.04 (t, *J* = 5.9 Hz, 2H), 3.79 (d, *J* = 16.2 Hz, 1H), 3.61 (d, *J* = 16.2 Hz, 1H), 2.42 - 2.26 (m, 2H), 2.19 - 2.11 (m, 1H), 2.10 - 2.00 (m, 2H), 1.30 (s, 9H), 1.19 - 1.10 (m, 2H), 0.86 - 0.78 (m, 2H). LCMS Anal. Calc'd for $C_{25}H_{29}F_6NO_3S_2$ 569.1, found [M+H] 570.0.

1B. (*S*)-3-Amino-1-(5-cyclopropylthiophen-2-yl)-4,4,4-trifluoro-3-(4-(4,4,4-trifluorobutoxy)phenyl)butan-1-one: To a solution of 1A (40.0 mg, 0.070 mmol) in MeOH (0.351 mL) was added HCl (4 M in dioxane) (0.083 mL, 0.330 mmol) and the

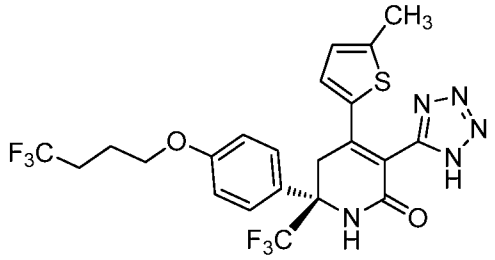
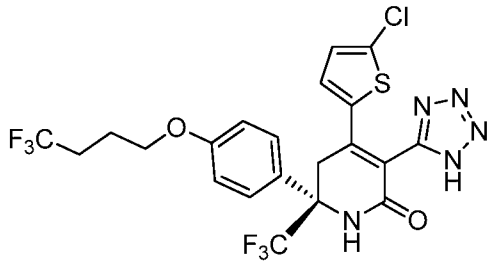
reaction mixture stirred under argon for 1 h. The solvent was removed *in vacuo* and the residue was dissolved in EtOAc, washed with sat. $NaHCO_3$ and brine. The organic layer was dried over anhydrous Na_2SO_4, filtered, concentrated to yield 1B (29.4 mg, 0.063 mmol, 90% yield) as a crude light yellow oil which was used in the next step without further purification. LCMS Anal. Calc'd for $C_{21}H_{21}F_6NO_2S$ 465.12, found [M+H] 466.0.

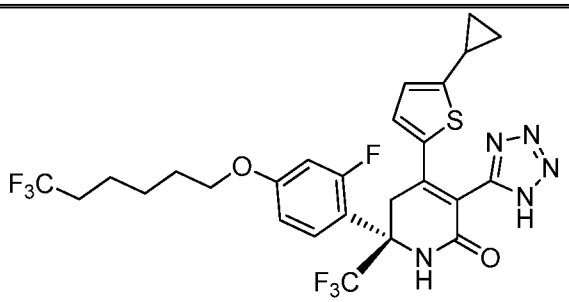
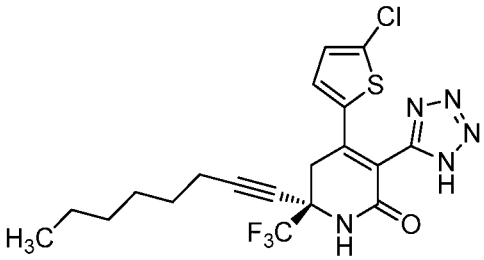
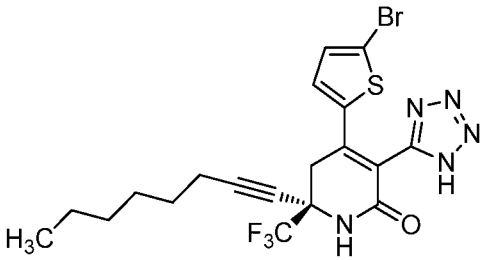
1C. (*S*)-*N*-(4-(5-Cyclopropylthiophen-2-yl)-1,1,1-trifluoro-4-oxo-2-(4-(4,4,4-trifluorobutoxy)phenyl)butan-2-yl)-2-(1*H*-tetrazol-5-yl)acetamide: To a solution of 1B (29.4 mg, 0.063 mmol) and N,N′-methanediylidenedicyclohexanamine (39.1 mg, 0.189 mmol) in THF (0.545) mL) was added a solution of (1*H*-tetrazol-5-yl)-acetic acid (24.27 mg, 0.189 mmol) in THF (0.545 mL) and the reaction mixture stirred at rt under argon, 1 atm for 2 h. The solids formed were filtered and the residue was purified by chromatography to yield 1C (32.1 mg, 0.056 mmol, 88% yield) as a white solid. LCMS Anal. Calc'd for $C_{24}H_{23}F_6N_5O_3S$ 576.50, found [M+H] 577.0.

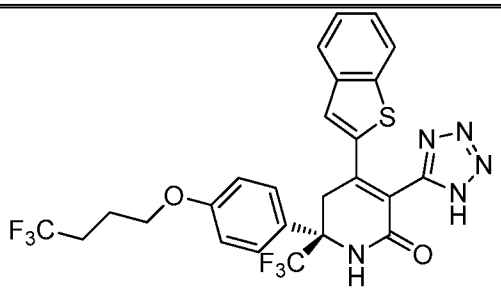
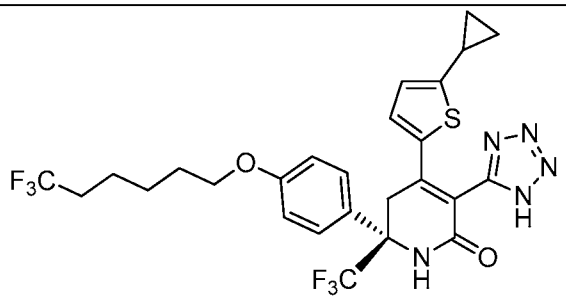
Example 1: To a solution of 1C (30.1 mg, 0.052 mmol) in EtOH (1.090 mL) was added piperidine (7.25 μL, 0.073 mmol) and the reaction mixture stirred at 80 °C in a sealed vial for 24 h. The solvent was removed *in vacuo*. The residue was purified by prep HPLC to yield Example 1 (19.7 mg, 0.056 mmol, 66% yield). LCMS Anal. Calc'd for $C_{24}H_{21}F_6N_5O_2S$ 558.13, found [M+H] 559.0. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.49 (br. s., 1H), 7.69 - 7.57 (m, 3H), 7.01 (d, *J* = 8.5 Hz, 2H), 6.79 (d, *J* = 3.9 Hz, 1H), 4.06 (t, *J* = 6.1 Hz, 2H), 3.92 (d, *J* = 17.3 Hz, 1H), 3.59 (d, *J* = 17.3 Hz, 1H), 2.47 - 2.33 (m, 2H), 2.03 - 1.97 (m, 1H), 1.97 - 1.89 (m, 2H), 1.05 - 0.90 (m, 2H), 0.66 - 0.51 (m, 2H).

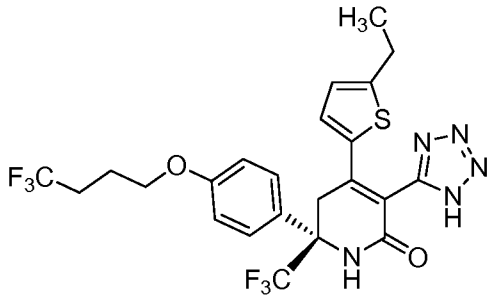
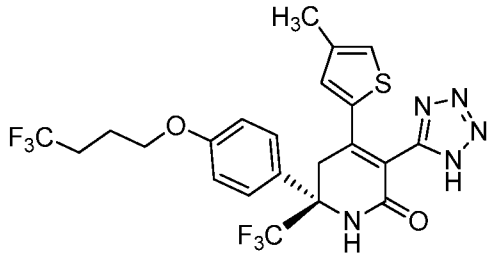
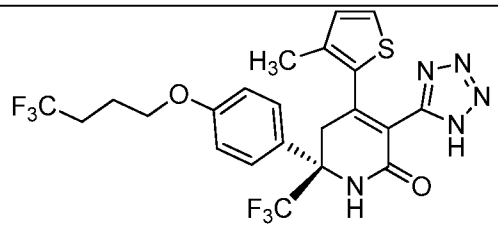
The following Examples in Table 2 were prepared in a similar manner as Example 1 utilizing sulfinamide (Intermediates 1-5 and 17-19) and heterocyclic ketone (Intermediates 6-16 and 20-13, or commercially available ketones) as starting materials.

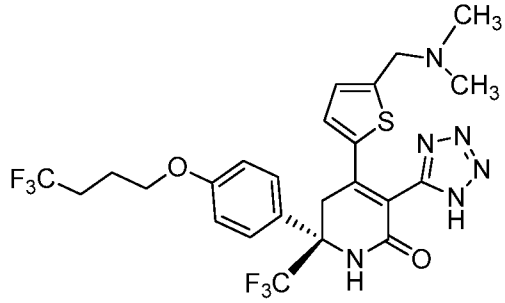
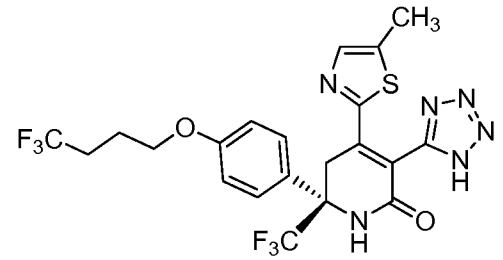
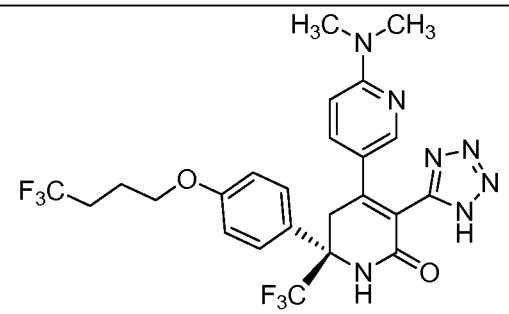
Table 2

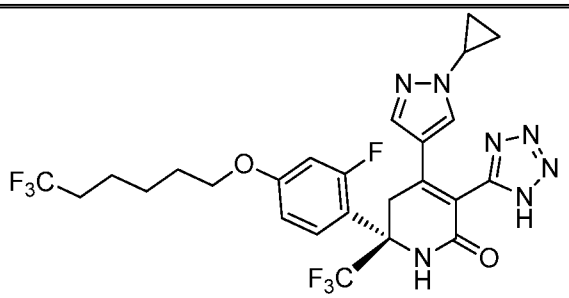
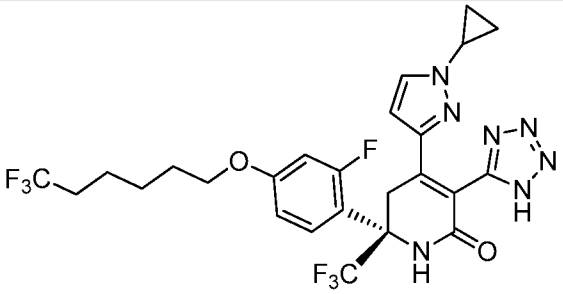
Example No.	Structure and Name	Analytical Data
2	 (*S*)-4-(5-Methylthiophen-2-yl)-3-(1*H*-tetrazol-5-yl)-6-(4-(4,4,4-trifluorobutoxy) phenyl)-6-(trifluoromethyl)-5,6-dihydropyridin-2(1*H*)-one	^{1}H NMR (500 MHz, 1:1 MeOD:$CDCl_3$) δ 7.51 (d, *J* = 8.8 Hz, 2H), 7.05 (d, *J* = 3.9 Hz, 1H), 6.93 (d, *J* = 8.8 Hz, 2H), 6.67 (dd, *J* = 3.9, 0.8 Hz, 1H), 4.02 (t, *J* = 5.9 Hz, 2H), 3.79 - 3.70 (m, 1H), 3.67 - 3.58 (m, 1H), 2.34 (s, 3H), 2.33 - 2.25 (m, 2H), 2.07 - 1.97 (m, 2H). MS(ESI) *m/z*: 532.2 $(M+H)^+$.
3	 (*S*)-4-(5-Chlorothiophen-2-yl)-3-(1*H*-tetrazol-5-yl)-6-(4-(4,4,4-trifluorobutoxy) phenyl)-6-(trifluoromethyl)-5,6-dihydropyridin-2(1*H*)-one	^{1}H NMR (500 MHz, MeOD) δ 7.59 (d, *J* = 8.8 Hz, 2H), 7.42 (d, *J* = 4.4 Hz, 1H), 7.04 - 6.97 (m, 3H), 4.07 (t, *J* = 6.2 Hz, 2H), 3.91 (d, *J* = 17.1 Hz, 1H), 3.70 (d, *J* = 17.3 Hz, 1H), 2.43 - 2.30 (m, 2H), 2.08 - 1.96 (m, 2H). MS(ESI) *m/z*: 552.0 $(M+H)^+$.

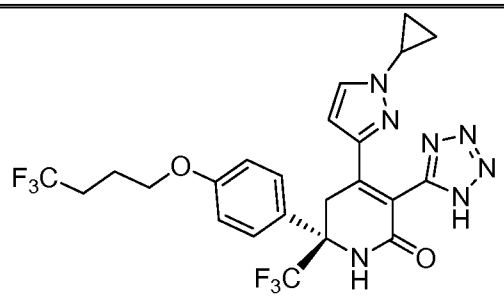
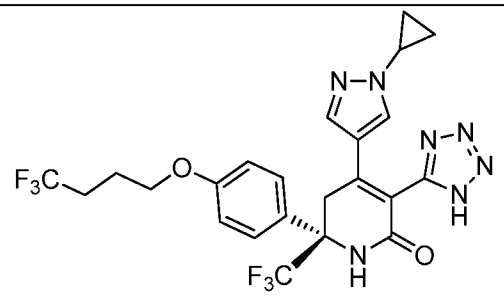
Example No.	Structure and Name	Analytical Data
4	 (*S*)-4-(5-Cyclopropylthiophen-2-yl)-6-(2-fluoro-4-((6,6,6-trifluorohexyl)oxy) phenyl)-3-(1*H*-tetrazol-5-yl)-6-(trifluoromethyl)-5,6-dihydropyridin-2(1*H*)-one	^{1}H NMR (500 MHz, DMSO) δ 9.43 (br. s., 1H), 7.63 (d, *J* = 8.0 Hz, 2H), 7.57 (br. s., 1H), 7.00 (d, *J* = 8.0 Hz, 2H), 6.78 (br. s., 1H), 4.01 (br. s., 2H), 3.91 (d, *J* = 16.8 Hz, 1H), 3.59 (d, *J* = 17.3 Hz, 1H), 2.36 - 2.18 (m, 2H), 1.99 (d, *J* = 3.9 Hz, 1H), 1.75 (br. s., 2H), 1.57 - 1.44 (m, 4H), 0.98 (d, *J* = 7.2 Hz, 2H), 0.58 (br. s., 2H). MS(ESI) *m/z*: 604.1 $(M+H)^+$.
5	 (*S*)-4-(5-Chlorothiophen-2-yl)-6-(oct-1-yn-1-yl)-3-(1*H*-tetrazol-5-yl)-6-(trifluoromethyl)-5,6-dihydropyridin-2(1*H*)-one	^{1}H NMR (500 MHz, 1:1 MeOD:$CDCl_3$) δ 7.10 (d, *J* = 4.5 Hz, 1H), 6.87 (d, *J* = 4.0 Hz, 1H), 3.47 (d, *J* = 5.0 Hz, 2H), 2.27 (t, *J* = 7.2 Hz, 2H), 1.59 - 1.48 (m, 2H), 1.45 - 1.35 (m, 2H), 1.32 - 1.20 (m, 4H), 0.88 (t, *J* = 6.9 Hz, 3H). MS(ESI) *m/z*: 458.0 $(M+H)^+$.
6	 (*S*)-4-(5-Bromothiophen-2-yl)-6-(oct-1-yn-1-yl)-3-(1*H*-tetrazol-5-yl)-6-(trifluoromethyl)-5,6-dihydropyridin-2(1*H*)-one	^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 - 6.97 (m, 2H), 6.91 (s, 1H), 3.56 - 3.35 (m, 2H), 2.22 (t, *J* = 7.2 Hz, 2H), 1.50 (quin, *J* = 7.3 Hz, 2H), 1.40 - 1.14 (m, 6H), 0.86 (t, *J* = 6.8 Hz, 3H). MS(ESI) *m/z*: 504.2 $(M+H)^+$.

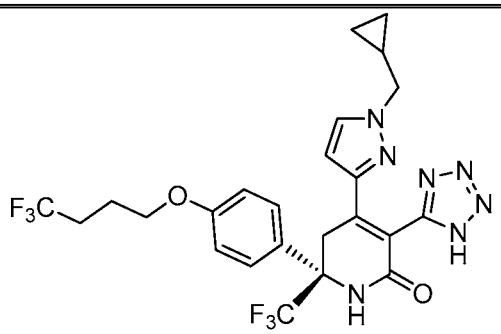
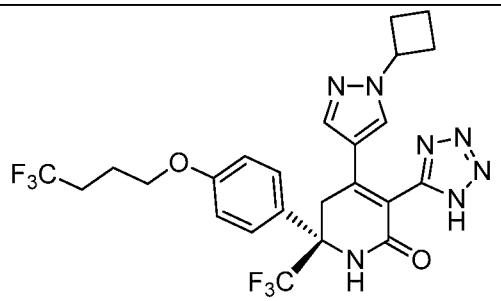
Example No.	Structure and Name	Analytical Data
7	 (*S*)-4-(Benzo[*b*]thiophen-2-yl)-3-(1*H*-tetrazol-5-yl)-6-(4-(4,4,4-trifluorobutoxy) phenyl)-6-(trifluoromethyl)-5,6-dihydropyridin-2(1*H*)-one	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.68 (br. s., 1H), 8.25 (br. s., 1H), 7.89 (d, *J* = 6.3 Hz, 1H), 7.82 (d, *J* = 6.1 Hz, 1H), 7.69 (d, *J* = 8.0 Hz, 2H), 7.40 (d, *J* = 3.9 Hz, 2H), 7.03 (d, *J* = 8.0 Hz, 2H), 4.16 - 3.99 (m, 3H), 3.81 (d, *J* = 7.6 Hz, 1H), 2.45 - 2.31 (m, 2H), 1.93 (br. s., 2H). MS(ESI) *m/z*: 568.1 $(M+H)^+$.
8	 (*S*)-4-(5-Cyclopropylthiophen-2-yl)-3-(1*H*-tetrazol-5-yl)-6-(4-((6,6,6-trifluorohexyl) oxy)phenyl)-6-(trifluoromethyl)-5,6-dihydropyridin-2(1*H*)-one	^{1}H NMR (500 MHz, 1:1 MeOD:$CDCl_3$) δ 7.46 (t, *J* = 9.4 Hz, 1H), 7.07 (d, *J* = 3.5 Hz, 1H), 6.77 (dd, *J* = 8.9, 2.5 Hz, 1H), 6.71 - 6.56 (m, 2H), 4.14 (d, *J* = 16.8 Hz, 1H), 3.98 (t, *J* = 6.2 Hz, 2H), 3.58 (d, *J* = 16.8 Hz, 1H), 2.23 - 2.05 (m, 2H), 1.98 - 1.90 (m, 1H), 1.85 - 1.74 (m, 2H), 1.66 - 1.49 (m, 4H), 1.02 - 0.91 (m, 2H), 0.65 - 0.51 (m, 2H). MS(ESI) *m/z*: 587.0 $(M+H)^+$.

