(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
27 February 2014 (27.02.2014)

WIPO | PCT

(10) International Publication Number
WO 2014/031465 A1

(51) International Patent Classification:
A61P 3/10 (2006.01) *A61K 31/415* (2006.01)
A61K 31/4184 (2006.01) *A61K 31/454* (2006.01)

(21) International Application Number:
PCT/US2013/055240

(22) International Filing Date:
16 August 2013 (16.08.2013)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/692,028 22 August 2012 (22.08.2012) US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

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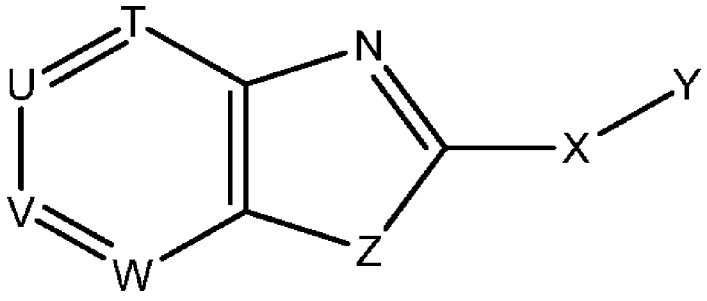
(54) Title: NOVEL AZABENZIMIDAZOLE TETRAHYDROPYRAN DERIVATIVES



(I)

(57) Abstract: Novel compounds of the structural formula (I) are activators of AMP-protein kinase and may be useful in the treatment, prevention and suppression of diseases mediated by the AMPKactivated protein kinase. The compounds of the present invention may be useful in the treatment of Type 2 diabetes, hyperglycemia, metabolic syndrome, obesity, hypercholesterolemia, and hypertension.

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Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

Published:

— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

TITLE OF THE INVENTION

NOVEL AZABENZIMIDAZOLE TETRAHYDROPYRAN DERIVATIVES

BACKGROUND OF THE INVENTION

Diabetes is characterized by elevated levels of plasma glucose (hyperglycemia) in the fasting state or after administration of glucose during an oral glucose tolerance test. In Type 1 diabetes, or insulin-dependent diabetes mellitus (IDDM), patients produce little or no insulin, the hormone which regulates glucose utilization. In Type 2 diabetes, or noninsulin-dependent diabetes mellitus (NIDDM), insulin is still produced by islet cells in the pancreas. Patients with Type 2 diabetes have a resistance to the effects of insulin in stimulating glucose and lipid metabolism in the main insulin-sensitive tissues, including muscle, liver and adipose tissues. These patients often have normal levels of insulin, and may have hyperinsulinemia (elevated plasma insulin levels), as they compensate for the reduced effectiveness of insulin by secreting increased amounts of insulin (Polonsky, Int. J. Obes. Relat. Metab. Disord. 24 Suppl 2:S29-31, 2000). Insulin resistance is not primarily caused by a diminished number of insulin receptors but rather by a post-insulin receptor binding defect that is not yet completely understood. This lack of responsiveness to insulin results in insufficient insulin-mediated activation of uptake, oxidation and storage of glucose in muscle, and inadequate insulin-mediated repression of lipolysis in adipose tissue and of glucose production and secretion in the liver. Eventually, a patient may be become diabetic due to the inability to properly compensate for insulin resistance. In humans, the beta cells within the pancreatic islets initially compensate for insulin resistance by increasing insulin output. The onset of Type 2 diabetes due to insufficient increases (or actual declines) in beta cell mass is apparently due to increased beta cell apoptosis relative to non-diabetic insulin resistant individuals (Butler et al., Diabetes 52:102-110, 2003).

Persistent or uncontrolled hyperglycemia is associated with increased and premature morbidity and mortality. Often abnormal glucose homeostasis is associated both directly and indirectly with obesity, hypertension, and alterations of the lipid, lipoprotein and apolipoprotein metabolism, as well as other metabolic and hemodynamic disease. Patients with Type 2 diabetes mellitus have a significantly increased risk of macrovascular and microvascular complications, including atherosclerosis, coronary heart disease, stroke, peripheral vascular disease, hypertension, nephropathy, neuropathy, and retinopathy. Therefore, effective therapeutic control of glucose homeostasis, lipid metabolism, obesity, and hypertension are critically important in the clinical management and treatment of diabetes mellitus.

Patients who have insulin resistance often exhibit several symptoms that together are referred to as Syndrome X or Metabolic Syndrome. According to one widely used definition, a patient having Metabolic Syndrome is characterized as having three or more symptoms selected

from the following group of five symptoms: (1) abdominal obesity; (2) hypertriglyceridemia; (3) low high-density lipoprotein cholesterol (HDL); (4) high blood pressure; and (5) elevated fasting glucose, which may be in the range characteristic of Type 2 diabetes if the patient is also diabetic. Each of these symptoms is defined clinically in the Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III, or ATP III), National Institutes of Health, 2001, NIH Publication No. 01-3670. Patients with Metabolic Syndrome, whether or not they have or develop overt diabetes mellitus, have an increased risk of developing the macrovascular and microvascular complications that occur with Type 2 diabetes, such as atherosclerosis and coronary heart disease.

There are several available treatments for Type 2 diabetes, each of which has its own limitations and potential risks. Physical exercise and a reduction in dietary intake of calories often dramatically improve the diabetic condition and are the usual recommended first-line treatment of Type 2 diabetes and of pre-diabetic conditions associated with insulin resistance. Compliance with this treatment is generally very poor because of well-entrenched sedentary lifestyles and excess food consumption, especially of foods containing high amounts of fat and carbohydrates. Pharmacologic treatments for diabetes have largely focused on three areas of pathophysiology: (1) hepatic glucose production (biguanides, such as phenformin and metformin), (2) insulin resistance (PPAR agonists, such as rosiglitazone, troglitazone, engliazone, balaglitazone, MCC-555, netoglitazone, T-131, LY-300512, LY-818 and pioglitazone), (3) insulin secretion (sulfonylureas, such as tolbutamide, glipizide and glimipiride); (4) incretin hormone mimetics (GLP-1 derivatives and analogs, such as exenatide and liraglutide); and (5) inhibitors of incretin hormone degradation (DPP-4 inhibitors, such as sitagliptin).