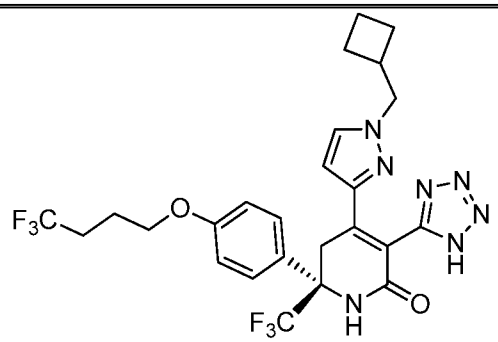
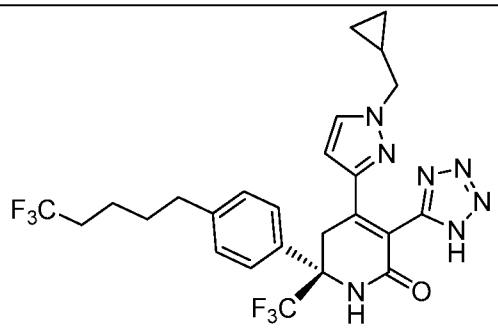
Example No.	Structure and Name	Analytical Data
9	 (*S*)-4-(5-Ethylthiophen-2-yl)-3-(1*H*-tetrazol-5-yl)-6-(4-(4,4,4-trifluorobutoxy) phenyl)-6-(trifluoromethyl)-5,6-dihydropyridin-2(1*H*)-one	^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, *J* = 8.8 Hz, 2H), 7.20 (d, *J* = 3.7 Hz, 1H), 7.12 (br. s., 1H), 6.94 (d, *J* = 8.8 Hz, 2H), 6.79 (d, *J* = 4.0 Hz, 1H), 4.03 (t, *J* = 5.9 Hz, 2H), 3.75, 3.68 (ABq, *J* = 17.4 Hz, 2H), 2.85 (q, *J* = 7.5 Hz, 2H), 2.41 - 2.25 (m, 2H), 2.08 (dt, *J* = 15.7, 6.0 Hz, 2H), 1.31 (t, *J* = 7.5 Hz, 3H). MS(ESI) *m/z*: 546.3 $(M+H)^+$.
10	 (*S*)-4-(4-Methylthiophen-2-yl)-3-(1*H*-tetrazol-5-yl)-6-(4-(4,4,4-trifluorobutoxy) phenyl)-6-(trifluoromethyl)-5,6-dihydropyridin-2(1*H*)-one	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.54 (br. s., 1H), 7.58 (d, *J* = 7.7 Hz, 2H), 7.46 (br. s., 1H), 7.02 (d, *J* = 6.9 Hz, 2H), 6.73 (br. s., 1H), 4.07 (br. s., 2H), 3.65 (d, *J* = 17.3 Hz, 1H), 3.52 (br. s., 1H), 2.42 (d, *J* = 3.6 Hz, 2H), 1.93 (br. s., 2H), 1.63 (br. s., 3H). MS(ESI) *m/z*: 532.1 $(M+H)^+$.
11	 (*S*)-4-(3-Methylthiophen-2-yl)-3-(1*H*-tetrazol-5-yl)-6-(4-(4,4,4-trifluorobutoxy) phenyl)-6-(trifluoromethyl)-5,6-dihydropyridin-2(1*H*)-one	^{1}H NMR (500 MHz, $CDCl_3$) δ 9.36 (br. s., 1H), 7.64 (d, *J* = 7.7 Hz, 2H), 7.49 (br. s., 1H), 7.22 (br. s., 1H), 7.01 (d, *J* = 7.7 Hz, 2H), 4.06 (br. s., 2H), 3.87 (d, *J* = 16.8 Hz, 1H), 3.59 (d, *J* = 17.3 Hz, 1H), 2.47 - 2.31 (m, 2H), 2.14 (br. s., 3H), 1.93 (br. s., 2H). MS(ESI) *m/z*: 532.1 $(M+H)^+$.

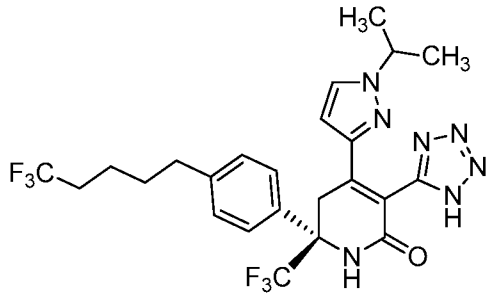
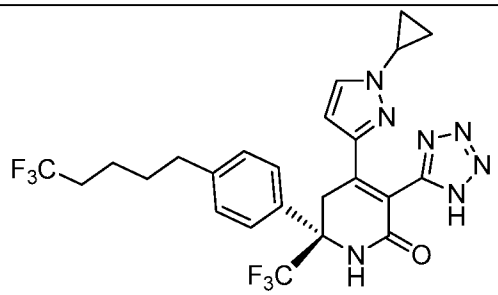
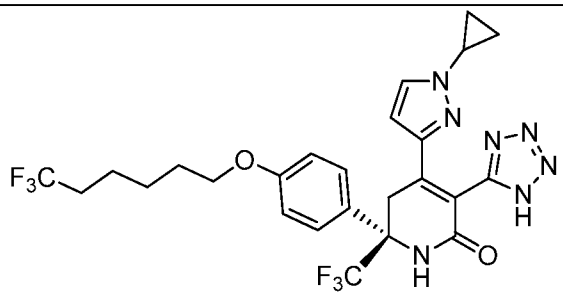
Example No.	Structure and Name	Analytical Data
12	 (*S*)-4-(5-((Dimethylamino)methyl) thiophen-2-yl)-3-(1*H*-tetrazol-5-yl)-6-(4-(4,4,4-trifluorobutoxy)phenyl)-6-(trifluoromethyl)-5,6-dihydropyridin-2(1*H*)-one	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.66 (s, 1H), 7.83 (d, *J* = 3.9 Hz, 1H), 7.66 (d, *J* = 8.8 Hz, 2H), 7.27 (d, *J* = 3.9 Hz, 1H), 7.03 (d, *J* = 9.1 Hz, 2H), 4.36 (s, 2H), 4.07 (t, *J* = 6.1 Hz, 2H), 3.97 (d, *J* = 17.6 Hz, 1H), 3.71 (d, *J* = 17.6 Hz, 1H), 3.25 - 3.19 (m, 2H), 2.63 (s, 6H), 2.47 - 2.35 (m, 2H). MS(ESI) *m/z*: 575.2 $(M+H)^+$.
13	 (*S*)-4-(5-Methylthiazol-2-yl)-3-(1*H*-tetrazol-5-yl)-6-(4-(4,4,4-trifluorobutoxy) phenyl)-6-(trifluoromethyl)-5,6-dihydropyridin-2(1*H*)-one	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.83 (br. s., 1H), 7.76 (s, 1H), 7.55 (d, *J* = 8.8 Hz, 2H), 7.03 (d, *J* = 8.8 Hz, 2H), 4.21 (d, *J* = 17.6 Hz, 1H), 4.05 (t, *J* = 6.1 Hz, 2H), 3.73 (d, *J* = 17.6 Hz, 1H), 2.46 - 2.33 (m, 5H), 1.98 - 1.82 (m, 2H). MS(ESI) *m/z*: 533.1 $(M+H)^+$.
14	 (*S*)-6-(Dimethylamino)-3′-(1*H*-tetrazol-5-yl)-6′-(4-(4,4,4-trifluorobutoxy)phenyl)-6′-(trifluoromethyl)-5′,6′-dihydro-[3,4′-bipyridin]-2′(1′*H*)-one	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.54 (s, 1H), 7.78 (d, *J* = 2.5 Hz, 1H), 7.64 (d, *J* = 8.8 Hz, 2H), 7.14 (dd, *J* = 9.1, 2.2 Hz, 1H), 7.01 (d, *J* = 8.8 Hz, 2H), 6.62 (d, *J* = 8.8 Hz, 1H), 4.07 (t, *J* = 6.2 Hz, 2H), 3.80 - 3.62 (m, 2H), 3.04 (s, 6H), 2.47 - 2.30 (m, 2H), 1.99 - 1.85 (m, 2H). MS(ESI) *m/z*: 556.1 $(M+H)^+$.

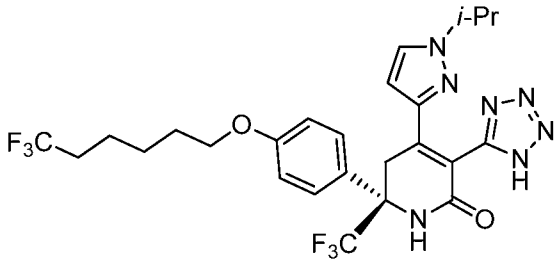
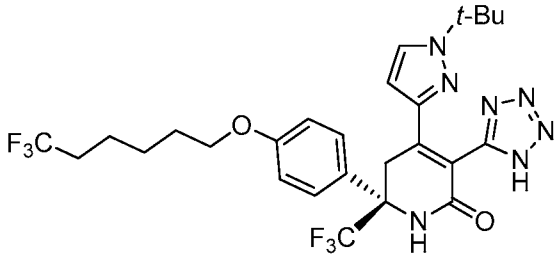
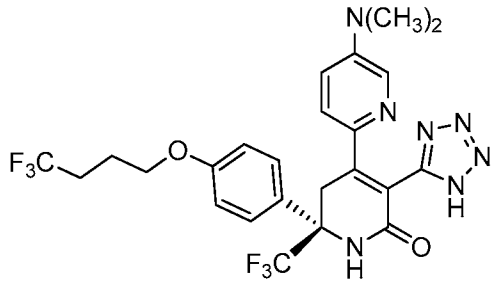
Example No.	Structure and Name	Analytical Data
15	 (*S*)-4-(1-Cyclopropyl-1*H*-pyrazol-4-yl)-6-(2-fluoro-4-((6,6,6-trifluorohexyl)oxy) phenyl)-3-(1*H*-tetrazol-5-yl)-6-(trifluoromethyl)-5,6-dihydropyridin-2(1*H*)-one	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.40 (br. s., 1H), 7.91 (br. s., 1H), 7.55 (t, *J* = 9.5 Hz, 1H), 6.91 (dd, *J* = 7.3, 2.1 Hz, 1H), 4.02 (t, *J* = 6.3 Hz, 2H), 3.95 (d, *J* = 17.3 Hz, 1H), 3.75 - 3.66 (m, 1H), 3.50 (d, *J* = 17.3 Hz, 1H), 2.34 - 2.20 (m, 2H), 1.74 (quin, *J* = 6.9 Hz, 2H), 1.60 - 1.43 (m, 4H), 1.04 - 0.91 (m, 4H). MS(ESI) *m/z*: 588.2 $(M+H)^+$.
16	 (*S*)-4-(1-Cyclopropyl-1*H*-pyrazol-3-yl)-6-(2-fluoro-4-((6,6,6-trifluorohexyl)oxy) phenyl)-3-(1*H*-tetrazol-5-yl)-6-(trifluoromethyl)-5,6-dihydropyridin-2(1*H*)-one	^{1}H NMR (500 MHz, MeOD) δ 7.60 (d, *J* = 2.5 Hz, 1H), 7.54 (t, *J* = 9.2 Hz, 1H), 6.83 (dd, *J* = 8.8, 2.5 Hz, 1H), 6.77 (dd, *J* = 14.9, 2.5 Hz, 1H), 5.66 (d, *J* = 2.5 Hz, 1H), 4.40 - 4.33 (m, 1H), 4.05 - 4.01 (m, 2H), 3.71 - 3.65 (m, 1H), 3.64 - 3.57 (m, 1H), 2.26 - 2.14 (m, 2H), 1.87 - 1.79 (m, 2H), 1.71 - 1.54 (m, 4H), 1.01 - 0.94 (m, 4H). MS(ESI) *m/z*: 588.2 $(M+H)^+$.

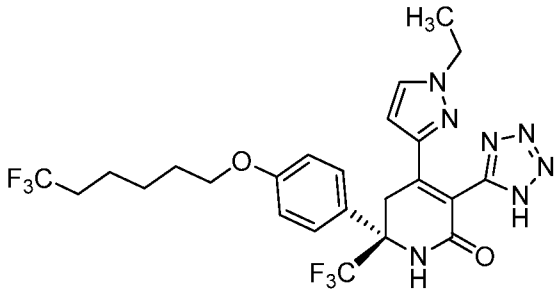
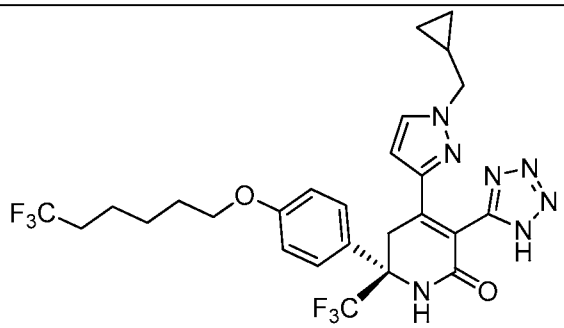
Example No.	Structure and Name	Analytical Data
17	 (*S*)-4-(1-Cyclopropyl-1*H*-pyrazol-3-yl)-3-(1*H*-tetrazol-5-yl)-6-(4-(4,4,4-trifluorobutoxy)phenyl)-6-(trifluoromethyl)-5,6-dihydropyridin-2(1*H*)-one	^{1}H NMR (400 MHz, MeOD) δ 7.58 (d, *J* = 8.8 Hz, 3H), 7.07 - 6.91 (m, 2H), 5.60 (d, *J* = 2.2 Hz, 1H), 4.15 - 4.01 (m, 3H), 3.73 - 3.55 (m, 2H), 2.43 - 2.23 (m, 2H), 2.08 - 1.93 (m, 2H), 1.00 - 0.90 (m, 4H). MS(ESI) *m/z*: 542.2 $(M+H)^+$.
18	 (*S*)-4-(1-Cyclopropyl-1*H*-pyrazol-4-yl)-3-(1*H*-tetrazol-5-yl)-6-(4-(4,4,4-trifluorobutoxy)phenyl)-6-(trifluoromethyl)-5,6-dihydropyridin-2(1*H*)-one	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.43 (br. s., 1H), 8.11 (s, 1H), 7.67 (d, *J* = 8.3 Hz, 2H), 7.03 (d, *J* = 8.0 Hz, 2H), 6.50 (s, 1H), 4.08 (t, *J* = 5.9 Hz, 2H), 3.80 (d, *J* = 17.6 Hz, 1H), 3.73 - 3.66 (m, 1H), 3.55 (d, *J* = 17.6 Hz, 1H), 2.01 - 1.85 (m, 2H), 1.80 - 1.46 (m, 4H), 1.36 - 1.03 (m, 2H). MS(ESI) *m/z*: 542.2 $(M+H)^+$.

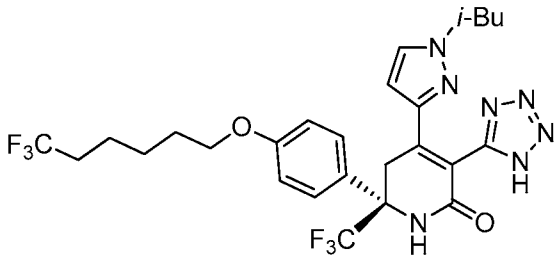
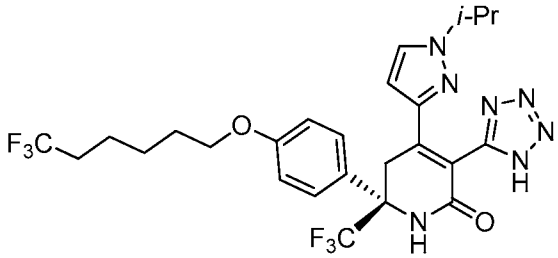
Example No.	Structure and Name	Analytical Data
19	 (*S*)-4-(1-(Cyclopropylmethyl)-1*H*-pyrazol-3-yl)-3-(1*H*-tetrazol-5-yl)-6-(4-(4,4,4-trifluorobutoxy)phenyl)-6-(trifluoromethyl)-5,6-dihydropyridin-2(1*H*)-one	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.47 (br. s., 1H), 7.68 (br. s., 1H), 7.60 (d, *J* = 8.0 Hz, 2H), 7.03 (d, *J* = 8.3 Hz, 3H), 5.25 (br. s., 1H), 4.17 - 4.03 (m, 2H), 3.95 (t, *J* = 8.7 Hz, 2H), 3.54 (d, *J* = 17.3 Hz, 1H), 2.49 - 2.34 (m, 2H), 2.03 - 1.87 (m, 2H), 1.16 (d, *J* = 6.3 Hz, 1H), 0.51 (d, *J* = 7.7 Hz, 2H), 0.33 (br. s., 2H). MS(ESI) *m/z*: 556.1 $(M+H)^+$.
20	 (*S*)-4-(1-Cyclobutyl-1*H*-pyrazol-4-yl)-3-(1*H*-tetrazol-5-yl)-6-(4-(4,4,4-trifluorobutoxy)phenyl)-6-(trifluoromethyl)-5,6-dihydropyridin-2(1*H*)-one	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.54 (br. s., 1H), 7.76 (br. s., 1H), 7.62 (d, *J* = 8.3 Hz, 2H), 7.04 (d, *J* = 8.0 Hz, 2H), 5.65 (br. s., 1H), 4.78 (quin, *J* = 8.3 Hz, 1H), 4.13 - 3.97 (m, 3H), 3.58 (d, *J* = 17.9 Hz, 1H), 2.48 - 2.37 (m, 2H), 2.35 - 2.20 (m, 4H), 1.99 - 1.88 (m, 2H), 1.82 - 1.67 (m, 2H). MS(ESI) *m/z*: 556.1 $(M+H)^+$.

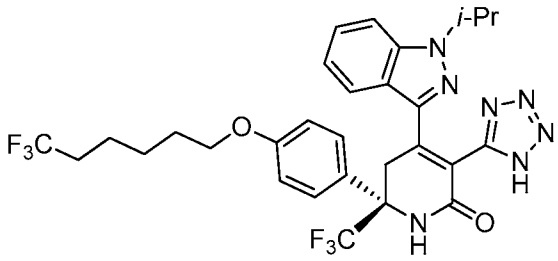
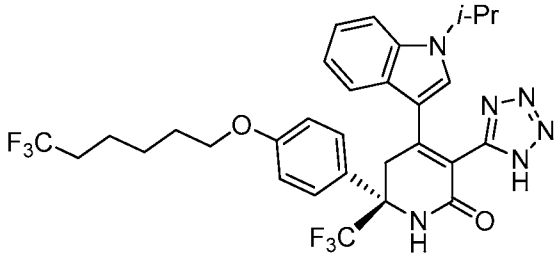
Example No.	Structure and Name	Analytical Data
21	 (*S*)-4-(1-(Cyclobutylmethyl)-1*H*-pyrazol-3-yl)-3-(1*H*-tetrazol-5-yl)-6-(4-(4,4,4-trifluorobutoxy)phenyl)-6-(trifluoromethyl)-5,6-dihydropyridin-2(1*H*)-one	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.54 (br. s., 1H), 7.65 (br. s., 1H), 7.59 (d, *J* = 8.3 Hz, 2H), 7.03 (d, *J* = 8.3 Hz, 2H), 5.34 (br. s., 1H), 4.18 - 4.00 (m, 5H), 3.55 (d, *J* = 17.6 Hz, 1H), 2.65 (t, *J* = 7.4 Hz, 1H), 2.43 (dd, *J* = 17.5, 10.0 Hz, 2H), 2.01 - 1.66 (m, 8H). MS(ESI) *m/z*: 570.2 $(M+H)^+$.
22	 (*S*)-4-(1-(Cyclopropylmethyl)-1*H*-pyrazol-3-yl)-3-(1*H*-tetrazol-5-yl)-6-(trifluoromethyl)-6-(4-(5,5,5-trifluoropentyl)phenyl)-5,6-dihydropyridin-2(1*H*)-one	^{1}H NMR (500 MHz, MeOD) δ 7.69 - 7.48 (m, 3H), 7.28 (d, *J* = 8.5 Hz, 2H), 5.50 (d, *J* = 2.2 Hz, 1H), 4.18 (d, *J* = 17.9 Hz, 1H), 4.04 - 3.83 (m, 2H), 3.65 (d, *J* = 17.6 Hz, 1H), 2.66 (t, *J* = 7.7 Hz, 2H), 2.25 - 2.07 (m, 2H), 1.71 (t, *J* = 7.8 Hz, 2H), 1.63 - 1.49 (m, 2H), 1.19 (s, 1H), 0.64 - 0.51 (m, 2H), 0.37 - 0.28 (m, 2H). MS(ESI) *m/z*: 554.3 $(M+H)^+$.

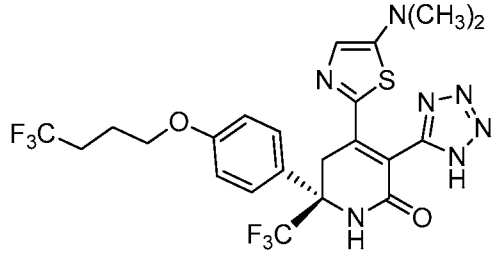
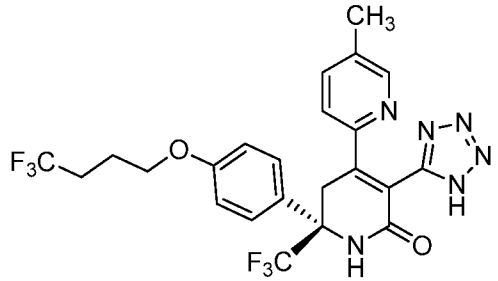
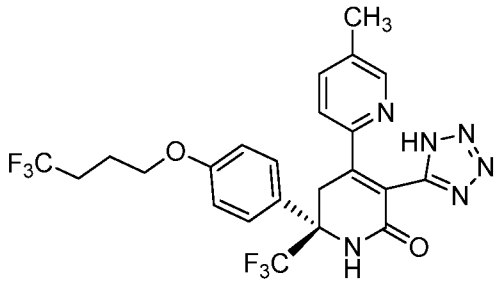
Example No.	Structure and Name	Analytical Data
23	 (*S*)-4-(1-Isopropyl-1*H*-pyrazol-3-yl)-3-(1*H*-tetrazol-5-yl)-6-(trifluoromethyl)-6-(4-(5,5,5-trifluoropentyl)phenyl)-5,6-dihydropyridin-2(1*H*)-one	^{1}H NMR (500 MHz, MeOD) δ 7.65 - 7.47 (m, 3H), 7.28 (d, *J* = 8.5 Hz, 2H), 5.67 (d, *J* = 2.5 Hz, 1H), 4.43 (dt, *J* = 13.4, 6.6 Hz, 1H), 4.19 - 4.06 (m, 1H), 3.71 - 3.59 (m, 1H), 2.66 (t, *J* = 7.7 Hz, 2H), 2.24 - 2.08 (m, 2H), 1.78 - 1.66 (m, 2H), 1.63 - 1.51 (m, 2H), 1.36 (dd, *J* = 6.6, 5.0 Hz, 6H). MS(ESI) *m/z*: 542.3 $(M+H)^+$.
24	 (*S*)-4-(1-Cyclopropyl-1*H*-pyrazol-3-yl)-3-(1*H*-tetrazol-5-yl)-6-(trifluoromethyl)-6-(4-(5,5,5-trifluoropentyl)phenyl)-5,6-dihydropyridin-2(1*H*)-one	^{1}H NMR (500 MHz, MeOD) δ 6.06 - 5.90 (m, 3H), 5.70 (d, *J* = 8.3 Hz, 2H), 4.01 (d, *J* = 2.2 Hz, 1H), 2.51 (d, *J* = 17.9 Hz, 1H), 2.13 - 2.01 (m, 2H), 1.12 - 1.04 (m, 2H), 0.66 - 0.48 (m, 2H), 0.17 - 0.07 (m, 2H), 0.04 - 0.06 (m, 2H). MS(ESI) *m/z*: 540.3 $(M+H)^+$.
25	 (*S*)-4-(1-Cyclopropyl-1*H*-pyrazol-3-yl)-3-(1*H*-tetrazol-5-yl)-6-(4-((6,6,6-trifluorohexyl)oxy)phenyl)-6-(trifluoromethyl)-5,6-dihydropyridin-2(1*H*)-one	^{1}H NMR (500 MHz, MeOD) δ 7.62 - 7.49 (m, 3H), 6.96 (d, *J* = 9.1 Hz, 2H), 5.58 (d, *J* = 2.2 Hz, 1H), 4.09 (d, *J* = 17.6 Hz, 1H), 4.00 (t, *J* = 6.3 Hz, 2H), 3.69 - 3.63 (m, 1H), 3.62 - 3.56 (m, 1H), 2.27 - 2.08 (m, 2H), 1.90 - 1.75 (m, 2H), 1.69 - 1.48 (m, 4H), 1.01 - 0.91 (m, 4H). MS(ESI) *m/z*: 570.3 $(M+H)^+$.

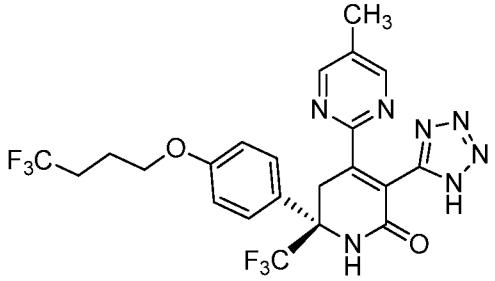
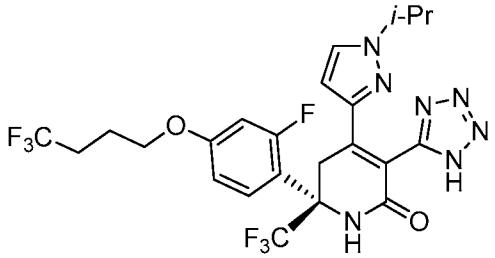
Example No.	Structure and Name	Analytical Data
26	 (*S*)-4-(1-Isopropyl-1*H*-pyrazol-3-yl)-3-(1*H*-tetrazol-5-yl)-6-(4-((6,6,6-trifluorohexyl) oxy)phenyl)-6-(trifluoromethyl)-5,6-dihydropyridin-2(1*H*)-one	^{1}H NMR (500 MHz, MeOD) δ 7.61 - 7.48 (m, 3H), 7.00 - 6.92 (m, 2H), 5.67 (d, *J* = 2.5 Hz, 1H), 4.49 - 4.35 (m, 1H), 4.12 (d, *J* = 17.6 Hz, 1H), 4.05 - 3.94 (m, 2H), 3.61 (d, *J* = 17.6 Hz, 1H), 2.25 - 2.08 (m, 2H), 1.83 - 1.75 (m, 2H), 1.68 - 1.51 (m, 4H), 1.36 (dd, *J* = 6.6, 5.0 Hz, 6H). MS(ESI) *m/z*: 572.3 $(M+H)^+$.
27	 (*S*)-4-(1-(*tert*-Butyl)-1*H*-pyrazol-3-yl)-3-(1*H*-tetrazol-5-yl)-6-(4-((6,6,6-trifluorohexyl)oxy)phenyl)-6-(trifluoromethyl)-5,6-dihydropyridin-2(1*H*)-one	^{1}H NMR (500 MHz, MeOD) δ 7.63 (d, *J* = 2.8 Hz, 1H), 7.58 (d, *J* = 8.8 Hz, 2H), 6.99 - 6.90 (m, 2H), 5.90 (d, *J* = 2.8 Hz, 1H), 4.10 (d, *J* = 17.6 Hz, 1H), 4.00 (td, *J* = 6.3, 1.1 Hz, 2H), 3.61 (d, *J* = 17.6 Hz, 1H), 2.27 - 2.08 (m, 2H), 1.85 - 1.74 (m, 2H), 1.67 - 1.51 (m, 4H), 1.42 (s, 9H). MS(ESI) *m/z*: 586.3 $(M+H)^+$.
28	 (*S*)-5-(Dimethylamino)-3′-(1*H*-tetrazol-5-yl)-6′-(4-(4,4,4-trifluorobutoxy)phenyl)-6′-(trifluoromethyl)-5′,6′-dihydro-[2,4′-bipyridin]-2′(1′*H*)-one	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.43 (br. s., 1H), 8.04 (br. s., 1H), 7.59 (d, *J* = 8.3 Hz, 2H), 7.00 (d, *J* = 8.3 Hz, 2H), 6.79 (d, *J* = 9.1 Hz, 1H), 6.58 (d, *J* = 8.8 Hz, 1H), 4.14 - 3.98 (m, 3H), 3.49 (br. s., 1H), 2.93 (s, 6H), 2.41 (dd, *J* = 16.9, 10.6 Hz, 2H), 1.99 - 1.84 (m, 2H). MS(ESI) *m/z*: 556.3 $(M+H)^+$.

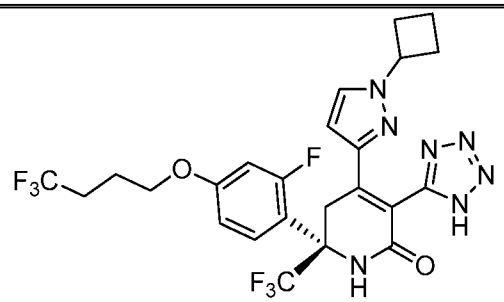
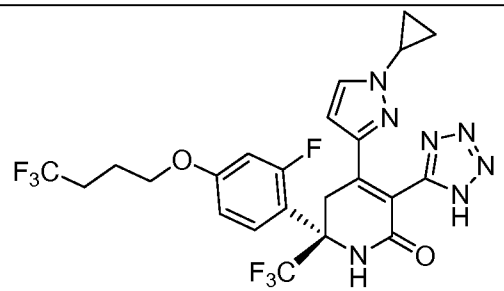
Example No.	Structure and Name	Analytical Data
29	 (*S*)-4-(1-Ethyl-1*H*-pyrazol-3-yl)-3-(1*H*-tetrazol-5-yl)-6-(4-((6,6,6-trifluorohexyl) oxy)phenyl)-6-(trifluoromethyl)-5,6-dihydropyridin-2(1*H*)-one	^{1}H NMR (500 MHz, CD_3OD) δ 7.57 (d, *J* = 8.80 Hz, 2H), 7.49 (d, *J* = 2.48 Hz, 1H), 6.95 (d, *J* = 9.08 Hz, 2H), 5.48 (d, *J* = 2.48 Hz, 1H), 4.16 (d, *J* = 17.33 Hz, 1H), 4.12 (q, *J* = 7.43 Hz, 2H), 4.00 (t, *J* = 6.33 Hz, 2H), 3.62 (d, *J* = 17.61 Hz, 1H), 2.12-2.22 (m, 2H), 1.77-1.83 (m, 2H), 1.53-1.66 (m, 4H), 1.36 (t, *J* = 7.15, 9H). MS(ESI) *m/z*: 558.2 $(M+H)^+$.
30	 (*S*)-4-(1-(Cyclopropylmethyl)-1*H*-pyrazol-3-yl)-3-(1*H*-tetrazol-5-yl)-6-(4-((6,6,6-trifluorohexyl)oxy)phenyl)-6-(trifluoromethyl)-5,6-dihydropyridin-2(1*H*)-one	^{1}H NMR (500 MHz, CD_3OD) δ 7.57 (d, *J* = 8.80 Hz, 2H), 7.55 (d, *J* = 2.48 Hz, 1H), 6.96 (d, *J* = 8.80 Hz, 2H), 5.50 (d, *J* = 2.48 Hz, 1H), 4.17 (d, *J* = 17.61 Hz, 1H), 4.00 (t, *J* = 6.33 Hz, 2H), 3.89-3.98 (m, 2H), 3.61 (d, *J* = 17.61 Hz, 1H), 2.12-2.22 (m, 2H), 1.77-1.83 (m, 2H), 1.55-1.66 (m, 4H), 1.16-1.22 (m, 1H), 0.54-0.58 (m, 2H), 0.31-0.34 (m, 2H). MS(ESI) *m/z*: 584.3 $(M+H)^+$.

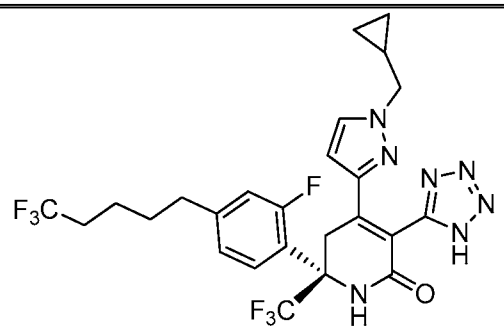
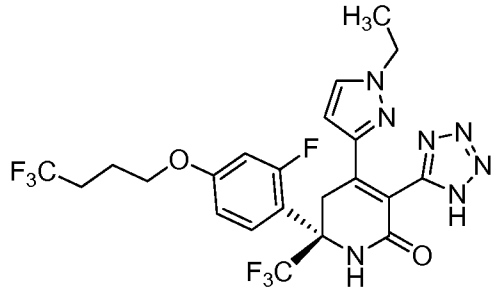
Example No.	Structure and Name	Analytical Data
31	 (*S*)-4-(1-Isobutyl-1*H*-pyrazol-3-yl)-3-(1*H*-tetrazol-5-yl)-6-(4-((6,6,6-trifluorohexyl) oxy)phenyl)-6-(trifluoromethyl)-5,6-dihydropyridin-2(1*H*)-one	^{1}H NMR (500 MHz, CD_3OD) δ 7.56 (d, *J* = 8.80 Hz, 2H), 7.47 (d, *J* = 2.48 Hz, 1H), 6.95 (d, *J* = 9.08 Hz, 2H), 5.51 (d, *J* = 2.20 Hz, 1H), 4.17 (d, *J* = 17.61 Hz, 1H), 4.00 (t, *J* = 6.33 Hz, 2H), 3.85-3.92 (m, 2H), 3.60 (d, *J* = 17.61 Hz, 1H), 2.12-2.22 (m, 2H), 2.04-2.09 (m, 1H), 1.77-1.83 (m, 2H), 1.53-1.66 (m, 4H), 0.84 (t, *J* = 6.60 Hz, 6H). MS(ESI) *m/z*: 586.3 $(M+H)^+$.
32	 (*S*)-4-(1-Isopropyl-1*H*-pyrazol-3-yl)-3-(1*H*-tetrazol-5-yl)-6-(4-((6,6,6-trifluorohexyl) oxy)phenyl)-6-(trifluoromethyl)-5,6-dihydropyridin-2(1*H*)-one	^{1}H NMR (500 MHz, CD_3OD) δ 7.58 (d, *J* = 8.53 Hz, 2H), 7.06 (s, 1H), 6.95 (d, *J* = 9.08 Hz, 2H), 6.68 (t, *J* = 2.75 Hz, 1H), 5.15 (s, 1H), 4.21 (sept, *J* = 6.60 Hz, 1H), 4.00 (t, *J* = 6.33 Hz, 2H), 3.80 (d, *J* = 17.06 Hz, 1H), 3.57 (d, *J* = 17.33 Hz, 1H), 2.12-2.22 (m, 2H), 1.78-1.83 (m, 2H), 1.53-1.66 (m, 4H), 1.36 (d, *J* = 6.88 Hz, 6H). MS(ESI) *m/z*: 571.3 $(M+H)^+$