Many of the current treatments for diabetes have unwanted side effects. Phenformin and metformin can induce lactic acidosis, nausea/vomiting, and diarrhea. Metformin has a lower risk of side effects than phenformin and is widely prescribed for the treatment of Type 2 diabetes. The currently marketed PPAR gamma agonists are modestly effective in reducing plasma glucose and hemoglobinA1C, and do not greatly improve lipid metabolism or the lipid profile. Sulfonylureas and related insulin secretagogues can cause insulin secretion even if the glucose level is low, resulting in hypoglycemia, which can be fatal in severe cases. The administration of insulin secretagogues must therefore be carefully controlled. There remains a need for treatments for diabetes that work by novel mechanisms of action and that exhibit fewer side effects.

AMP-activated protein kinase (AMPK) has been identified as a regulator of carbohydrate and fatty acid metabolism that helps maintain energy balance in response to environmental and nutritional stress. There is evidence that activation of AMPK results in a number of beneficial

effects on lipid and glucose metabolism by reducing glucogenesis and de novo lipogenesis (fatty acid and cholesterol synthesis), and by increasing fatty acid oxidation and skeletal muscle glucose uptake. Inhibition of ACC, by phosphorylation by AMPK, leads to a decrease in fatty acid synthesis and to an increase in fatty acid oxidation, while inhibition of HMG-CoA reductase, by phosphorylation by AMPK, leads to a decrease in cholesterol synthesis (Carling, D. et.al., FEBS Letters 223:217 (1987)).

In the liver, AMPK activation results in a decrease in fatty acid and cholesterol synthesis, inhibiting hepatic glucose production and increasing fatty acid oxidation. It has been shown that AMP-activated protein kinase regulates triacylglycerol synthesis and fatty acid oxidation in liver and muscle via glycerol-3-phosphate acyltransferase (Muoio, D. M. et.al.,. Biochem. J. 338:783 (1999)). Another substrace of AMPK, hepatocyte nuclear factor-4α, has been shown to be involved in type-1 maturity onset diabetes (Leclerc, I. et.al., Diabetes 50:1515 (2001)). Additional processes believed to be regulated through AMPK activation include the stimulation of glucose transport in skeletal muscle and the regulation of key genes in fatty acid and glucose metabolism in the liver (Hardie, D. G. and Hawley, S. A., Bioessays 23: 1112 (2001), Kemp, B. E. et.al., Biochem. Soc. Transactions 31:162 (2003), Musi, N. and Goodyear, L. J.. Current Drug Targets-Immune, Endocrine and Metabolic Disorders 2:119 (2002); Lochhead, P. A. et.al., Diabetes 49:896 (2000); and Zhou, G. et.al., J. of Clin. Invest. 108: 1167 (2001).

In vivo studies have demonstrated the following beneficial effects of both acute and chronic administration of AICAR, an AMPK activator, in rodent models of obesity and type 2 diabetes: 1) an improvement in glucose homeostasis in insulin-resistant diabetic (ob/ob) mice; 2) a decrease in blood glucose concentrations in ob/ob and db/db mice and a blood glucose reduction of 35% following 8 weeks of administration; and 3) a reduction in metabolic disturbances and a reduction of blood pressure in rats displaying characteristics of insulin resistance syndrome (Bergeron, R. et.al., Diabetes 50:1076 (2001); Song, S. M. et.al., Diabetologia 45:56 (2002); Halseth, A. E. et.al., Biochem. and Biophys. Res. Comm. 294:798 (2002); and Buhl, E. S. et.al., Diabetes 51: 2199 (2002)). A further study of 7 week AICAR administration in obese Zucker (fa/fa) rats lead to a reduction in plasma triglycerides and free fatty acids; an increase in HDL cholesterol; and a normalization of glucose metabolism as assessed by an oral glucose tolerance test (Minokoshi, Y. et.al., Nature 415: 339 (2002)). Expression of dominant negative AMPK in skeletal muscle of transgenic mice has demonstrated that the AICAR effect on stimulation of glucose transport is dependent on AMPK activation (Mu, J. et.al., Molecular Cell 7: 1085 (2001)).

Recent data also suggest that AMPK activation is involved in the glucose and lipid-lowering effects of the anti-diabetic drug metformin. It has been shown that the diabetes drug metformin can activate AMPK in vivo at high concentrations (Zhou, G. et.al., J. of Clin. Invest. 108: 1167 (2001); Musi, N. et.al. Diabetes 51: 2074 (2002)).

Based on these studies, it is expected that the in vivo activation of AMPK in the liver may result in the reduction of hepatic glucose output, an improvement in overall glucose homeostasis, a decrease in fatty acid and cholesterol synthesis, and an increase in fatty acid oxidation. Stimulation of AMPK in skeletal muscle is expected to result in an increase in glucose uptake and fatty acid oxidation with resulting improvement of glucose homeostasis, and an improvement in insulin action. Finally, the resulting increase in energy expenditure may lead to a decrease in body weight. The lowering of blood pressure has also been reported to be a consequence of AMPK activation.

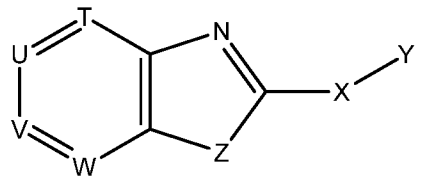
Increased fatty acid synthesis is a characteristic of many tumor cells, therefore decreasing the synthesis of fatty acids via AMPK activation may also be useful as a cancer therapy. Activation of AMPK may also be useful to treat ischemic events in the brain (Blazquez, C. et.al., J. Neurochem. 73: 1674 (1999)); to prevent damage from reactive oxygen species (Zhou, M. et.al., Am. J. Physiol. Endocrinol. Metab. 279: E622 (2000)); and to improve local circulatory systems (Chen, Z.-P., et.al. AMP-activated protein kinase phosphorylation of endothelial NO synthase. FEBS Letters 443: 285 (1999)).

Compounds that activate AMPK may be useful to treat type 2 diabetes mellitus, obesity, hypertension, dyslipidemia, cancer, and metabolic syndrome, as well as cardiovascular diseases, such as myocardial infarction and stroke, by improving glucose and lipid metabolism and by reducing body weight. There is a need for potent AMPK activators that have pharmacokinetic and pharmacodynamic properties suitable for use as human pharmaceuticals.

Benzimidazole compounds are disclosed in WO 2010/051206; WO 2010/051176; WO 2010/047982; WO 2010/036613; WO 93/07124; WO 95/29897; WO 98/39342; WO 98/39343; WO 00/03997; WO 00/14095; WO 01/53272; WO 01/53291; WO 02/092575; WO 02/40019; WO 03/018061; WO 05/002520; WO 05/018672; WO 06/094209; US 6,312,662; US 6,489,476; US 2005/0148643; DE 3 316 095; JP 6 298 731; EP 0 126 030; EP 0 128 862; EP 0 129 506; and EP 0 120 403. AMPK activators are disclosed in WO 08/006432; WO 05/051298; WO 05/020892; US 2007/015665; US 2007/032529; US 2006/287356; and US 2005/038068. Azabenzimidazole compounds are disclosed in WO 2012/33149.

SUMMARY OF THE INVENTION

The present invention is concerned with novel benzimidazole derivatives of structural Formula I:



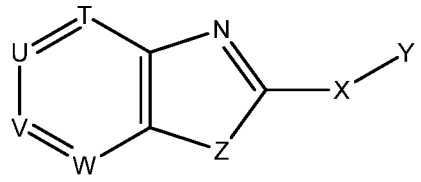
(I)

and pharmaceutically acceptable salts thereof. The compounds of structural formula I, and salts thereof, are activators of AMP-activated protein kinase (AMPK) and are useful in the treatment, prevention and suppression of diseases, disorders and conditions mediated by activation of AMP-activated protein kinase. As AMPK activators, the compounds of structural formula I may be useful to treat Type 2 diabetes mellitus, insulin resistance, hyperglycemia, dyslipidemia, lipid disorders, obesity, hypertension, Metabolic Syndrome and atherosclerosis.

The present invention also relates to pharmaceutical compositions comprising the compounds of the present invention and a pharmaceutically acceptable carrier. The present invention also relates to methods for the treatment, control or prevention of disorders, diseases, and conditions that are responsive to activation of AMP-activated protein kinase in a subject in need thereof by administering the compounds and pharmaceutical compositions of the present invention. The present invention also relates to the use of compounds of the present invention for manufacture of a medicament useful in treating diseases, disorders and conditions are responsive to the activation of AMP-activated protein kinase. The present invention is also concerned with treatment of these diseases, disorders and conditions by administering the compounds of the present invention in combination with a therapeutically effective amount of another agent useful to treat the disease, disorder and condition. The invention is further concerned with processes for preparing the compounds of this invention.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is concerned with novel compounds of structural Formula I:



(I)

or a pharmaceutically acceptable salt thereof, wherein:

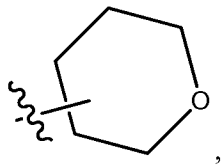
T is selected from the group consisting of: CR^3, N and N-oxide;

U is selected from the group consisting of: CR^1, N and N-oxide;

V is selected from the group consisting of: CR^2, N and N-oxide;
W is selected from the group consisting of: CR^4, N and N-oxide,
provided that at least one of T, U, V and W is N or N-oxide;
X is selected from:

(1) $-CH_2-$,
(2) -CHF-,
(3) $-CF_2-$,
(4) -S-,
(5) -O-,
(6) $-O-CH_2-$,
(7) $-O-CH_2CH_2-$,
(8) -NH-,
(9) -C(O)-,
(10) -NHC(O)-,
(11) -C(O)NH-,
(12) $-NHSO_2-$,
(13) $-SO_2NH-$, and
(14) $-CO_2-$,

wherein each CH_2 is unsubstituted or substituted with 1 or 2 substituents selected from: hydroxy, halogen, NH_2, C_{1-6}alkyl, CO_2H, CO_2C_{1-6}alkyl, COC_{1-6}alkyl, phenyl and -CH_2phenyl, and wherein each NH is unsubstituted or substituted with 1 substituent selected from: C_{1-6}alkyl, CO_2H, CO_2C_{1-6}alkyl, COC_{1-6}alkyl, phenyl and -CH_2phenyl;
Y is selected from:



,

wherein Y is unsubstituted or substituted with 1, 2, 3, 4 or 5 substituents selected from R^b;
Z is selected from:

(1) NR^5,
(2) -S-, and
(3) -O-;

each R^1 and R^2 is independently selected from:

(1) hydrogen,
(2) halogen,
(3) CN,
(4) CF_3,
(5) -C_{1-6}alkyl,

(6) -C_{2-6}alkenyl,
(7) -C_{2-6}alkynyl,
(8) -$(CH_2)_pC_{3-10}$cycloalkyl,
(9) -$(CH_2)_pC_{3-7}$cycloalkyl-aryl,
(10) -$(CH_2)_pC_{3-7}$cycloalkyl-heteroaryl,
(11) -$(CH_2)_pC_{4-10}$cycloalkenyl,
(12) -$(CH_2)_pC_{4-7}$cycloalkenyl-aryl,
(13) -$(CH_2)_pC_{4-7}$cycloalkenyl-heteroaryl,
(14) -$(CH_2)_pC_{2-10}$cycloheteroalkyl,
(15) -$(CH_2)_pC_{2-10}$cycloheteroalkenyl,
(16) -$(CH_2)_p$aryl,
(17) -$(CH_2)_p$aryl-C_{1-8}alkyl,
(18) -$(CH_2)_p$aryl-C_{2-8}alkenyl,
(19) -$(CH_2)_p$aryl-C_{2-8}alkynyl-C_{1-8}alkyl,
(20) -$(CH_2)_p$aryl-C_{2-8}alkynyl-C_{3-7}cycloalkyl,
(21) -$(CH_2)_p$aryl-C_{2-8}alkynyl-C_{3-7}cycloalkenyl,
(22) -$(CH_2)_p$aryl-C_{2-8}alkynyl-C_{2-10}cycloheteroalkyl,
(23) -$(CH_2)_p$aryl-C_{2-8}alkynyl-C_{2-10}cycloheteroalkenyl,
(24) -$(CH_2)_p$aryl-C_{2-8}alkynyl-aryl,
(25) -$(CH_2)_p$aryl-C_{2-8}alkynyl-heteroaryl,
(26) -$(CH_2)_p$aryl-C_{3-7}cycloalkyl,
(27) -$(CH_2)_p$aryl-C_{2-10}cycloheteroalkyl,
(28) -$(CH_2)_p$aryl-C_{2-10}cycloheteroalkenyl,
(29) -$(CH_2)_p$aryl-aryl,
(30) -$(CH_2)_p$aryl-heteroaryl,
(31) -$(CH_2)_p$heteroaryl,
(32) -$(CH_2)_p$heteroaryl-C_{3-7}cycloalkyl,
(33) -$(CH_2)_p$heteroaryl-C_{2-10}cycloheteroalkyl,
(34) -$(CH_2)_p$heteroaryl-C_{2-10}cycloheteroalkenyl,
(35) -$(CH_2)_p$heteroaryl-aryl,
(36) -$(CH_2)_p$heteroaryl-heteroaryl,
(37) -C_{2-6}alkenyl-alkyl,
(38) -C_{2-6}alkenyl-aryl,
(39) -C_{2-6}alkenyl-heteroaryl,
(40) -C_{2-6}alkenyl-C_{3-7}cycloalkyl,
(41) -C_{2-6}alkenyl-C_{3-7}cycloalkenyl,
(42) -C_{2-6}alkenyl-C_{2-7}cycloheteroalkyl,