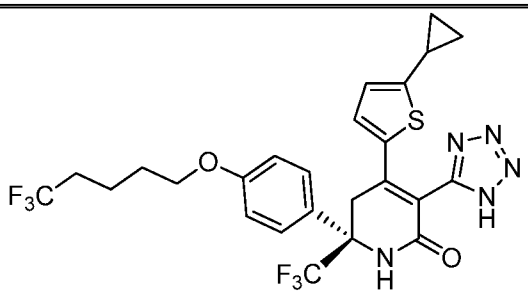
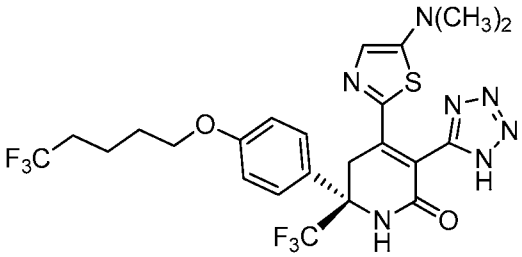
Example No.	Structure and Name	Analytical Data
33	 (*S*)-4-(1-Isopropyl-1*H*-indazol-3-yl)-3-(1*H*-tetrazol-5-yl)-6-(4-((6,6,6-trifluorohexyl) oxy)phenyl)-6-(trifluoromethyl)-5,6-dihydropyridin-2(1*H*)-one	^{1}H NMR (500 MHz, CD_3OD) δ 7.62 (d, *J* = 8.80 Hz, 2H), 7.58 (d, *J* = 8.53 Hz, 1H), 7.34 (t, *J* = 7.70 Hz, 1H), 7.06 (t, *J* = 7.98 Hz, 1H), 7.03 (d, *J* = 8.25 Hz, 1H), 6.97 (d, *J* = 9.08 Hz, 2H), 4.91 (sept, J = 6.60 Hz, 1H), 4.19 (d, *J* = 17.61 Hz, 1H), 3.99 (t, *J* = 6.33 Hz, 2H), 3.88 (d, *J* = 17.61 Hz, 1H), 2.11-2.21 (m, 2H), 1.76-1.82 (m, 2H), 1.52-1.64 (m, 4H), 1.43 (d, *J* = 6.60 Hz, 6H). MS(ESI) *m/z*: 622.4 $(M+H)^+$.
34	 (*S*)-4-(1-Isopropyl-1*H*-indol-3-yl)-3-(1*H*-tetrazol-5-yl)-6-(4-((6,6,6-trifluorohexyl) oxy)phenyl)-6-(trifluoromethyl)-5,6-dihydropyridin-2(1*H*)-one	^{1}H NMR (500 MHz, CD_3OD) δ 7.59 (d, *J* = 8.80 Hz, 2H), 7.43 (d, *J* = 8.25 Hz, 1H), 7.40 (s, 1H), 7.14 (t, *J* = 7.43 Hz, 1H), 6.95 (d, *J* = 9.08 Hz, 2H), 6.94 (t, *J* = 6.33 Hz, 1H), 6.89 (d, *J* = 7.98 Hz, 1H), 4.70 (sept, *J* = 6.88 Hz, 1H), 3.98 (t, *J* = 6.33 Hz, 2H), 3.89 (d, *J* = 17.33 Hz, 1H), 3.84 (d, *J* = 17.06 Hz, 1H), 2.11-2.21 (m, 2H), 1.76-1.82 (m, 2H), 1.52-1.65 (m, 4H), 1.45 (d, *J* = 6.60 Hz, 6H). MS(ESI) *m/z*: 621.3 $(M+H)^+$.

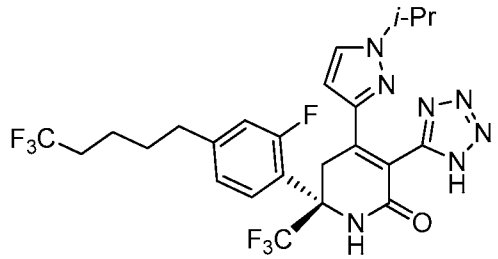
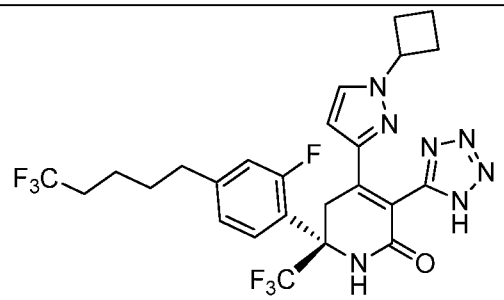
Example No.	Structure and Name	Analytical Data
35	 (*S*)-4-(5-(Dimethylamino)thiazol-2-yl)-3-(1*H*-tetrazol-5-yl)-6-(4-(4,4,4-trifluorobutoxy)phenyl)-6-(trifluoromethyl)-5,6-dihydropyridin-2(1*H*)-one	^{1}H NMR (500 MHz, DMSO-d$_6$) δ 9.35 (br. s., 1H), 7.52 (d, *J* = 8.5 Hz, 2H), 7.02 (d, *J* = 6.6 Hz, 2H), 7.00 (s, 1H), 4.22 (d, *J* = 17.1 Hz, 1H), 4.05 (t, *J* = 6.1 Hz, 2H), 3.48 (d, *J* = 17.1 Hz, 1H), 2.84 (s, 6H), 2.44 - 2.33 (m, 2H), 1.98 - 1.88 (m, 2H). MS(ESI) *m/z*: 562.2 (M+H)$^+$.
36	 (*S*)-5-Methyl-3′-(1*H*-tetrazol-5-yl)-6′-(4-(4,4,4-trifluorobutoxy)phenyl)-6′-(trifluoromethyl)-5′,6′-dihydro-[2,4′-bipyridin]-2′(1′*H*)-one	^{1}H NMR (500 MHz, DMSO-d$_6$) δ 9.68 (s, 1H), 8.34 (s, 1H), 7.63 (d, *J* = 8.5 Hz, 2H), 7.50 (d, *J* = 8.0 Hz, 1H), 7.02 (d, *J* = 8.8 Hz, 2H), 6.91 (d, *J* = 7.4 Hz, 1H), 4.06 (t, *J* = 6.1 Hz, 2H), 3.95 - 3.84 (m, 1H), 3.69 (d, *J* = 17.9 Hz, 1H), 2.45 - 2.34 (m, 2H), 2.26 (s, 3H), 1.99 - 1.86 (m, 2H). MS(ESI) *m/z*: 527.2 (M+H)$^+$.
37	 (*S*)-5-Methyl-3′-(1*H*-tetrazol-5-yl)-6′-(4-(4,4,4-trifluorobutoxy)phenyl)-6′-(trifluoromethyl)-5′,6′-dihydro-[2,4′-bipyridin]-2′(1′*H*)-one	^{1}H NMR (500 MHz, DMSO-d$_6$) δ 9.58 (br. s., 1H), 8.35 (s, 1H), 7.62 (d, *J* = 8.5 Hz, 2H), 7.44 (d, *J* = 8.0 Hz, 1H), 7.01 (d, *J* = 8.5 Hz, 2H), 6.81 (d, *J* = 8.0 Hz, 1H), 4.06 (t, *J* = 6.1 Hz, 2H), 3.94 - 3.83 (m, 1H), 3.65 (d, *J* = 18.2 Hz, 1H), 2.46 - 2.33 (m, 2H), 2.25 (s, 3H), 2.01 - 1.84 (m, 2H). MS(ESI) *m/z*: 527.2 (M+H)$^+$.

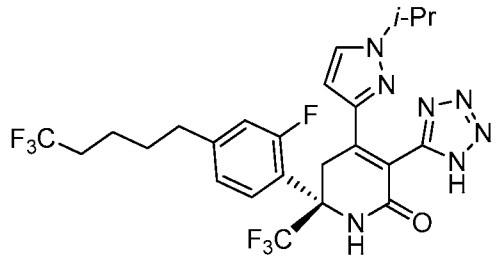
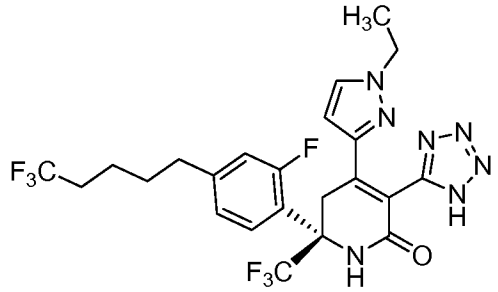
Example No.	Structure and Name	Analytical Data
38	 (*S*)-4-(5-Methylpyrimidin-2-yl)-3-(1*H*-tetrazol-5-yl)-6-(4-(4,4,4-trifluorobutoxy) phenyl)-6-(trifluoromethyl)-5,6-dihydropyridin-2(1*H*)-one	^{1}H NMR (500 MHz, $CDCl_3$) δ 8.63 (d, *J* = 0.8 Hz, 2H), 7.55 (d, *J* = 8.8 Hz, 2H), 6.98 - 6.88 (m, 2H), 6.72 (s, 1H), 4.10 (d, *J* = 19.0 Hz, 1H), 4.02 (t, *J* = 6.1 Hz, 2H), 3.77 (d, *J* = 18.7 Hz, 1H), 2.39 (s, 3H), 2.36 - 2.23 (m, 2H), 2.10 - 2.02 (m, 2H). MS(ESI) *m/z*: 528.1 $(M+H)^+$.
39	 (*S*)-6-(2-Fluoro-4-(4,4,4-trifluorobutoxy) phenyl)-4-(1-isopropyl-1*H*-pyrazol-3-yl)-3-(1*H*-tetrazol-5-yl)-6-(trifluoromethyl)-5,6-dihydropyridin-2(1*H*)-one	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.52 (s, 1H), 7.72 (d, *J* = 2.1 Hz, 1H), 7.57 (t, *J* = 9.2 Hz, 1H), 6.97 - 6.87 (m, 2H), 5.44 (s, 1H), 4.50 - 4.40 (m, 1H), 4.30 (d, *J* = 17.4 Hz, 1H), 4.10 (t, *J* = 6.1 Hz, 2H), 3.57 (d, *J* = 17.7 Hz, 1H), 2.49 - 2.35 (m, 2H), 2.01 - 1.87 (m, 2H), 1.31 (t, *J* = 6.9 Hz, 6H). MS(ESI) *m/z*: 562.2 $(M+H)^+$.

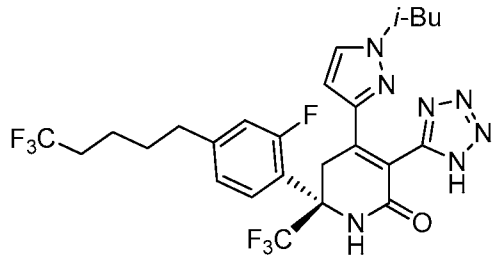
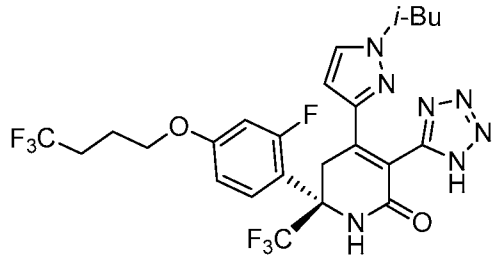
Example No.	Structure and Name	Analytical Data
40	 (*S*)-4-(1-Cyclobutyl-1*H*-pyrazol-3-yl)-6-(2-fluoro-4-(4,4,4-trifluorobutoxy)phenyl)-3-(1*H*-tetrazol-5-yl)-6-(trifluoromethyl)-5,6-dihydropyridin-2(1*H*)-one	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.54 (br. s., 1H), 7.96 (s, 1H), 7.74 (br. s., 1H), 7.57 (t, *J* = 9.0 Hz, 1H), 6.99 - 6.87 (m, 2H), 5.46 (br. s., 1H), 4.78 (quin, *J* = 8.2 Hz, 1H), 4.30 (d, *J* = 17.4 Hz, 1H), 4.09 (t, *J* = 5.5 Hz, 2H), 3.58 (d, *J* = 17.4 Hz, 1H), 2.48 - 2.36 (m, 2H), 2.35 - 2.22 (m, 4H), 2.01 - 1.88 (m, 2H), 1.81 - 1.68 (m, 2H). MS(ESI) *m/z*: 574.2 $(M+H)^+$.
41	 (*S*)-4-(1-Cyclopropyl-1*H*-pyrazol-3-yl)-6-(2-fluoro-4-(4,4,4-trifluorobutoxy)phenyl)-3-(1*H*-tetrazol-5-yl)-6-(trifluoromethyl)-5,6-dihydropyridin-2(1*H*)-one	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.33 (br. s., 1H), 7.64 (s, 1H), 7.54 (t, *J* = 9.2 Hz, 1H), 6.93 - 6.86 (m, 2H), 5.13 (br. s., 1H), 4.25 (d, *J* =17.4 Hz, 1H), 4.08 (t, *J* = 5.8 Hz, 2H), 3.76 - 3.68 (m, 1H), 3.49 (d, *J* = 17.7 Hz, 1H), 2.47 - 2.31 (m, 2H), 1.99 - 1.86 (m, 2H), 0.98 - 0.85 (m, 4H). MS(ESI) *m/z*: 560.3 $(M+H)^+$.

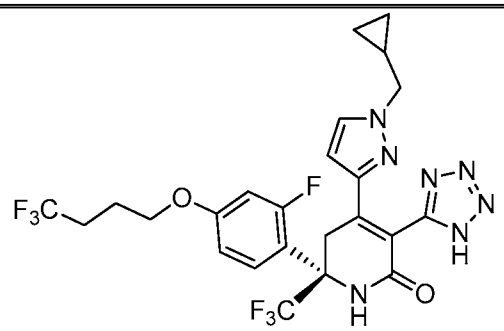
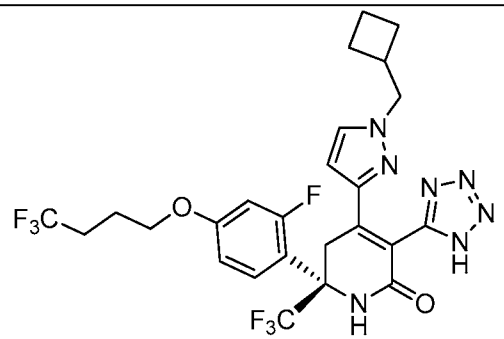
Example No.	Structure and Name	Analytical Data
42	 (*S*)-4-(1-(Cyclopropylmethyl)-1*H*-pyrazol-3-yl)-6-(2-fluoro-4-(5,5,5-trifluoropentyl) phenyl)-3-(1*H*-tetrazol-5-yl)-6-(trifluoromethyl)-5,6-dihydropyridin-2(1*H*)-one	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.52 (s, 1H), 7.70 (d, *J* = 2.5 Hz, 1H), 7.58 (t, *J* = 8.7 Hz, 1H), 7.21 - 7.09 (m, 2H), 5.21 (d, *J* = 1.9 Hz, 1H), 4.31 (d, *J* = 17.6 Hz, 1H), 4.01 - 3.83 (m, 2H), 3.62 (d, *J* = 17.6 Hz, 1H), 2.64 (t, *J* = 7.7 Hz, 2H), 2.36 - 2.18 (m, 2H), 1.72 - 1.61 (m, 2H), 1.57 - 1.41 (m, 2H), 1.20 - 1.06 (m, 1H), 0.53 - 0.44 (m, 2H), 0.37 - 0.28 (m, 2H). MS(ESI) *m/z*: 572.4 $(M+H)^+$.
43	 (*S*)-4-(1-Ethyl-1*H*-pyrazol-3-yl)-6-(2-fluoro-4-(4,4,4-trifluorobutoxy)phenyl)-3-(1*H*-tetrazol-5-yl)-6-(trifluoromethyl)-5,6-dihydropyridin-2(1*H*)-one	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.45 (s, 1H), 7.60 (s, 1H), 7.49 (t, *J* = 9.2 Hz, 1H), 6.85 (d, J = 11.6 Hz, 2H), 5.17 (br. s., 1H), 4.22 (d, *J* = 17.4 Hz, 2H), 4.06 - 3.98 (m, 4H), 3.51 (d, *J* = 17.7 Hz, 1H), 2.40 - 2.25 (m, 2H), 1.93 - 1.80 (m, 2H), 1.22 (t, *J* = 7.2 Hz, 3H). MS(ESI) *m/z*: 548.1 $(M+H)^+$.

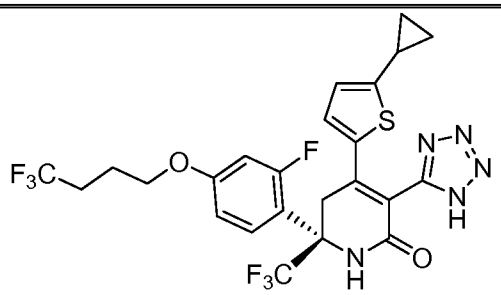
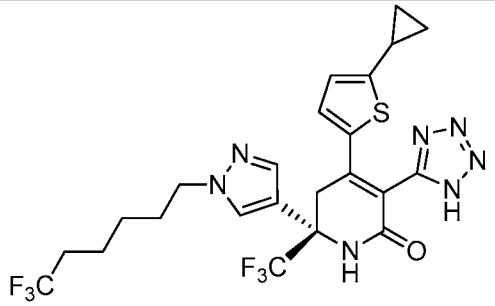
Example No.	Structure and Name	Analytical Data
44	 (*S*)-4-(5-Cyclopropylthiophen-2-yl)-3-(1*H*-tetrazol-5-yl)-6-(trifluoromethyl)-6-(4-((5,5,5-trifluoropentyl)oxy)phenyl)-5,6-dihydropyridin-2(1*H*)-one	^{1}H NMR (500 MHz, DMSO-d_6) δ 7.62 (d, *J* = 8.4 Hz, 2H), 7.49 (d, *J* = 3.4 Hz, 1H), 6.99 (d, *J* = 8.8 Hz, 2H), 6.74 (d, *J* = 3.7 Hz, 1H), 4.02 (t, *J* = 6.1 Hz, 2H), 3.94 - 3.79 (m, 1H), 3.62 - 3.46 (m, 1H), 2.40 - 2.24 (m, 2H), 2.02 - 1.91 (m, 1H), 1.83 - 1.77 (m, 2H), 1.66 - 1.57 (m, 2H), 0.98 - 0.88 (m, 2H), 0.59 - 0.44 (m, 2H). MS(ESI) *m/z*: 572.1 $(M+H)^+$.
45	 (*S*)-4-(5-(Dimethylamino)thiazol-2-yl)-3-(1*H*-tetrazol-5-yl)-6-(trifluoromethyl)-6-(4-((5,5,5-trifluoropentyl)oxy)phenyl)-5,6-dihydropyridin-2(1*H*)-one	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.44 (br. s., 1H), 7.48 (d, *J* = 8.2 Hz, 2H), 7.05 (s, 1H), 6.97 (d, *J* = 8.2 Hz, 2H), 4.21 (d, *J* = 17.1 Hz, 1H), 3.98 (t, *J* = 6.0 Hz, 2H), 3.51 (d, *J* = 17.1 Hz, 1H), 2.84 (s, 6H), 2.32 - 2.14 (m, 2H), 1.84 - 1.69 (m, 2H), 1.67 - 1.53 (m, 2H). MS(ESI) *m/z*: 576.1 $(M+H)^+$.