(43) -C_{2-6}alkenyl-C_{2-7}cycloheteroalkenyl,
(44) -C_{2-6} alkynyl-$(CH_2)_{1-3}$-O-aryl,
(45) -C_{2-6}alkynyl-alkyl,
(46) -C_{2-6}alkynyl-aryl,
(47) -C_{2-6}alkynyl-heteroaryl,
(48) -C_{2-6}alkynyl-C_{3-7}cycloalkyl,
(49) -C_{2-6}alkynyl-C_{3-7}cycloalkenyl,
(50) -C_{2-6}alkynyl-C_{2-7}cycloheteroalkyl,
(51) -C_{2-6}alkynyl-C_{2-7}cycloheteroalkenyl, and
(52) –C(O)NH-$(CH_2)_{0-3}$phenyl,

wherein each CH_2 is unsubstituted or substituted with 1 or 2 substituents selected from: halogen, CF_3, -OH, -NH_2, –C_{1-6}alkyl, -OC_{1-6}alkyl, –NHC_{1-6}alkyl, and –N(C_{1-6}alkyl)$_2$, and wherein each alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloheteroalkyl, cycloheteroalkenyl, phenyl, aryl and heteroaryl is unsubstituted or substituted with 1, 2, 3 or 4 substituents independently selected from R^a,

provided that at least one of and only one of R^1 and R^2 is selected from the group consisting of: hydrogen, halogen, -CN, -CF_3, -C_{1-6}alkyl, –C_{2-6}alkenyl and–C_{2-6}alkynyl;

R^3 and R^4 are each independently selected from:

(1) hydrogen,
(2) halogen,
(3) –C_{1-6}alkyl,
(4) –C_{2-6}alkenyl,
(5) –C_{2-6}alkynyl,
(6) –C_{3-10}cycloalkyl,
(7) –C_{3-10}cycloalkenyl,
(8) aryl,
(9) heteroaryl,
(10) –CN,
(11) –CF_3,
(12) –OH,
(13) -OC_{1-6}alkyl,
(14) –NH_2,
(15) –NHC_{1-6}alkyl,
(16) –N(C_{1-6}alkyl)$_2$,
(17) -SC_{1-6}alkyl,
(18) -SOC_{1-6}alkyl,
(19) –SO_2C_{1-6}alkyl,

(20) –NHSO$_2$C$_{1-6}$alkyl,
(21) –NHC(O)C$_{1-6}$alkyl,
(22) –SO$_2$NHC$_{1-6}$alkyl, and
(23) –C(O)NHC$_{1-6}$alkyl;

R^5 is selected from:
(1) hydrogen,
(2) -C$_{1-6}$alkyl,
(3) -C$_{1-6}$alkenyl,
(4) -(CH$_2$)$_u$OH,
(5) -CH$_2$CO$_2$H, and
(6) -CH$_2$CO$_2$C$_{1-6}$alkyl;

each R^a is independently selected from the group consisting of:
(1) -(CH$_2$)$_m$-halogen,
(2) oxo,
(3) -(CH$_2$)$_m$OH,
(4) -(CH$_2$)$_m$N(R^j)$_2$,
(5) -(CH$_2$)$_m$NO$_2$,
(6) -(CH$_2$)$_m$CN,
(7) -C$_{1-6}$alkyl,
(8) -(CH$_2$)$_m$CF$_3$,
(9) -(CH$_2$)$_m$OCF$_3$,
(10) -O-(CH$_2$)$_m$-OC$_{1-6}$ alkyl,
(11) -(CH$_2$)$_m$N(R^j)C(O)R^f,
(12) -(CH$_2$)$_m$N(R^j)CO$_2$R^f,
(13) -(CH$_2$)$_m$C(=N-OH)N(R^j)$_2$,
(14) -(CH$_2$)$_m$OC$_{1-6}$alkyl,
(15) -(CH$_2$)$_m$O-(CH$_2$)$_m$-C$_{3-7}$cycloalkyl,
(16) -(CH$_2$)$_m$O-(CH$_2$)$_m$-C$_{2-7}$cycloheteroalkyl,
(17) -(CH$_2$)$_m$O-(CH$_2$)$_m$-aryl,
(18) -(CH$_2$)$_m$O-(CH$_2$)$_m$-heteroaryl,
(19) -(CH$_2$)$_m$SC$_{1-6}$alkyl,
(20) -(CH$_2$)$_m$S(O)C$_{1-6}$alkyl,
(21) -(CH$_2$)$_m$SO$_2$C$_{1-6}$alkyl,
(22) -(CH$_2$)$_m$SO$_2$(CH$_2$)$_m$-C$_{3-7}$cycloalkyl,
(23) -(CH$_2$)$_m$SO$_2$(CH$_2$)$_m$-C$_{2-7}$cycloheteroalkyl,
(24) -(CH$_2$)$_m$SO$_2$(CH$_2$)$_m$-aryl,
(25) -(CH$_2$)$_m$SO$_2$(CH$_2$)$_m$-heteroaryl,

(26) -$(CH_2)_mSO_2NH_2$,
(27) -$(CH_2)_mSO_2NHC_{1-6}$alkyl,
(28) -$(CH_2)_mSO_2NHC_{3-7}$cycloalkyl,
(29) -$(CH_2)_mSO_2NHC_{2-7}$cycloheteroalkyl,
(30) -$(CH_2)_mSO_2$NH-aryl,
(31) -$(CH_2)_mSO_2$NH-heteroaryl,
(32) -$(CH_2)_mNHSO_2C_{1-6}$alkyl,
(33) -$(CH_2)_mNHSO_2$-C_{3-7}cycloalkyl,
(34) -$(CH_2)_mNHSO_2$-C_{2-7}cycloheteroalkyl,
(35) -$(CH_2)_mNHSO_2$-aryl,
(36) -$(CH_2)_mNHSO_2$NH-heteroaryl,
(37) -$(CH_2)_mN(R^j)$-C_{1-6}alkyl,
(38) -$(CH_2)_mN(R^j)$-C_{3-7}cycloalkyl,
(39) -$(CH_2)_mN(R^j)$-C_{2-7}cycloheteroalkyl,
(40) -$(CH_2)_mN(R^j)$-C_{2-7}cycloheteroalkenyl,
(41) -$(CH_2)_mN(R^j)$-aryl,
(42) -$(CH_2)_mN(R^j)$-heteroaryl,
(43) -$(CH_2)_mC(O)R^f$,
(44) -$(CH_2)_mC(O)N(R^j)_2$,
(45) -$(CH_2)_mN(R^j)C(O)N(R^j)_2$,
(46) -$(CH_2)_mCO_2H$,
(47) -$(CH_2)_m$OCOH,
(48) -$(CH_2)_mCO_2R^f$,
(49) -$(CH_2)_mOCOR^f$,
(50) -$(CH_2)_mC_{3-7}$cycloalkyl,
(51) -$(CH_2)_mC_{3-7}$cycloalkenyl,
(52) -$(CH_2)_mC_{2-6}$cycloheteroalkyl,
(53) -$(CH_2)_mC_{2-6}$cycloheteroalkenyl,
(54) -$(CH_2)_m$aryl, and
(55) -$(CH_2)_m$heteroaryl,

wherein each CH_2 is unsubstituted or substituted with 1 or 2 substituents selected from: oxo, -OH, -$(CH_2)_{1-3}$OH, -CN, -NH_2, -NH(C_{1-6}alkyl), -N(C_{1-6}alkyl)$_2$, oxo, -C_{1-6}alkyl, -C_{1-6}alkyl substituted with 1-5 OH, -OC_{1-6}alkyl, halogen, -CH_2F, -CHF_2, -CF_3, -CO_2H, -CO_2C_{1-6}alkyl, -C_{3-7}cycloalkyl, phenyl, CH_2phenyl, heteroaryl and CH_2heteroaryl, and wherein alkyl, cycloalkyl, cycloalkenyl, cycloheteroalkyl, cycloheteroalkenyl, aryl and heteroaryl are unsubstituted or substituted with 1, 2, 3 or 4 substituents selected from: oxo, -OH, -$(CH_2)_{1-5}$OH, -$(CH_2)_{1-5}$CN, -CN, -NH_2, -NH(C_{1-6}alkyl), -N(C_{1-6}alkyl)$_2$, -C_{1-6}alkyl, -C_{1-6}alkyl

substituted with 1-5 OH, -OC$_{1-6}$alkyl, halogen, -CH$_2$F, -CHF$_2$, -CF$_3$, -(CH$_2$)$_{1-5}$CF$_3$ optionally substituted with 1, 2 or 3 -OH, -CO$_2$H, -CO$_2$C$_{1-6}$alkyl, -SO$_2$C$_{1-6}$alkyl, -C$_{3-7}$cycloalkyl, phenyl, CH$_2$phenyl, heteroaryl and CH$_2$heteroaryl;

each R^b is independently selected from:

(1) hydrogen,
(2) -C$_{1-6}$alkyl,
(3) -C$_{1-6}$alkenyl,
(4) -(CH$_2$)nC$_{3-10}$cycloalkyl,
(5) -(CH$_2$)nC$_{3-10}$cycloalkenyl,
(6) -(CH$_2$)nC$_{2-10}$cycloheteroalkyl,
(7) -(CH$_2$)nC$_{2-10}$cycloheteroalkenyl,
(8) -(CH$_2$)naryl,
(9) -(CH$_2$)nheteroaryl,
(10) oxo,
(11) -(CH$_2$)nCF$_3$,
(12) -(CH$_2$)nCN,
(13) -(CH$_2$)t-halogen,
(14) -(CH$_2$)s-OH,
(15) -(CH$_2$)nNO$_2$,
(16) -(CH$_2$)nNH$_2$,
(17) -(CH$_2$)nNH(C$_{1-6}$alkyl),
(18) -(CH$_2$)nN(C$_{1-6}$alkyl)$_2$,
(19) -(CH$_2$)nNHCO$_2$H,
(20) -(CH$_2$)nOC$_{1-6}$alkyl,
(21) -(CH$_2$)nOC$_{1-6}$alkenyl,
(22) –(CH$_2$)$_n$COC$_{1-6}$alkyl,
(23) –(CH$_2$)$_n$CO$_2$H,
(24) –(CH$_2$)$_n$OCOH,
(25) –(CH$_2$)$_n$CO$_2$R^i,
(26) –(CH$_2$)$_n$OC(O)R^i,
(27) -(CH$_2$)qC(O)N(R^e)$_2$,
(28) -(CH$_2$)qCO$_2$N(R^e)$_2$,
(29) –(CH$_2$)$_n$C(O)(CH$_2$)$_n$N(Rg)$_2$,
(30) –(CH$_2$)$_n$OC(O)(CH$_2$)$_n$N(Rg)$_2$,
(31) -(CH$_2$)nN(R^e)C(O)C$_{1-6}$alkyl,
(32) –(CH$_2$)$_n$N(R^e)SO$_2$R^i,
(33) –(CH$_2$)$_n$SO$_2$C$_{1-6}$alkyl,