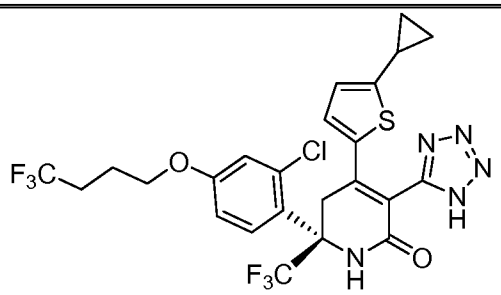
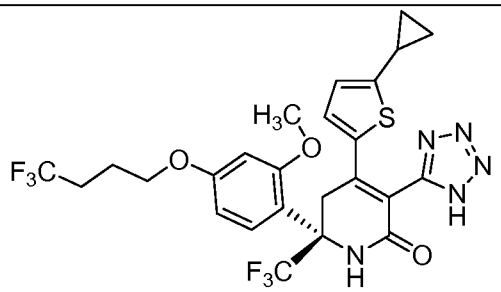
Example No.	Structure and Name	Analytical Data
46	 (*S*)-6-(2-Fluoro-4-(5,5,5-trifluoropentyl) phenyl)-4-(1-isopropyl-1*H*-pyrazol-3-yl)-3-(1*H*-tetrazol-5-yl)-6-(trifluoromethyl)-5,6-dihydropyridin-2(1*H*)-one	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.58 (br. s., 1H), 7.76 (br. s., 1H), 7.63 (br. t, *J* = 7.3 Hz, 1H), 7.27 - 7.18 (m, 2H), 5.50 (br. s., 1H), 4.56 - 4.43 (m, 1H), 4.35 (d, *J* = 17.7 Hz, 1H), 3.67 (d, *J* = 17.7 Hz, 1H), 2.71 (t, *J* = 6.6 Hz, 2H), 2.41 - 2.24 (m, 2H), 1.78 - 1.67 (m, 2H), 1.62 - 1.49 (m, 2H), 1.41 - 1.31 (m, 6H). MS(ESI) *m/z*: 560.6 $(M+H)^+$.
47	 (*S*)-4-(1-Cyclobutyl-1*H*-pyrazol-3-yl)-6-(2-fluoro-4-(5,5,5-trifluoropentyl)phenyl)-3-(1*H*-tetrazol-5-yl)-6-(trifluoromethyl)-5,6-dihydropyridin-2(1*H*)-one	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.57 (br. s., 1H), 7.74 (br. s., 1H), 7.58 (t, *J* = 8.4 Hz, 1H), 7.22 - 7.12 (m, 2H), 5.41 (br. s., 1H), 4.83 - 4.73 (m, 1H), 4.30 (d, *J* = 17.8 Hz, 1H), 3.61 (d, *J* = 17.5 Hz, 1H), 2.64 (t, *J* = 7.6 Hz, 2H), 2.35 - 2.19 (m, 6H), 1.78 - 1.71 (m, 2H), 1.70 - 1.61 (m, 2H), 1.55 - 1.45 (m, 2H). MS(ESI) *m/z*: 572.6 $(M+H)^+$.

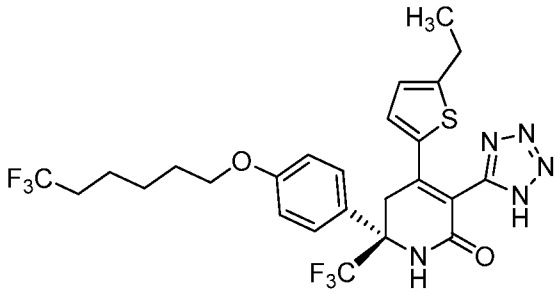
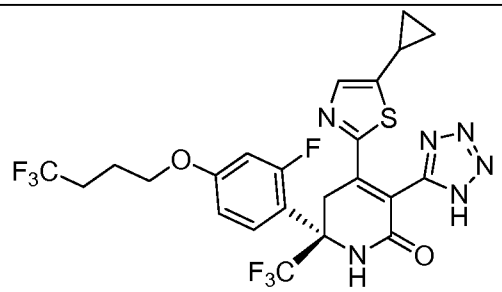
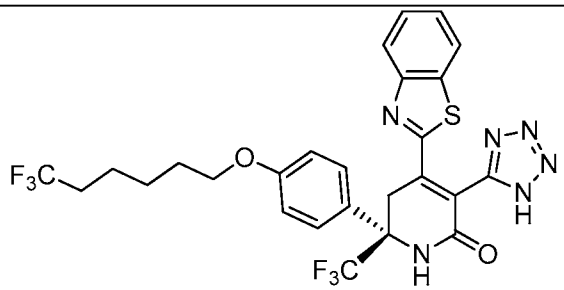
Example No.	Structure and Name	Analytical Data
48	 (*S*)-6-(2-Fluoro-4-(5,5,5-trifluoropentyl) phenyl)-4-(1-isopropyl-1*H*-pyrazol-3-yl)-3-(1*H*-tetrazol-5-yl)-6-(trifluoromethyl)-5,6-dihydropyridin-2(1*H*)-one	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.11 (br. s., 1H), 7.95 (s, 1H), 7.58 (t, *J* = 8.2 Hz, 1H), 7.20 - 7.11 (m, 2H), 7.07 (br. s., 1H), 6.74 (br. s., 1H), 4.87 (br. s., 1H), 4.25 - 4.14 (m, 1H), 3.97 (d, *J* =17.2 Hz, 1H), 3.44 (d, *J* = 17.2 Hz, 1H), 2.64 (t, J=7.6 Hz, 2H), 2.35 - 2.18 (m, 2H), 1.72 - 1.61 (m, 2H), 1.55 - 1.44 (m, 2H), 1.28 (d, *J* = 6.1 Hz, 6H). MS(ESI) *m/z*: 559.6 $(M+H)^+$.
49	 (*S*)-4-(1-Ethyl-1*H*-pyrazol-3-yl)-6-(2-fluoro-4-(5,5,5-trifluoropentyl)phenyl)-3-(1*H*-tetrazol-5-yl)-6-(trifluoromethyl)-5,6-dihydropyridin-2(1*H*)-one	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.57 (br. s., 1H), 7.95 (s, 1H), 7.68 (s, 1H), 7.57 (t, *J* = 5.7 Hz, 1H), 7.23 - 7.08 (m, 2H), 5.24 (s, 1H), 4.29 (d, *J* = 17.5 Hz, 1H), 4.16 - 4.01 (m, 2H), 3.62 (d, *J* = 17.2 Hz, 1H), 2.69 - 2.57 (m, 2H), 2.35 - 2.18 (m, 2H), 1.73 - 1.59 (m, 2H), 1.58 - 1.42 (m, 2H), 1.35 - 1.20 (m, 3H). MS(ESI) *m/z*: 546.6 $(M+H)^+$.

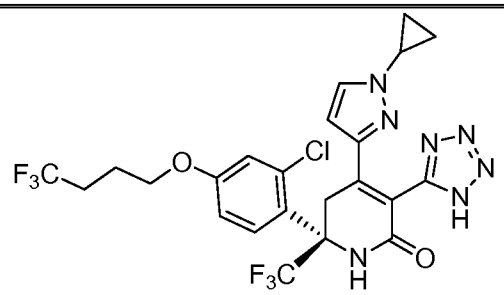
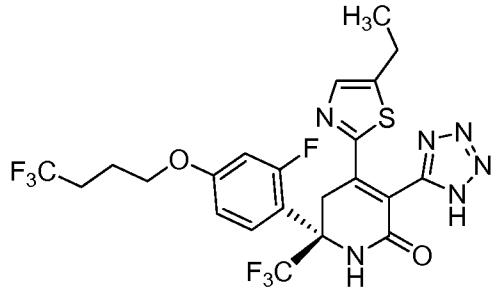
Example No.	Structure and Name	Analytical Data
50	 (*S*)-6-(2-Fluoro-4-(5,5,5-trifluoropentyl) phenyl)-4-(1-isobutyl-1*H*-pyrazol-3-yl)-3-(1*H*-tetrazol-5-yl)-6-(trifluoromethyl)-5,6-dihydropyridin-2(1*H*)-one	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.55 (s, 1H), 7.64 (s, 1H), 7.56 (t, J=8.4 Hz, 1H), 7.20 - 7.08 (m, 2H), 5.24 (s, 1H), 4.31 (d, J=17.4 Hz, 1H), 3.88 (d, J=7.0 Hz, 2H), 3.60 (d, J=17.7 Hz, 1H), 2.64 (t, J=7.5 Hz, 2H), 2.34 - 2.18 (m, 2H), 2.05 - 1.90 (m, 1H), 1.71 - 1.60 (m, 2H), 1.55 - 1.44 (m, 2H), 0.78 (d, J=6.4 Hz, 6H). MS(ESI) *m/z*: 574.5 $(M+H)^+$.
51	 (*S*)-6-(2-Fluoro-4-(4,4,4-trifluorobutoxy) phenyl)-4-(1-isobutyl-1*H*-pyrazol-3-yl)-3-(1*H*-tetrazol-5-yl)-6-(trifluoromethyl)-5,6-dihydropyridin-2(1*H*)-one	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.43 (s, 1H), 7.58 (d, J=1.8 Hz, 1H), 7.51 (t, J=9.3 Hz, 1H), 6.90 - 6.81 (m, 2H), 5.15 (s, 1H), 4.28 (d, J=17.1 Hz, 1H), 4.04 (t, J=6.0 Hz, 2H), 3.84 (d, J=6.7 Hz, 2H), 3.50 (d, J=17.4 Hz, 1H), 2.41 - 2.33 (m, 2H), 2.00 - 1.94 (m, 1H), 1.94 - 1.85 (m, 2H), 0.75 (d, J=6.4 Hz, 6H). MS(ESI) *m/z*: 576.5 $(M+H)^+$.

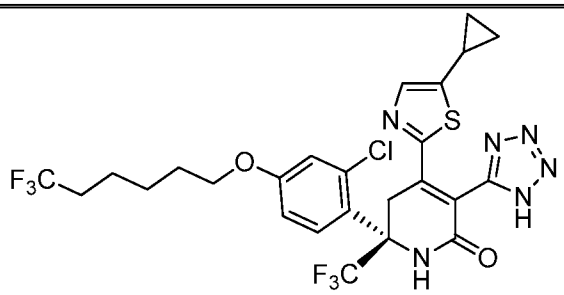
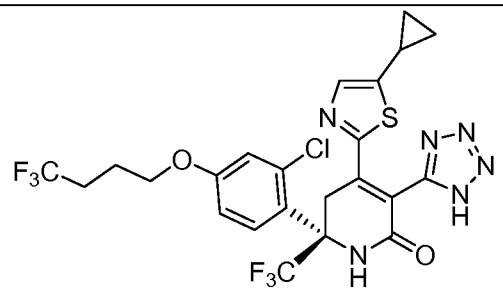
Example No.	Structure and Name	Analytical Data
52	 (*S*)-4-(1-(Cyclopropylmethyl)-1*H*-pyrazol-3-yl)-6-(2-fluoro-4-(4,4,4-trifluorobutoxy) phenyl)-3-(1*H*-tetrazol-5-yl)-6-(trifluoromethyl)-5,6-dihydropyridin-2(1*H*)-one	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.51 (s, 1H), 7.68 (d, *J* = 2.4 Hz, 1H), 7.53 (t, *J* = 9.2 Hz, 1H), 6.94 - 6.80 (m, 2H), 5.24 (d, *J* = 2.4 Hz, 1H), 4.30 (d, *J* = 17.7 Hz, 1H), 4.06 (t, *J* = 6.0 Hz, 2H), 3.97 - 3.83 (m, 2H), 3.57 (d, *J* = 17.1 Hz, 1H), 2.45 - 2.32 (m, 2H), 1.97 - 1.86 (m, 2H), 1.16 - 1.06 (m, 1H), 0.47 (d, *J* = 7.9 Hz, 2H), 0.33 - 0.23 (m, 2H). MS(ESI) *m/z*: 574.5 $(M+H)^+$.
53	 (*S*)-4-(1-(Cyclobutylmethyl)-1*H*-pyrazol-3-yl)-6-(2-fluoro-4-(4,4,4-trifluorobutoxy) phenyl)-3-(1*H*-tetrazol-5-yl)-6-(trifluoromethyl)-5,6-dihydropyridin-2(1*H*)-one	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.45 (s, 1H), 7.56 (d, *J* = 2.1 Hz, 1H), 7.47 (t, *J* = 9.2 Hz, 1H), 6.88 - 6.78 (m, 2H), 5.14 (d, *J* = 1.5 Hz, 1H), 4.24 (d, *J* = 17.7 Hz, 1H), 4.05 - 3.98 (m, 4H), 3.50 (d, *J* = 17.7 Hz, 1H), 2.60 - 2.51 (m, 1H), 2.40 - 2.27 (m, 2H), 1.91 - 1.81 (m, 4H), 1.80 - 1.69 (m, 2H), 1.67 - 1.56 (m, 2H). MS(ESI) *m/z*: 588.6 $(M+H)^+$.

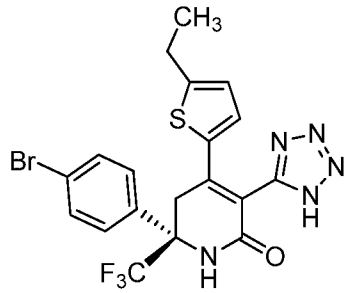
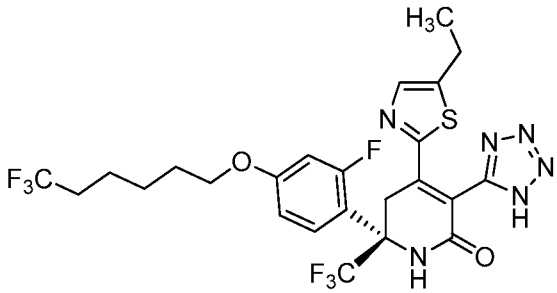
Example No.	Structure and Name	Analytical Data
54	 (*S*)-4-(5-Cyclopropylthiophen-2-yl)-6-(2-fluoro-4-(4,4,4-trifluorobutoxy)phenyl)-3-(1*H*-tetrazol-5-yl)-6-(trifluoromethyl)-5,6-dihydropyridin-2(1*H*)-one	^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 - 7.22 (m, 2H), 6.92 (br. s., 1H), 6.74 - 6.63 (m, 3H), 4.09 (d, *J* = 17.9 Hz, 1H), 4.00 (t, *J* = 5.9 Hz, 2H), 3.54 (d, *J* = 18.2 Hz, 1H), 2.36 - 2.23 (m, 2H), 2.10 - 1.97 (m, 3H), 1.12 - 1.04 (m, 2H), 0.80 - 0.73 (m, 2H). MS(ESI) *m/z*: 576.2 $(M+H)^+$.
55	 (*S*)-4-(5-Cyclopropylthiophen-2-yl)-3-(1*H*-tetrazol-5-yl)-6-(1-(6,6,6-trifluorohexyl)-1*H*-pyrazol-4-yl)-6-(trifluoromethyl)-5,6-dihydropyridin-2(1*H*)-one	^{1}H NMR (500 MHz, DMSO-d_6) δ 8.01 (s, 1H), 7.74 (s, 1H), 7.36 (d, *J* = 3.1 Hz, 1H), 6.73 (d, *J* = 3.7 Hz, 1H), 4.10 (t, *J* = 6.9 Hz, 2H), 3.62 (d, *J* = 17.7 Hz, 1H), 3.53 (d, *J* = 17.7 Hz, 1H), 2.27 - 2.11 (m, 2H), 2.01 - 1.93 (m, 1H), 1.83 - 1.73 (m, 2H), 1.52 - 1.39 (m, 2H), 1.34 - 1.20 (m, 2H), 0.95 (d, *J* = 6.1 Hz, 2H), 0.56 (d, *J* = 4.6 Hz, 2H). MS(ESI) *m/z*: 560.4 $(M+H)^+$.

Example No.	Structure and Name	Analytical Data
56	 (*S*)-6-(2-Chloro-4-(4,4,4-trifluorobutoxy) phenyl)-4-(5-cyclopropylthiophen-2-yl)-3-(1*H*-tetrazol-5-yl)-6-(trifluoromethyl)-5,6-dihydropyridin-2(1*H*)-one	^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (d, *J* = 8.8 Hz, 1H), 7.25 (d, *J* =3.9 Hz, 1H), 7.07 - 7.02 (m, 1H), 7.00 (d, *J* = 2.8 Hz, 1H), 6.88 - 6.81 (m, 1H), 6.74 - 6.68 (m, 1H), 4.27 - 4.15 (m, 1H), 4.03 (s, 2H), 3.57 (d, *J* = 18.4 Hz, 1H), 2.39 - 2.26 (m, 2H), 2.15 - 2.02 (m, 3H), 1.13 - 1.05 (m, 2H), 0.81 - 0.73 (m, 2H). MS(ESI) *m/z* 592.0 $(M+H)^+$.
57	 (*S*)-4-(5-Cyclopropylthiophen-2-yl)-6-(2-methoxy-4-(4,4,4-trifluorobutoxy)phenyl)-3-(1*H*-tetrazol-5-yl)-6-(trifluoromethyl)-5,6-dihydropyridin-2(1*H*)-one	^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 - 7.95 (m, 1H), 7.27 (d, J = 8.8 Hz, 1H), 7.21 (d, J = 3.9 Hz, 1H), 6.72 (d, J = 3.9 Hz, 1H), 6.56 (d, J = 2.5 Hz, 1H), 6.53 - 6.48 (m, 1H), 4.09 - 3.96 (m, 3H), 3.92 (s, 3H), 3.67 (s, 1H), 2.41 - 2.25 (m, 2H), 2.13 - 2.02 (m, 3H), 1.09 (dd, J = 8.3, 1.9 Hz, 2H), 0.83 - 0.75 (m, 2H). MS(ESI) *m/z*: 588.0 $(M+H)^+$.

Example No.	Structure and Name	Analytical Data
58	 (*S*)-4-(5-Ethylthiophen-2-yl)-3-(1*H*-tetrazol-5-yl)-6-(4-((6,6,6-trifluorohexyl) oxy)phenyl)-6-(trifluoromethyl)-5,6-dihydropyridin-2(1*H*)-one	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.44 (br. s., 1H), 7.56 (br. s., 3H), 6.96 (br. s., 2H), 6.82 (br. s., 1H), 3.95 (br. s., 2H), 2.97 (br. s., 1H), 2.60 (br. s., 2H), 2.19 (d, *J* = 10.1 Hz, 2H), 1.70 (br. s., 2H), 1.63 (br. s., 1H), 1.40-1.56 (m, 4H), 1.05 (br. s., 3H). MS(ESI) *m/z*: 574.2 $(M+H)^+$.
59	 (*S*)-4-(5-Cyclopropylthiazol-2-yl)-6-(2-fluoro-4-(4,4,4-trifluorobutoxy)phenyl)-3-(1*H*-tetrazol-5-yl)-6-(trifluoromethyl)-5,6-dihydropyridin-2(1*H*)-one	^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (s, 1H), 7.43 (t, *J* = 9.1 Hz, 1H), 6.73 - 6.56 (m, 2H), 4.58 (d, *J* = 18.2 Hz, 1H), 3.98 (t, *J* = 5.6 Hz, 2H), 3.68 (d, *J* = 18.2 Hz, 1H), 2.38 - 2.20 (m, 2H), 2.12 - 1.93 (m, 3H), 1.18 - 1.07 (m, 2H), 0.78 (br. s., 2H). MS(ESI) *m/z*: 577.1 $(M+H)^+$.
60	 (*S*)-4-(Benzo[d]thiazol-2-yl)-3-(1*H*-tetrazol-5-yl)-6-(4-((6,6,6-trifluorohexyl) oxy)phenyl)-6-(trifluoromethyl)-5,6-dihydropyridin-2(1*H*)-one	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.95 (s, 1H), 8.14 (d, J = 8.2 Hz, 1H), 8.05 (d, *J* = 7.9 Hz, 1H), 7.59 (d, *J* = 8.5 Hz, 3H), 7.46-7.54 (m, 1H), 7.02 (d, *J* = 8.5 Hz, 2H), 4.28 (d, *J* = 17.7 Hz, 1H), 3.86-4.08 (m, 3H), 2.17-2.32 (m, 2H), 1.66-1.81 (m, 2H), 1.40-1.62 (m, 4H). MS(ESI) *m/z*: 597.1 $(M+H)^+$.

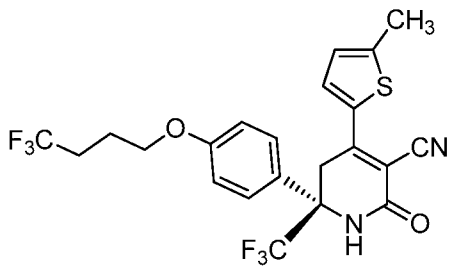
Example No.	Structure and Name	Analytical Data
61	 (*S*)-6-(2-Chloro-4-(4,4,4-trifluorobutoxy) phenyl)-4-(1-cyclopropyl-1H-pyrazol-3-yl)-3-(1*H*-tetrazol-5-yl)-6-(trifluoromethyl)-5,6-dihydropyridin-2(1*H*)-one	^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (d, *J* = 9.1 Hz, 1H), 7.43 (d, *J* = 2.5 Hz, 1H), 6.98 - 6.92 (m, 2H), 6.79 (dd, *J* = 9.1, 2.8 Hz, 1H), 6.42 (d, *J* = 2.5 Hz, 1H), 4.56 (d, *J* = 19.0 Hz, 1H), 4.00 (t, *J* = 5.9 Hz, 2H), 3.66 (dt, *J* = 7.4, 3.6 Hz, 1H), 3.55 (d, *J* = 18.7 Hz, 1H), 2.36 - 2.21 (m, 2H), 2.10 - 2.02 (m, 2H), 1.23 - 1.16 (m, 2H), 1.13 - 1.06 (m, 2H). MS(ESI) *m/z*: 576.0 $(M+H)^+$.
62	 (*S*)-4-(5-Ethylthiazol-2-yl)-6-(2-fluoro-4-(4,4,4-trifluorobutoxy)phenyl)-3-(1*H*-tetrazol-5-yl)-6-(trifluoromethyl)-5,6-dihydropyridin-2(1*H*)-one	^{1}H NMR (400 MHz, CD_3OD) δ 7.73 - 7.67 (m, 1H), 7.55 (t, *J* = 9.2 Hz, 1H), 6.90 - 6.80 (m, 2H), 4.60 (dd, *J* = 17.6, 1.3 Hz, 1H), 4.10 (t, *J* = 6.1 Hz, 2H), 3.75 (d, *J* = 17.7 Hz, 1H), 2.85 (q, *J* = 7.5, 1.0 Hz, 2H), 2.45 - 2.30 (m, 2H), 2.10 - 2.01 (m, 2H), 1.25 (t, *J* = 7.5 Hz, 3H). MS(ESI) *m/z*: 565.3 $(M+H)^+$.

Example No.	Structure and Name	Analytical Data
63	 (*S*)-6-(2-Chloro-4-((6,6,6-trifluorohexyl) oxy)phenyl)-4-(5-cyclopropylthiazol-2-yl)-3-(1*H*-tetrazol-5-yl)-6-(trifluoromethyl)-5,6-dihydropyridin-2(1*H*)-one	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.36 (br. s., 1H), 7.67 (s, 1H), 7.53 (d, *J* = 8.5 Hz, 1H), 7.14 (br. s., 1H), 7.01 (d, *J* = 9.2 Hz, 1H), 4.27 (d, *J* = 18.6 Hz, 1H), 4.03 (br. s., 2H), 3.72 (d, *J* = 19.2 Hz, 1H), 2.25 (br. s., 2H), 2.07 (br. s., 1H), 1.74 (br. s., 2H), 1.60 - 1.39 (m, 4H), 1.00 (d, *J* = 7.3 Hz, 2H), 0.61 (br. s., 2H). MS(ESI) *m/z*: 621.1 $(M+H)^+$.
64	 (*S*)-6-(2-Chloro-4-(4,4,4-trifluorobutoxy) phenyl)-4-(5-cyclopropylthiazol-2-yl)-3-(1*H*-tetrazol-5-yl)-6-(trifluoromethyl)-5,6-dihydropyridin-2(1*H*)-one	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.54 (s, 1H), 7.72 (s, 1H), 7.54 (d, *J* = 8.5 Hz, 1H), 7.25 - 7.13 (m, 1H), 7.10 - 6.96 (m, 1H), 4.24 (d, *J* = 18.9 Hz, 1H), 4.10 (t, *J* = 6.1 Hz, 2H), 3.78 (d, *J* = 19.2 Hz, 1H), 2.42 (dd, *J* = 16.3, 11.4 Hz, 2H), 2.17 - 2.05 (m, 1H), 1.98 - 1.82 (m, 2H), 1.13 - 0.89 (m, 2H), 0.69 - 0.55 (m, 2H). MS(ESI) *m/z*: 593.0 $(M+H)^+$.

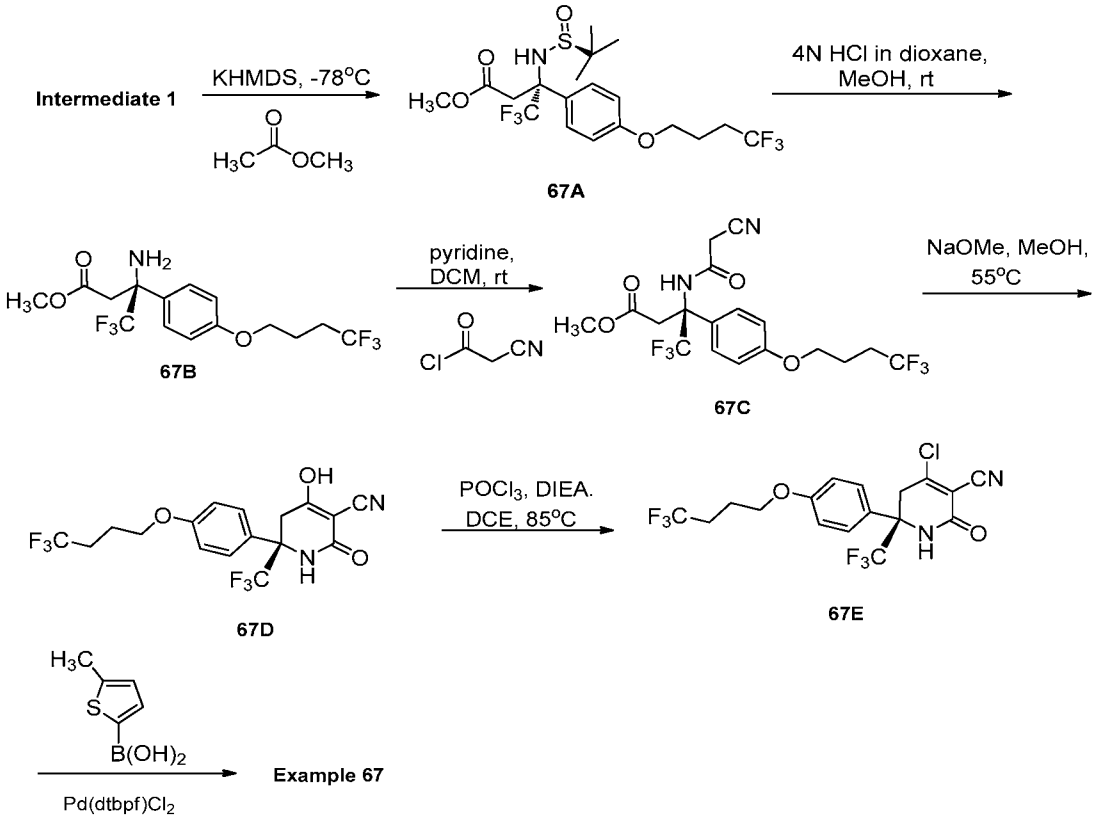
Example No.	Structure and Name	Analytical Data
65	 (*S*)-6-(4-Bromophenyl)-4-(5-ethylthiophen-2-yl)-3-(1*H*-tetrazol-5-yl)-6-(trifluoromethyl)-5,6-dihydropyridin-2(1*H*)-one	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.64 (s, 2H), 6.89 (d, *J* = 4.1 Hz, 2H), 3.98 (d, *J* = 17.2 Hz, 1H), 3.68 (d, *J* = 17.5 Hz, 1H), 2.66 (q, *J* = 7.5 Hz, 2H), 1.08 (t, *J* = 7.5 Hz, 3H). MS(ESI) *m/z*: 500.2 $(M+H)^+$.
66	 (*S*)-4-(5-Ethylthiazol-2-yl)-6-(2-fluoro-4-((6,6,6-trifluorohexyl)oxy)phenyl)-3-(1*H*-tetrazol-5-yl)-6-(trifluoromethyl)-5,6-dihydropyridin-2(1*H*)-one	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.81 (s, 1H), 7.77 (s, 1H), 7.50 (t, *J* = 9.2 Hz, 1H), 6.99 - 6.79 (m, 2H), 4.45 (d, *J* = 17.6 Hz, 1H), 3.99 (t, *J* = 6.4 Hz, 2H), 3.72 (d, *J* = 17.9 Hz, 1H), 2.76 (q, *J* = 7.4 Hz, 2H), 2.32 - 2.15 (m, 2H), 1.79 - 1.65 (m, 2H), 1.57 - 1.37 (m, 4H), 1.11 (t, *J* = 7.4 Hz, 3H). MS(ESI) *m/z*: 593.3 $(M+H)^+$.

Example 67

(*S*)-4-(5-Methylthiophen-2-yl)-2-oxo-6-(4-(4,4,4-trifluorobutoxy)phenyl)-6-(trifluoromethyl)-1,2,5,6-tetrahydropyridine-3-carbonitrile



Synthetic Scheme 2



67A. (*R*)-Methyl 3-((*S*)-1,1-dimethylethylsulfinamido)-4,4,4-trifluoro-3-(4-(4,4,4-trifluorobutoxy)phenyl)butanoate: To a solution of methyl acetate (3.54 g, 47.8 mmol) in ether (335 mL) was added KHMDS in THF (35.8 mL, 35.8 mmol) dropwise over 10 min at -78 °C. The reaction mixture was stirred at -78 °C for 30 min. At -78 °C, a solution of Intermediate 1 (9.64 g, 23.90 mmol) in ether (335 mL) was added dropwise over 20 min. and the reaction mixture was stirred at -78 °C for 1 h. The reaction mixture was quenched with sat. aq. NaCl (400 mL). The reaction mixture was diluted with ether (400 mL) and sat. aq. NaCl (400 mL). The organic phase was dried over $MgSO_4$ and concentrated to a yellow oil that was purified by chromatography to give the desired product as a clear oil (9.8873 g, 87% yield). LCMS Anal. Calc'd for $C_{19}H_{25}F_6NO_4S$ 477.14, found [M+H] 478.2.

67B. (*S*)-Methyl 3-amino-4,4,4-trifluoro-3-(4-(4,4,4-trifluorobutoxy)phenyl) butanoate: To a solution of 67A (9.3151 g, 19.51 mmol) in MeOH (230 mL) was added HCl in dioxane (24.39 mL, 98 mmol) and the reaction mixture was stirred at rt for 1 h. The reaction solvent was removed under vacuum, the residue was dissolved in EtOAc (30

mL) and the solution was washed with sat. aq. $NaHCO_3$ (20 mL). The organic phase was dried over $MgSO_4$ and concentrated *in vacuo* to give the desired product as pale yellow oil (7.7 g, 105% yield). LCMS Anal. Calc'd for $C_{15}H_{17}F_6NO_3$ 373.11, found [M+H] 374.0.

67C. (*S*)-Methyl 3-(2-cyanoacetamido)-4,4,4-trifluoro-3-(4-(4,4,4-trifluorobutoxy)phenyl)butanoate: To a solution of 2-cyanoacetyl chloride (7.25 g, 19.42 mmol) in DCM (400 mL) was added pyridine (9.42 mL, 117 mmol) followed by a solution of 67B (8.04 g, 78 mmol) in DCM (100 mL). The reaction mixture was stirred at rt for 1 h. The reaction solvent was removed under vacuum, the residue was dissolved in EtOAc (2 x 60 mL) and the solution was washed with sat. aq. NH_4Cl (50 mL). The organic phase was dried over $MgSO_4$ and concentrated. The residue was purified by chromatography to give the desired product as a pale yellow oil (7.03 g, 82% yield). LCMS Anal. Calc'd for $C_{18}H_{18}F_6N_2O_4$ 440.12, found [M+H] 441.0.

67D. (*S*)-4-Hydroxy-2-oxo-6-(4-(4,4,4-trifluorobutoxy)phenyl)-6-(trifluoromethyl)-1,2,5,6-tetrahydropyridine-3-carbonitrile: To a solution of 67C (7.0257 g, 15.96 mmol) in MeOH (200 mL) was added sodium methoxide (18.26 mL, 80 mmol) and the reaction mixture was stirred at 55 °C for 2h. The reaction solvent was removed under vacuum, the residue was dissolved in EtOAc (100 mL) and the solution was washed with 1N HCl (100 mL). The organic phase was dried over $MgSO_4$ and concentrated *in vacuo* to give the desired product as a yellow solid (6.966, 107% yield). LCMS Anal. Calc'd for $C_{17}H_{14}F_6N_2O_3$ 408.09, found [M+H] 409.0.

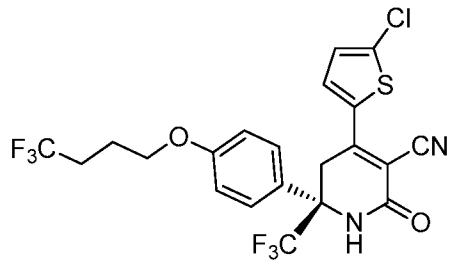
67E. (*S*)-4-Chloro-2-oxo-6-(4-(4,4,4-trifluorobutoxy)phenyl)-6-(trifluoromethyl)-1,2,5,6-tetrahydropyridine-3-carbonitrile: To a solution of 67D (5.47 g, 13.40 mmol) in DCE (550 mL) was added $POCl_3$ (1.499 mL, 16.08 mmol) and DIEA (3.28 mL, 18.76 mmol) and the reaction mixture was stirred at rt for 30 min. and heated to 85 °C for 3h. The reaction mixture was concentrated *in vacuo* to a yellow oil that was dissolved in EtOAc (100 mL), washed with sat. aq. NH_4Cl (50 mL), dried over $MgSO_4$ and concentrated. The residue was purified by chromatography to give the desired product as a yellow solid (3.7334 g, 65.3% yield). LCMS Anal. Calc'd for $C_{17}H_{13}F_6ClN_2O_2$ 426.06, found [M+H] 427.0.