(34) $-(CH_2)_nSO_2N(R^e)R^g$,
(35) $-(CH_2)_nSO_2N(R^e)C(O)R^i$,
(36) $-(CH_2)_nSO_2N(R^e)CO_2R^i$,
(37) $-(CH_2)_nSO_2N(R^e)CON(R^g)_2$,
(38) $-(CH_2)_nC(O)N(R^e)SO_2R^i$,
(39) $-(CH_2)_nN(R^e)C(O)N(R^g)_2$,
(40) =N(OH), and
(41) $=N(OC_{1-6}alkyl)$,

wherein each CH_2 is unsubstituted or substituted with 1 or 2 substituents selected from: $-C_{1-6}$alkyl, -OH, halogen and $-NH_2$ wherein each NH is unsubstituted or substituted with 1 substituent selected from R^c, and wherein each alkyl, cycloalkyl, cycloalkenyl, cycloheteroalkyl, cycloheteroalkenyl, aryl and heteroaryl is unsubstituted or substituted with 1, 2, 3 or 4 substituents selected from R^c, or

wherein two R^b substituents and the carbon to which they are attached may form a 3 to 6 membered cycloalkyl ring, a 3-6 membered cycloalkenyl ring, a 3-6 membered cycloheteroalkyl ring or a 3-6 membered cycloheteroalkenyl ring, wherein the ring is unsubstituted or substituted with 1, 2, 3 or 4 substituents selected from R^c;

each R^c is independently selected from:

(1) halogen,
(2) oxo,
(3) $-(CH_2)_rOH$,
(4) $-(CH_2)_rN(R^e)_2$,
(5) $-(CH_2)_rCN$,
(6) $-C_{1-6}$alkyl,
(7) $-CF_3$,
(8) $-C_{1-6}$alkyl-OH,
(9) $-OCH_2OC_{1-6}$alkyl,
(10) $-(CH_2)_rOC_{1-6}$alkyl,
(11) $-OCH_2$aryl,
(12) $-(CH_2)_rSC_{1-6}$alkyl,
(13) $-(CH_2)_rC(O)R^f$,
(14) $-(CH_2)_rC(O)N(R^e)_2$,
(15) $-(CH_2)_rCO_2H$,
(16) $-(CH_2)_rCO_2R^f$,
(17) $-(CH_2)_rC_{3-7}$cycloalkyl,
(18) $-(CH_2)_rC_{2-6}$cycloheteroalkyl,
(19) $-(CH_2)_r$aryl, and

(20) -$(CH_2)_r$heteroaryl,

wherein each CH_2 is unsubstituted or substituted with 1 or 2 substituents selected from: oxo, –OH, -CN, -$N(R^h)_2$, -C_{1-6}alkyl, -OC_{1-6}alkyl, halogen, -CH_2F, -CHF_2, -CF_3, -CO_2H, -CO_2C_{1-6}alkyl, -C_{3-7}cycloalkyl and heteroaryl, and wherein alkyl, cycloalkyl, cycloheteroalkyl, aryl and heteroaryl are unsubstituted or substituted with 1, 2, 3 or 4 substituents selected from: oxo, –OH, -CN, -$N(R^h)_2$, -C_{1-6}alkyl, -OC_{1-6}alkyl, halogen, -CH_2F, -CHF_2, -CF_3, -CO_2H, -CO_2C_{1-6}alkyl, -C_{3-7}cycloalkyl and heteroaryl;

each R^e, R^g and R^h is independently selected from:

(1) hydrogen,

(2) –C_{1-6}alkyl, and

(3) –O-C_{1-6}alkyl,

wherein alkyl is unsubstituted or substituted with 1, 2, 3 or 4 substituents selected from: -OH, oxo, halogen, C_{1-6}alkyl, -OC_{1-6}alkyl, –NH_2, -NH(C_{1-6}alkyl), and -N(C_{1-6}alkyl)$_2$;

each R^j is independently selected from:

(1) hydrogen,

(2) C_{1-6}alkyl,

(3) C_{3-6}cycloalkyl,

(4) –C(O)R^i,

(5) –CO_2R^i, and

(6) –SO_2R^i,

wherein alkyl and cycloalkyl are unsubstituted or substituted with 1, 2, 3 or 4 substituents selected from: -OH, oxo, halogen, C_{1-6}alkyl, -OC_{1-6}alkyl, –NH_2, -NH(C_{1-6}alkyl), and -N(C_{1-6}alkyl)$_2$;

each R^f and R^i is independently selected from:

(1) C_{1-6}alkyl,

(2) -$(CH_2)_r$$C_{4-7}$cycloalkyl,

(3) -$(CH_2)_r$$C_{4-7}$cycloalkenyl,

(4) -$(CH_2)_r$$C_{3-7}$cycloheteroalkyl,

(5) -$(CH_2)_r$$C_{3-7}$cycloheteroalkenyl,

(6) -$(CH_2)_r$aryl, and

(7) -$(CH_2)_r$heteroaryl,

wherein alkyl, cycloalkyl, cycloalkenyl, cycloheteroalkyl, cycloheteroalkenyl, aryl and heteroaryl are unsubstituted or substituted with 1, 2, 3 or 4 substituents selected from: oxo, -OH, -CN, -NH_2, -NH(C_{1-6}alkyl), -N(C_{1-6}alkyl)$_2$, -C_{1-6}alkyl, -OC_{1-6}alkyl, halogen, -CH_2F, -CHF_2, -CF_3, -CO_2H, -CO_2C_{1-6}alkyl, -C_{3-7}cycloalkyl, and heteroaryl;

n is 0, 1, 2, 3 or 4;

m is 0, 1, 2, 3 or 4;

p is 0, 1, 2, or 3;
q is 0, 1, 2, 3 or 4;
r is 0, 1 or 2;
s is 0, 1, 2, 3 or 4;
t is 0, 1, 2, 3 or 4, and
u is 0, 1, 2, 3 or 4.

In one embodiment of the present invention, T is selected from the group consisting of: -CR^3-, N, and N-oxide. In a class of this embodiment, T is -CR^3-. In another class of this embodiment, T is selected from the group consisting of: N, and N-oxide. In another class of this embodiment, T is N. In another class of this embodiment, T is N-oxide.

In another embodiment of the present invention, U is selected from the group consisting of: -CR^1-, N, and N-oxide. In a class of this embodiment, U is –CR^1-. In another class of this embodiment, U is selected from the group consisting of: N, and N-oxide. In another class of this embodiment, U is N. In another class of this embodiment, U is selected from the group consisting of: N-oxide.

In another embodiment of the present invention, V is selected from the group consisting of: -CR^2-, N, and N-oxide. In a class of this embodiment, V is -CR^2-. In another class of this embodiment, V is selected from the group consisting of: N, and N-oxide. In another class of this embodiment, V is N. In another class of this embodiment, V is N-oxide.

In another embodiment of the present invention, W is selected from the group consisting of:-CR^4-, N, and N-oxide. In a class of this embodiment, W is selected from the group consisting of: -CR^4-. In another class of this embodiment, W is selected from the group consisting of: N, and N-oxide. In another class of this embodiment, W is N. In another class of this embodiment, W is N-oxide.

In another embodiment of the present invention, one of T and W is N or N-oxide, U is CR^1 and V is CR^2, provided that if W is N or N-oxide then R^1 is selected from hydrogen, halogen, -CN, -CF_3, -C_{1-6}alkyl, –C_{2-6}alkenyl and–C_{2-6}alkynyl, and if T is N or N-oxide then R^2 is selected from hydrogen, halogen, -CN, -CF_3, -C_{1-6}alkyl, –C_{2-6}alkenyl and–C_{2-6}alkynyl.

In another embodiment of the present invention, one of T and W is N or N-oxide, U is CR^1 and V is CR^2, provided that if W is N or N-oxide then R^1 is halogen, and if T is N or N-oxide then R^2 is halogen.

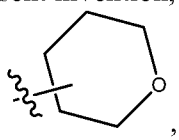
In another embodiment of the present invention, T is N or N-oxide; U is –CR^1-; V is -CR^2-; and W is -CR^4-. In a class of this embodiment, T is N or N-oxide; U is –CR^1-; V is -CR^2-, wherein R^2 is halogen; and W is -CR^4-. In another class of this embodiment, T is N; U is –CR^1-; V is -CR^2-, wherein R^2 is halogen; and W is -CR^4-. In another class of this embodiment, T is N; U is –CR^1-; V is -CR^2-, wherein R^2 is halogen; and W is -CR^4-.

In another embodiment of the present invention, X is selected from: -CH_2-, -CHF-, -

CF_2-, -S-, -O-, –O-CH_2-, –O-CH_2CH_2-, -NH-, -C(O)-, -NHC(O)-, -C(O)NH-, -$NHSO_2$-, -SO_2NH-, and -CO_2-, wherein each CH_2 is unsubstituted or substituted with 1 or 2 substituents selected from: hydroxy, halogen, NH_2, C_{1-6}alkyl, CO_2H, CO_2C_{1-6}alkyl, COC_{1-6}alkyl, phenyl and -CH_2phenyl, and wherein each NH is unsubstituted or substituted with 1 substituent selected from: C_{1-6}alkyl, CO_2H, CO_2C_{1-6}alkyl, COC_{1-6}alkyl, phenyl and -CH_2phenyl. In a class of this embodiment, X is selected from: -CH_2-, -CHF-, -CF_2-, -S-, -O-, –O-CH_2-, –O-CH_2CH_2-, -NH-, -C(O)-, -NHC(O)-, -C(O)NH-, -$NHSO_2$-, -SO_2NH-, and -CO_2-.

In another embodiment of the present invention, X is selected from: -S-, -O-, and -NH-. In another embodiment of the present invention, X is -O-. In another embodiment of the present invention, X is -S-. In another embodiment of the present invention, X is -NH-.

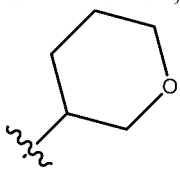
In another embodiment of the present invention, Y is selected from:



,

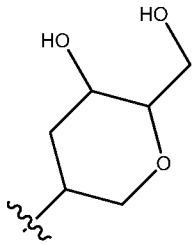
wherein Y is unsubstituted or substituted with 1, 2, 3, 4 or 5 substituents selected from R^b.

In another embodiment of the present invention, Y is selected from:



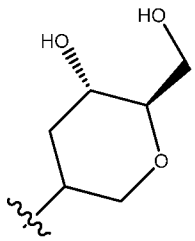
,

wherein Y is unsubstituted or substituted with 1, 2, 3, 4 or 5 substituents selected from R^b. In a class of this embodiment, Y is:



,

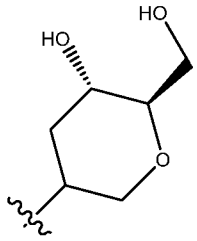
wherein Y is unsubstituted or substituted with 1, 2 or 3 substituents selected from R^b. In another class of this embodiment, Y is:



,

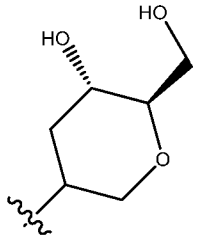
wherein Y is unsubstituted or substituted with 1, 2 or 3 substituents selected from R^b.

In another class of this embodiment, Y is:



,

wherein Y is unsubstituted or substituted with 1, 2 or 3 substituents selected from R^b. In another class of this embodiment, Y is:



,

wherein Y is unsubstituted or substituted with 1 or 2 substituents selected from R^b.

In another embodiment of the present invention, Z is selected from: NR^5, -S-, and -O-. In a class of this embodiment, Z is NR^5. In another class of this embodiment, Z is -S-. In another class of this embodiment, Z is –O-.