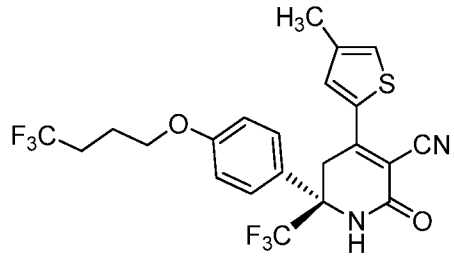
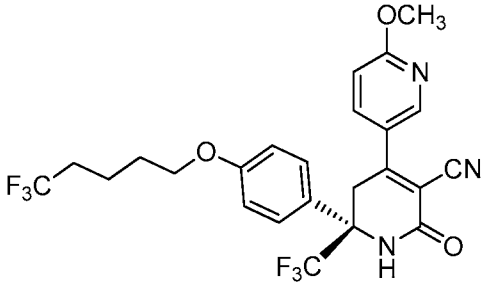
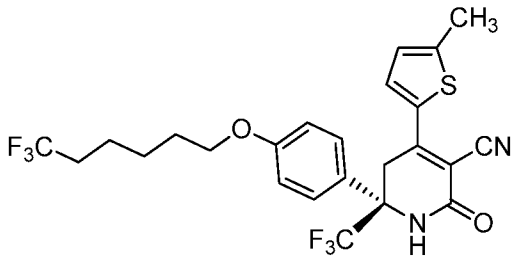
Example 67: To a vial was added 1,1′-bis(di-*tert*-butylphosphino)ferrocene palladium dichloride (4.58 mg, 7.03 μmol), CsF (21.36 mg, 0.141 mmol), dioxane (0.499

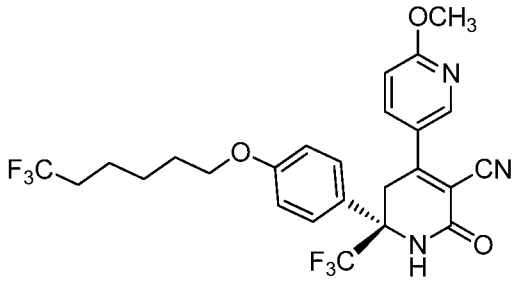
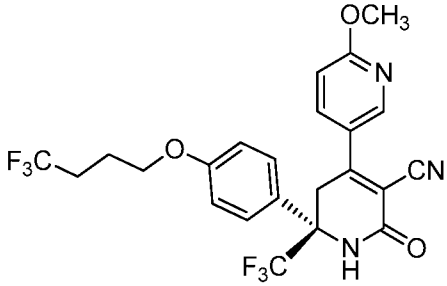
mL), (5-methylthiophen-2-yl)boronic acid (10 mg, 0.0709 mmol) and 67E (20 mg, 0,0937 mmol). The reaction mixture stirred at 80 °C in a sealed vial for 1.5 h. The solvent was removed *in vacuo*. The residue was purified by prep HPLC to yield Example 28 (1.1 mg, 0.002 mmol, 3.2% yield). LCMS Anal. Calc'd for $C_{22}H_{18}F_6N_2O_2S$ 488.10, found [M+H] 488.8. ^{1}H NMR (500 MHz, 1:1 $CDCl_3$:MeOD) δ 7.94 (d, *J* = 4.0 Hz, 1H), 7.45 (d, *J* = 8.9 Hz, 2H), 7.03 - 6.96 (m, 1H), 6.94 (d, *J* = 8.9 Hz, 2H), 4.03 (t, *J* = 5.9 Hz, 2H), 3.79 (d, *J* = 16.8 Hz, 1H), 3.56 (d, *J* = 17.3 Hz, 1H), 2.62 - 2.58 (m, 3H), 2.40 - 2.23 (m, 2H), 2.08 - 1.98 (m, 2H).

The following Examples in Table 3 were prepared in a similar manner as Example 67 utilizing Intermediate 1, 2, 4 and different commercially available heterocyclic boronic acids.

Table 3

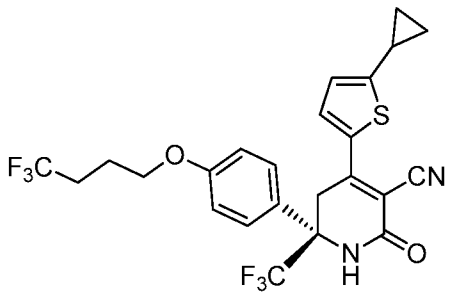
Example No.	Structure and Name	Analytical Data
68	 (S)-4-(5-Chlorothiophen-2-yl)-2-oxo-6-(4-(4,4,4-trifluorobutoxy)phenyl)-6-(trifluoromethyl)-1,2,5,6-tetrahydropyridine-3-carbonitrile	^{1}H NMR (500 MHz, 1:1 $CDCl_3$: MeOD) δ 7.95 - 7.87 (m, 1H), 7.48 - 7.42 (m, 2H), 7.18 - 7.12 (m, 1H), 6.96 - 6.88 (m, 2H), 4.11 - 3.98 (m, 2H), 3.81 - 3.70 (m, 1H), 3.56 (d, *J* = 17.3 Hz, 1H), 2.42 - 2.21 (m, 2H), 2.12 - 1.96 (m, 2H). MS(ESI) *m/z*: 509.4 $(M+H)^+$.

Example No.	Structure and Name	Analytical Data
69	 (S)-4-(4-Methylthiophen-2-yl)-2-oxo-6-(4-(4,4,4-trifluorobutoxy)phenyl)-6-(trifluoromethyl)-1,2,5,6-tetrahydropyridine-3-carbonitrile	^{1}H NMR (500 MHz, 1:1 $CDCl_3$: MeOD) δ 7.95 - 7.88 (m, 1H), 7.52 - 7.38 (m, 3H), 6.98 - 6.88 (m, 2H), 4.09 - 3.98 (m, 2H), 3.81 - 3.71 (m, 1H), 3.58 (d, *J* = 17.3 Hz, 1H), 2.42 - 2.24 (m, 5H), 2.09 - 1.97 (m, 2H). MS(ESI) *m/z*: 489.11 $(M+H)^+$.
70	 (S)-6-Methoxy-2′-oxo-6′-(trifluoromethyl)-6′-(4-((5,5,5-trifluoropentyl)oxy)phenyl)-1′,2′,5′,6′-tetrahydro-[3,4′-bipyridine]-3′-carbonitrile	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.82 (s, 1H), 8.65 - 8.44 (m, 1H), 8.03 (dd, *J* = 8.9, 2.7 Hz, 1H), 7.61 (d, *J* = 8.5 Hz, 2H), 7.01 (d, *J* = 8.5 Hz, 3H), 4.02 (t, *J* = 6.4 Hz, 2H), 3.94 (s, 3H), 3.88 (s, 1H), 3.73 (d, *J* = 18.3 Hz, 1H), 2.40 - 2.26 (m, 2H), 1.84 - 1.72 (m, 2H), 1.64 (d, *J* = 7.3 Hz, 2H). MS(ESI) *m/z*: 514.2 $(M+H)^+$.
71	 (S)-4-(5-Methylthiophen-2-yl)-2-oxo-6-(4-((6,6,6-trifluorohexyl)oxy)phenyl)-6-(trifluoromethyl)-1,2,5,6-tetrahydropyridine-3-carbonitrile	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.73 (s, 1H), 8.16 (d, *J* = 3.7 Hz, 1H), 7.54 (d, *J* = 8.8 Hz, 2H), 7.16 - 7.04 (m, 1H), 6.97 (d, *J* = 9.1 Hz, 2H), 3.97 (s, 2H), 3.68 - 3.62 (m, 1H), 3.48 - 3.35 (m, 1H), 2.56 (s, 3H), 2.32 - 2.14 (m, 2H), 1.79 - 1.63 (m, 2H), 1.58 - 1.36 (m, 4H). MS(ESI) *m/z*: 517.1 $(M+H)^+$.

Example No.	Structure and Name	Analytical Data
72	 (S)-6-Methoxy-2′-oxo-6′-(4-((6,6,6-trifluorohexyl)oxy)phenyl)-6′-(trifluoromethyl)-1′,2′,5′,6′-tetrahydro-[3,4′-bipyridine]-3′-carbonitrile	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.78 (s, 1H), 8.53 (d, *J* = 2.2 Hz, 1H), 8.04 (dd, *J* = 8.8, 2.6 Hz, 1H), 7.61 (d, *J* = 8.8 Hz, 2H), 7.00 (dd, *J* = 8.9, 2.8 Hz, 3H), 4.00 (t, *J* = 6.4 Hz, 2H), 3.94 (s, 3H), 3.87 - 3.84 (m, 1H), 3.73 (d, *J* = 18.3 Hz, 1H), 2.35 - 2.17 (m, 2H), 1.74 (quin, *J* = 6.7 Hz, 2H), 1.62 - 1.41 (m, 4H).
73	 (S)-6-Methoxy-2′-oxo-6′-(4-(4,4,4-trifluorobutoxy)phenyl)-6′-(trifluoromethyl)-1′,2′,5′,6′-tetrahydro-[3,4′-bipyridine]-3′-carbonitrile	^{1}H NMR (500 MHz, 1:1 $CDCl_3$: MeOD) δ 8.44 (d, *J* = 2.5 Hz, 1H), 7.90 (dd, *J* = 8.7, 2.7 Hz, 1H), 7.48 (d, *J* = 8.9 Hz, 2H), 6.97 (d, *J* = 8.9 Hz, 2H), 6.90 (d, *J* = 8.9 Hz, 1H), 4.06 (t, *J* = 5.9 Hz, 2H), 3.99 (s, 3H), 3.97 - 3.88 (m, 1H), 3.63 (d, *J* = 8.4 Hz, 1H), 2.33 (d, *J* = 5.0 Hz, 2H), 2.11 - 1.99 (m, 2H).

Example 74

(*S*)-4-(5-Cyclopropylthiophen-2-yl)-2-oxo-6-(4-(4,4,4-trifluorobutoxy)phenyl)-6-(trifluoromethyl)-1,2,5,6-tetrahydropyridine-3-carbonitrile

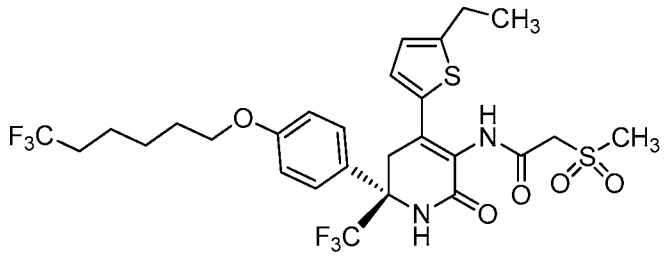


To a solution of Example 2B (30.0 mg, 0.064 mmol) and N,N′-methanediylidenedicyclohexanamine (39.9 mg, 0.193 mmol) in THF (0.555 mL) was

added a solution of 2-cyanoacetic acid (16.45 mg, 0.193 mmol) in THF (0.555 mL) and the reaction mixture stirred at rt under argon for 2 h. The solvent was removed *in vacuo* and the residue was taken up in EtOAc (10 mL). The solution was washed with water (1x10 mL) followed by sat. Na_2CO_3 (2 x10 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated. Purification by Prep HPLC afforded Example 35 (9.9 mg, 28%). LCMS Anal. Calc'd for $C_{24}H_{20}F_6N_2O_2S$ 514.11, found [M+H] 515.1. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.67 (s, 1H), 8.15 (d, *J* = 4.1 Hz, 1H), 7.55 (d, *J* = 8.8 Hz, 2H), 7.05 (d, *J* = 4.1 Hz, 1H), 6.98 (d, *J* = 8.8 Hz, 2H), 4.03 (t, *J* = 6.2 Hz, 2H), 3.98 (d, *J* = 17.6 Hz, 1H), 3.62 (d, *J* = 17.3 Hz, 1H), 2.45 - 2.33 (m, 2H), 2.31 - 2.23 (m, 1H), 1.94 - 1.79 (m, 2H), 1.23 - 1.11 (m, 2H), 0.87 - 0.77 (m, 2H).

Example 75

(*S*)-*N*-(4-(5-Ethylthiophen-2-yl)-2-oxo-6-(4-((6,6,6-trifluorohexyl)oxy)phenyl)-6-(trifluoromethyl)-1,2,5,6-tetrahydropyridin-3-yl)-2-(methylsulfonyl)acetamide



75A. (*S*)-3-Amino-1-(5-ethylthiophen-2-yl)-4,4,4-trifluoro-3-(4-((6,6,6-trifluorohexyl)oxy)phenyl)butan-1-one: 75A was prepared in a similar manner as Example 1A and 1B. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 4.0 Hz, 1H), 7.50 (d, *J* = 8.8 Hz, 2H), 6.86 (d, *J* = 8.8 Hz, 3H), 3.95 (t, *J* = 6.3 Hz, 2H), 3.87 (d, *J* = 16.5 Hz, 1H), 3.42 (d, *J* = 16.5 Hz, 1H), 2.88 (q, *J* = 7.6 Hz, 2H), 2.19 - 2.04 (m, 2H), 1.84 - 1.75 (m, 2H), 1.69 - 1.50 (m, 4H), 1.33 (t, *J* = 7.6 Hz, 3H).

75B. (*S*)-2-(1,3-Dioxoisoindolin-2-yl)-*N*-(4-(5-ethylthiophen-2-yl)-1,1,1-trifluoro-4-oxo-2-(4-((6,6,6-trifluorohexyl)oxy)phenyl)butan-2-yl)acetamide: Chloroacetonitrile (0.044 mL, 0.436 mmol) was added dropwise to a solution of 2-(1,3-dioxoisoindolin-2-yl)acetic acid (59.7 mg, 0.291 mmol) and triphenylphosphine (153 mg, 0.582 mmol) in DCM (2 mL) and stirred at rt for 1h. Then, a solution of 75A (70 mg, 0.145 mmol) in DCM (1 mL) followed by pyridine (0.035 mL, 0.436 mmol) were added and stirred at rt for 1h. Concentrated and the crude was purified using ISCO flash

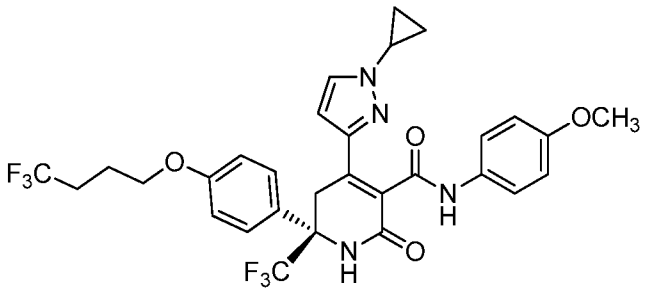
chromatography to give 75B (86 mg, 0.129 mmol, 88% yield) as a white foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.77 (s, 1H), 7.73 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.45 (d, *J* = 3.7 Hz, 1H), 7.39 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 9.0 Hz, 2H), 6.81 (d, *J* = 4.0 Hz, 1H), 4.49, 4.46 (ABq, *J* = 16.1 Hz, 2H), 3.94 (t, *J* = 6.3 Hz, 2H), 3.82 (d, *J* = 15.4 Hz, 1H), 3.40 (d, *J* = 15.4 Hz, 1H), 2.87 (q, *J* = 7.8 Hz, 2H), 2.18 - 2.04 (m, 2H), 1.84 - 1.75 (m, 2H), 1.69 - 1.51 (m, 4H), 1.33 (t, *J* = 7.5 Hz, 3H).

75C. (*S*)-3-Amino-4-(5-ethylthiophen-2-yl)-6-(4-((6,6,6-trifluorohexyl)oxy) phenyl)-6-(trifluoromethyl)-5,6-dihydropyridin-2(1*H*)-one: A mixture of 75B (86 mg, 0.129 mmol) and 1N NaOH (0.270 mL, 0.270 mmol) in MeOH (1 mL) was stirred under microwave at 130 °C for 15 min. Acidified with 1N HCl, diluted with DCM, washed with water, dried ($MgSO_4$), and concentrated. The crude mixture was dissolved in EtOH (1 mL) and 33% methylamine in ethanol (0.3 mL, 2.58 mmol) was added and stirred at 80 °C for 3h and stirred at 60 °C overnight. 0.3 mL of methylamine was added and stirred at 80 °C for 5h. The mixture was concentrated, diluted with DCM, washed with 1N NaOH, dried ($MgSO_4$), and concentrated to give 75C (53 mg, 0.102 mmol, 79% yield) as a yellow-brown gum. LCMS Anal. Calc'd for $C_{24}H_{26}F_6N_2O_2S$ 520.16, found [M+H] 521.3.

Example 75: Trichloroacetonitrile (0.029 mL, 0.288 mmol) was added dropwise to a solution of 2-(methylsulfonyl)acetic acid (26.5 mg, 0.192 mmol) and triphenylphosphine (101 mg, 0.384 mmol) in DCM (1 mL) and stirred at rt for 1h. Then, a solution of 75C in DCM (0.8 mL) followed by pyridine (0.023 mL, 0.288 mmol) were added and stirred at rt for 5h. The reaction mixture was concentrated and the crude mixture was purified using prep. HPLC to give Example 75 (28.3 mg, 0.043 mmol, 45.1% yield) as an off-white solid. LCMS Anal. Calc'd for $C_{27}H_{30}F_6N_2O_5S_2$ 640.15, found [M+H] 641.3. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (br. s., 1H), 7.42 (d, *J* = 8.6 Hz, 2H), 7.32 (d, *J* = 3.1 Hz, 1H), 6.91 (d, *J* = 8.8 Hz, 2H), 6.83 (d, *J* = 3.3 Hz, 1H), 6.67 (br. s., 1H), 4.04 (br. s., 2H), 3.96 (t, *J* = 6.2 Hz, 2H), 3.64, 3.62 (ABq, *J* = 17.2 Hz, 2H), 3.29 (s, 3H), 2.86 (q, *J* = 7.6 Hz, 2H), 2.19 - 2.04 (m, 2H), 1.84 - 1.76 (m, 2H), 1.68 - 1.49 (m, 4H), 1.31 (t, *J* = 7.5 Hz, 3H).

Example 76

(*S*)-4-(1-Cyclopropyl-1*H*-pyrazol-3-yl)-*N*-(4-methoxyphenyl)-2-oxo-6-(4-(4,4,4-trifluorobutoxy)phenyl)-6-(trifluoromethyl)-1,2,5,6-tetrahydropyridine-3-carboxamide



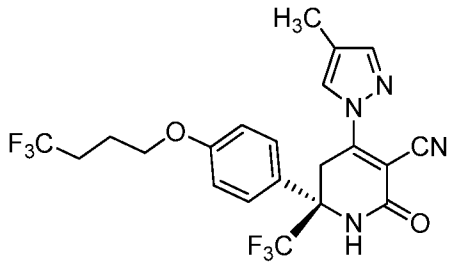
76A. (*S*)-3-Amino-1-(1-cyclopropyl-1*H*-pyrazol-3-yl)-4,4,4-trifluoro-3-(4-(4,4,4-trifluorobutoxy)phenyl)butan-1-one: 76A was prepared in a similar manner as Example 1A and 1B. LCMS Anal. Calc'd for $C_{27}H_{30}F_6N_2O_5S_2$ 449.15, found [M+H] 450.1.

76B. (*S*)-N^1-(4-(1-Cyclopropyl-1*H*-pyrazol-3-yl)-1,1,1-trifluoro-4-oxo-2-(4-(4,4,4-trifluorobutoxy)phenyl)butan-2-yl)-N^3-(4-methoxyphenyl)malonamide: To a solution of 3-((4-methoxyphenyl)amino)-3-oxopropanoic acid (13.97 mg, 0.067 mmol) in dichloromethane (1 mL) was added triphenylphosphine (17.51 mg, 0.067 mmol) and trichloroacetonitrile (9.64 mg, 0.067 mmol). After 1h, 76A (10mg, 0.022 mmol) in dichloromethane (1 mL) was added and the reaction was stirred for 16h. The reaction mixture was concentrated and the crude product was purified by flash chromatography to give 76B (13 mg, 0.020 mmol, 91% yield) as a light yellow oil. LCMS Anal. Calc'd for $C_{30}H_{30}F_6N_4O_5$ 640.21, found [M+H] 641.3.

Example 76: To a stirred solution of 76B (13mg, 0.020 mmol) in MeOH (3 mL) was added piperidine (10.05 µl, 0.101 mmol) and the reaction was heated to 60 °C for 16h. The reaction mixture was concentrated and purified by prep. HPLC to afford Example 76 (3.5 mg, 0.056 mmol, 28% yield) as a light yellow oil. LCMS Anal. Calc'd for $C_{30}H_{28}F_6N_4O_4$ 622.20, found [M+H] 623.2. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.11 (s, 1H), 9.27 (s, 1H), 7.80 (d, J = 2.5 Hz, 1H), 7.56 - 7.48 (m, 4H), 7.08 - 6.98 (m, 2H), 6.90 (d, J = 9.1 Hz, 2H), 6.36 (d, J = 2.2 Hz, 1H), 4.06 (t, J = 6.2 Hz, 2H), 3.90 - 3.78 (m, 2H), 3.74 - 3.71 (m, 4H), 2.47 - 2.31 (m, 2H), 1.99 - 1.86 (m, 2H), 1.16 - 0.90 (m, 4H).

Example 77

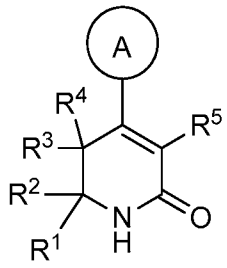
((*S*)-4-(4-Methyl-1*H*-pyrazol-1-yl)-2-oxo-6-(4-(4,4,4-trifluorobutoxy)phenyl)-6-(trifluoromethyl)-1,2,5,6-tetrahydropyridine-3-carbonitrile



A mixture of 67E (13 mg, 0.030 mmol) and 4-methyl-1*H*-pyrazole (25.01 mg, 0.305 mmol) were heated to 100 °C for 7min. The reaction mixture was concentrated and purified by prep. HPLC to afford Example 77 (12 mg, 0.025 mmol, 83% yield). LCMS Anal. Calc'd for $C_{21}H_{18}F_6N_4O_2$ 472.13, found [M+H] 473.1. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.74 (s, 1H), 8.56 (s, 1H), 7.93 (s, 1H), 7.57 (d, *J* = 8.8 Hz, 2H), 7.03 (d, *J* = 9.1 Hz, 2H), 4.23 (d, *J* = 17.6 Hz, 1H), 4.06 (t, *J* = 6.2 Hz, 2H), 3.89 (d, *J* = 17.9 Hz, 1H), 2.46 - 2.32 (m, 2H), 2.12 (s, 3H), 1.98 - 1.87 (m, 2H).

WHAT IS CLAIMED IS:

1. A compound of Formula (I):



(I)

or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, a polymorph, a solvate or a hydrate thereof, wherein:

ring A is independently a 5- to 6-membered heteroaryl comprising carbon atoms and 1-4 heteroatoms selected from N, NR^e, O and S; wherein said heteroaryl is substituted with 0-1 R^6 and 0-2 R^7;

R^1 is independently selected from: $-(CH_2)_m-(C_{3-6}$ carbocycle substituted with 0-2 R^b and 0-2 R^g), $-(CH_2)_m-$(5- to 6-membered heteroaryl comprising carbon atoms and 1-4 heteroatoms selected from N, NR^e, O and S; wherein said heteroaryl is substituted with 0-1 R^b and 0-2 R^g), and (a C_{1-12} hydrocarbon chain substituted with 0-3 R^a; wherein said hydrocarbon chain may be straight or branched, saturated or unsaturated);

R^2 is independently selected from: C_{1-4} alkyl, C_{3-4} cycloalkyl, and C_{1-4} haloalkyl;

R^3 is independently selected from: H, F, C_{1-4} alkyl and CN;

R^4 is independently selected from: H, F, and C_{1-4} alkyl;

R^3 and R^4 may be combined with the carbon atom to which they are attached to form a 3- to 6-membered carbocycle;

R^5 is independently selected from: H, halogen, C_{1-6} alkyl, CN, NO_2, R^c, NH_2, $-(CH_2)_n-(X)_t-(CH_2)_mR^c$, $-CONH(C_{1-6}$ alkyl), and $-NHCOX_1SO_2R^i$;

X is independently selected from the group consisting of O, S, NH, CONH, and NHCO;

X_1 is independently C_{1-4} hydrocarbon chain optionally substituted with C_{1-4} alkyl or C_{3-4} cycloalkyl;

R^6 is independently selected from: halogen, C_{1-6} alkyl substituted with 0-2 R^h, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, $CO(C_{1-4}$ alkyl), $-(CH_2)_m-C_{3-6}$ cycloalkyl,

$-(CH_2)_m-NR^fR^i$, CN, OR^i, SR^i, and (a 4- to 6-membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, NR^e, O, and S);

R^7 is independently selected from: halogen, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, and C_{1-4} haloalkoxy;

alternatively, R^6 and R^7, together with the carbon atoms to which they are attached, combine to form a 5- to 6-membered carbocyclic ring or a 5- to 6-membered heterocyclic ring comprising carbon atoms and 1-3 heteroatoms selected from N, NR^e, O, and S; wherein said heterocycle is substituted with 0-2 R^g;

R^a is, at each occurrence, independently selected from: halogen, OH, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, $N(C_{1-4}$ alkyl$)_2$, COOH, and $-(CH_2)_n-R^c$;

R^b is, at each occurrence, independently selected from: halogen, OH, C_{1-10} alkyl, C_{1-10} alkoxy, C_{1-10} haloalkyl, C_{1-10} haloalkoxy, C_{1-10} alkylthio, C_{1-10} haloalkylthio, $N(C_{1-4}$ alkyl$)_2$, $-CONH(C_{4-20}$ alkyl), $-CONH(C_{4-20}$ haloalkyl), $-O(CH_2)_sO(C_{1-6}$ alkyl), $-O(CH_2)_sO(C_{1-6}$ haloalkyl), R^c, and $-(CH_2)_n-(O)_t-(CH_2)_mR^c$;

R^c is, at each occurrence, independently selected from: C_{3-6} cycloalkyl substituted with 0-2 R^d, C_{3-6} cycloalkenyl substituted with 0-2 R^d, $-(CH_2)_m-$(phenyl substituted with 0-3 R^d), and a 5- to 6-membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, NR^e, O, and S; wherein said heterocycle is substituted with 0-2 R^d;

R^d is, at each occurrence, independently selected from: halogen, OH, CN, NO_2, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, tetrazolyl, OBn and phenyl;

R^e is, at each occurrence, independently selected from: H, C_{1-8} alkyl, C_{1-8} haloalkyl, $-(CH_2)_n-C_{3-6}$ carbocycle, $CO(C_{1-4}$ alkyl) and COBn;

R^f is, at each occurrence, independently selected from: H and C_{1-4} alkyl;

R^g is, at each occurrence, independently selected from: halogen, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, and C_{1-4} haloalkoxy;

R^h is, at each occurrence, independently selected from: OH, halogen, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, and C_{1-4} haloalkoxy;

R^i is, at each occurrence, independently selected from the group consisting of C_{1-4} alkyl, C_{3-4} cycloalkyl and phenyl;

n, at each occurrence, is independently 0 or 1;

m, at each occurrence, is independently 0, 1, 2, 3, or 4;

s, at each occurrence, is independently 1, 2, or 3; and

t, at each occurrence, is independently 0 or 1.

2. A compound according to claim 1, wherein:

R^1 is independently selected from: (C_{3-6} carbocycle substituted with 0-2 R^b and 0-2 R^g), (a 5- to 6-membered heteroaryl comprising carbon atoms and 1-4 heteroatoms selected from N, NR^e, O and S; wherein said heteroaryl is substituted with 0-1 R^b and 0-2 R^g), and (a C_{1-12} hydrocarbon chain substituted with 0-1 R^a; wherein said hydrocarbon chain may be straight or branched, saturated or unsaturated);

R^3 is independently selected from: H, F, C_{1-4} alkyl and CN;

R^4 is independently selected from: H, F, and C_{1-4} alkyl;

R^b is, at each occurrence, independently selected from: halogen, C_{1-10} alkyl, C_{1-10} alkoxy, C_{1-10} haloalkyl, C_{1-10} haloalkoxy, C_{1-10} alkylthio, C_{1-10} haloalkylthio, $N(C_{1-4}$ alkyl$)_2$, $-CONH(C_{4-20}$ alkyl), $-CONH(C_{4-20}$ haloalkyl), $-O(CH_2)_sO(C_{1-6}$ alkyl), $-O(CH_2)_sO(C_{1-6}$ haloalkyl), R^c, and $-(CH_2)_n-(O)_t-(CH_2)_mR^c$; and

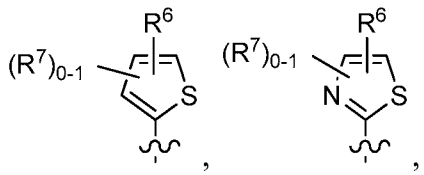
R^d is, at each occurrence, independently selected from: halogen, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, tetrazolyl, OBn and phenyl.

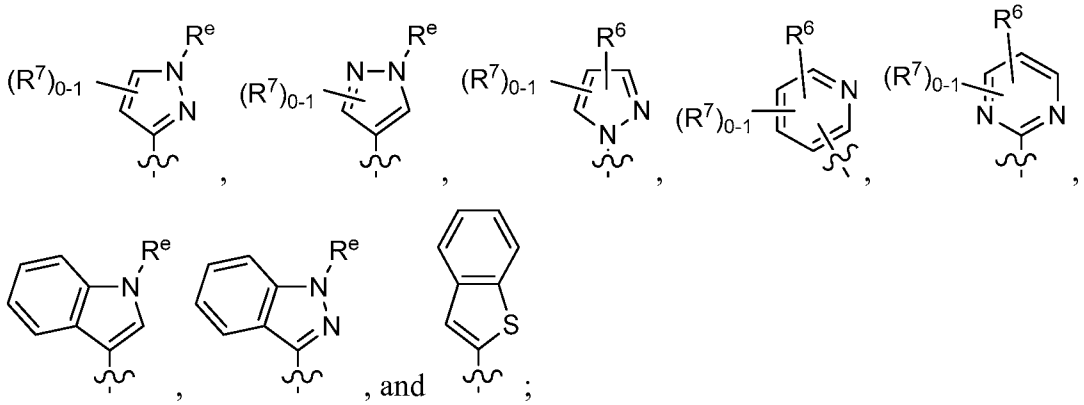
3. A compound according to claim 1, wherein:

ring A is independently selected from: pyrrolyl, thienyl, thiazolyl, pyrazolyl, pyridyl, and pyrimidinyl; wherein each ring moiety is substituted with 0-1 R^6 and 0-2 R^7; and

alternatively, R^6 and R^7, together with the carbon atoms to which they are attached, combine to form a 6-membered carbocyclic ring.

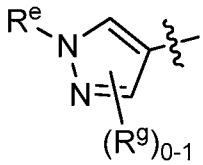
4. A compound according to claim 1, wherein:

ring A is independently selected from: 



, and ;

R^1 is independently selected from: (phenyl substituted with 1 R^b and 0-2 R^g),



, and a C_{1-12} hydrocarbon chain substituted with 0-1 R^a; wherein said hydrocarbon chain may be straight or branched, saturated or unsaturated;

R^2 is independently selected from: C_{1-4} alkyl and C_{1-4} haloalkyl;

R^3 is independently selected from: H and F;

R^4 is independently selected from: H and F;

R^5 is independently selected from: CN, NH_2, -CONH(C_{1-6} alkyl), R^c, -$CONHSO_2$(C_{1-4} alkyl), -$NHCOCH_2SO_2$(C_{1-4} alkyl), -NHCONH(C_{1-4} alkyl), -OCONH(C_{1-4} alkyl), and -CONH(Ph substituted with 0-1 R^g);

R^6 is independently selected from: halogen, C_{1-4} alkyl substituted with 0-1 N(C_{1-4} alkyl)$_2$, C_{1-4} alkoxy, and C_{3-6} cycloalkyl;

R^7 is independently selected from: halogen, C_{1-4} alkyl and C_{1-4} alkoxy;

R^a is, at each occurrence, independently selected from: halogen, OH, C_{1-4} alkoxy, C_{1-4} haloalkyl, and C_{1-4} haloalkoxy;

R^b is, at each occurrence, independently selected from: halogen, OH, C_{1-8} alkyl, C_{1-8} alkoxy, C_{1-8} haloalkyl, and C_{1-10} haloalkoxy;

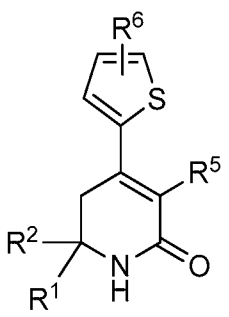
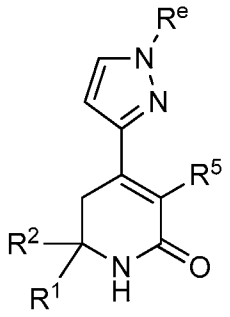
R^c is a 5- to 6-membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, NR^e, O, and S;

R^g is, at each occurrence, independently selected from: halogen, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, and C_{1-4} haloalkoxy;

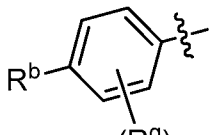
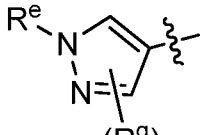
m, at each occurrence, is independently 0, 1, 2 or 3; and

s, at each occurrence, is independently 1, 2, or 3.

5. A compound of Formula (IIa) or (IIb):


(IIa),

(IIb)

or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, a polymorph, a solvate or a hydrate thereof, within the scope of any of the above aspects, wherein:

R^1 is independently selected from:  ,  , and (a C_{1-12} hydrocarbon chain; wherein said hydrocarbon chain may be straight or branched, saturated or unsaturated);

R^2 is independently selected from: CF_3 and CH_3;

R^5 is independently selected from: CN, tetrazolyl, $-CONHSO_2(C_{1-4}$ alkyl), $-NHCOCH_2SO_2(C_{1-4}$ alkyl), and $-CONH(4\text{-}C_{1-4}$ alkoxy-Ph);

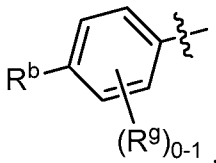
R^6 is independently selected from: halogen, C_{1-4} alkyl substituted with 0-1 $N(C_{1-4}$ alkyl$)_2$, C_{1-4} alkoxy, and C_{3-6} cycloalkyl;

R^b is independently selected from: $-O(CH_2)_{1-6}CF_3$, and $-O(CH_2)_{1-4}CF_2CF_3$;

R^e is independently selected from: $-(CH_2)_{1-6}CF_3$, and $-(CH_2)_{0-1}(C_{3-6}$ cycloalkyl); and

R^g is independently selected from: halogen and C_{1-4} alkoxy.

6. A compound according to claim 5, wherein:

R^1 is  .

7. A compound according to claims 1-6, wherein the compound is selected from the exemplified examples or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, a polymorph, a solvate or a hydrate thereof.

8. A pharmaceutical composition, comprising a pharmaceutically acceptable carrier and a compound of any one of claims 1-7.

9. A compound of any one of claims 1-7, wherein the compound has hMGAT2 IC_{50} values ≤ 1 μM, using the MGAT2 LCMS assay.

10. A compound of any one of claims 1-7, wherein the compound has hMGAT2 IC_{50} values ≤ 0.5 μM, using the MGAT2 LCMS assay.

11. A compound of any one of claims 1-7, wherein the compound has hMGAT2 IC_{50} values ≤ 0.1 μM, using the MGAT2 LCMS assay.

12. A pharmaceutical composition comprising a compound according to claims 1-7 and further comprising a dipeptidyl peptidase-IV (DPP4) inhibitor.

13. A method of treating a disease or disorder associated with the activity of the MGAT2 by administering a compound according to claims 1-7.

14. A method of treating at least one disease or disorder selected from the group consisting of diabetes, hyperglycemia, impaired glucose tolerance, gestational diabetes, insulin resistance, hyperinsulinemia, nonalcoholic fatty liver disease (NAFLD) including nonalcoholic steatohepatitis (NASH), retinopathy, neuropathy, nephropathy, delayed wound healing, atherosclerosis and its sequelae, abnormal heart function, myocardial ischemia, stroke, Metabolic Syndrome, hypertension, obesity, dyslipidemia, dyslipidemia, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, low high-density lipoprotein (HDL), high low-density lipoprotein (LDL), non-cardiac ischemia, lipid disorders and/or glaucoma with a compound according to claims 1-7.