In another embodiment of the present invention, each R^1 and R^2 is independently selected from: hydrogen, halogen, CN, CF_3,-C_{1-6}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -$(CH_2)_pC_{3-10}$cycloalkyl, -$(CH_2)_pC_{3-7}$cycloalkyl-aryl, -$(CH_2)_pC_{3-7}$cycloalkyl-heteroaryl, -$(CH_2)_pC_{4-10}$cycloalkenyl, -$(CH_2)_pC_{4-7}$cycloalkenyl-aryl, -$(CH_2)_pC_{4-7}$cycloalkenyl-heteroaryl, -$(CH_2)_pC_{2-10}$cycloheteroalkyl, -$(CH_2)_pC_{2-10}$cycloheteroalkenyl, -$(CH_2)_p$aryl, -$(CH_2)_p$aryl-C_{1-8}alkyl, -$(CH_2)_p$aryl-C_{2-8}alkenyl, -$(CH_2)_p$aryl-C_{2-8}alkynyl-C_{1-8}alkyl, -$(CH_2)_p$aryl-C_{2-8}alkynyl-C_{3-7}cycloalkyl, -$(CH_2)_p$aryl-C_{2-8}alkynyl-C_{3-7}cycloalkenyl, -$(CH_2)_p$aryl-C_{2-8}alkynyl-C_{2-10}cycloheteroalkyl, -$(CH_2)_p$aryl-C_{2-8}alkynyl-C_{2-10}cycloheteroalkenyl, -$(CH_2)_p$aryl-C_{2-8}alkynyl-aryl, -$(CH_2)_p$aryl-C_{2-8}alkynyl-heteroaryl, -$(CH_2)_p$aryl-C_{3-7}cycloalkyl, -$(CH_2)_p$aryl-C_{2-10}cycloheteroalkyl, -$(CH_2)_p$aryl-C_{2-10}cycloheteroalkenyl, -$(CH_2)_p$aryl-aryl, -$(CH_2)_p$aryl-heteroaryl, -$(CH_2)_p$heteroaryl, -$(CH_2)_p$heteroaryl-C_{3-7}cycloalkyl, -$(CH_2)_p$heteroaryl-C_{2-10}cycloheteroalkyl -$(CH_2)_p$heteroaryl-C_{2-10}cycloheteroalkenyl, -$(CH_2)_p$heteroaryl-aryl, -$(CH_2)_p$heteroaryl-heteroaryl, -C_{2-6}alkenyl-alkyl, -C_{2-6}alkenyl-aryl, -C_{2-6}alkenyl-heteroaryl, -C_{2-6}alkenyl-C_{3-7}cycloalkyl, -C_{2-6}alkenyl-C_{3-7}cycloalkenyl, -C_{2-6}alkenyl-C_{2-7}cycloheteroalkyl, -C_{2-6}alkenyl-C_{2-7}cycloheteroalkenyl, -C_{2-6} alkynyl-$(CH_2)_{1-3}$-O-aryl, -C_{2-6}alkynyl-alkyl, -C_{2-6}alkynyl-aryl, -C_{2-6}alkynyl-heteroaryl, -C_{2-6}alkynyl-C_{3-7}cycloalkyl, -C_{2-6}alkynyl-C_{3-7}cycloalkenyl, -C_{2-6}alkynyl-C_{2-7}cycloheteroalkyl, -C_{2-6}alkynyl-C_{2-7}cycloheteroalkenyl, and –C(O)NH-$(CH_2)_{0-3}$phenyl, wherein each CH_2 is unsubstituted or substituted with 1 or 2 substituents selected from: halogen, CF_3, -OH, -NH_2, –C_{1-6}alkyl, -OC_{1-6}alkyl, –NHC_{1-6}alkyl, and –N(C_{1-}

$_6$alkyl)$_2$, and wherein each alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloheteroalkyl, cycloheteroalkenyl, phenyl, aryl and heteroaryl is unsubstituted or substituted with 1, 2, 3 or 4 substituents independently selected from R^a, provided that at least one of and only one of R^1 and R^2 is selected from the group consisting of: hydrogen, halogen, -CN, -CF_3, -C_{1-6}alkyl, –C_{2-6}alkenyl and–C_{2-6}alkynyl. In a class of this embodiment, at least one of and only one of R^1 and R^2 is selected from halogen. In a subclass of this class, at least one of and only one of R^1 and R^2 is selected from: F and Cl.

In another class of this embodiment, each R^1 and R^2 is independently selected from: halogen, aryl-C_{2-8}alkynyl-heteroaryl, -C_{2-6}alkynyl-aryl, aryl, aryl-C_{3-7}cycloalkyl, aryl-C_{2-10}cycloheteroalkyl, aryl-aryl, aryl-heteroaryl, and heteroaryl, wherein each alkynyl, cycloalkyl, cycloheteroalkyl, aryl and heteroaryl is unsubstituted or substituted with 1, 2, 3 or 4 substituents independently selected from R^a, provided that at least one of and only one of R^1 and R^2 is selected from halogen. In a class of this embodiment, at least one of and only one of R^1 and R^2 is selected from: F and Cl. In another class of this embodiment, R^2 is halogen. In a subclass of this class, R^2 is selected from: F and Cl. In another subclass of this class, R^2 is Cl.

In another class of this embodiment, each R^1 and R^2 is independently selected from: halogen, aryl-C_2alkynyl-heteroaryl, -C_2alkynyl-aryl, aryl, aryl-C_{3-7}cycloalkyl, aryl-C_{2-10}cycloheteroalkyl, aryl-aryl, aryl-heteroaryl, and heteroaryl, wherein each alkynyl, cycloalkyl, cycloheteroalkyl, aryl and heteroaryl is unsubstituted or substituted with 1, 2, 3 or 4 substituents independently selected from R^a, provided that at least one of and only one of R^1 and R^2 is selected from halogen. In a class of this embodiment, at least one of and only one of R^1 and R^2 is selected from: F and Cl. In another class of this embodiment, R^2 is halogen. In a subclass of this class, R^2 is selected from: F and Cl. In another subclass of this class, R^2 is Cl.

In another class of this embodiment, each R^1 and R^2 is independently selected from: halogen, phenyl-ethynyl-tetrazole, ethynyl-phenyl, phenyl, phenyl-cyclopropyl, phenyl-pyrrolidine, phenyl-piperazine, phenyl-piperidine, phenyl-oxetane, phenyl-thiamorpholine, phenyl-azetidine, biphenyl, phenyl-pyrazole, phenyl-dihydropyrrolopyrazole, phenyl-pyridine, and benzodioxole, wherein each ethynyl, cycloalkyl, cycloheteroalkyl, phenyl and heteroaryl is unsubstituted or substituted with 1, 2, 3 or 4 substituents independently selected from R^a, provided that at least one of and only one of R^1 and R^2 is selected from halogen. In a subclass of this class, at least one of and only one of R^1 and R^2 is selected from: F and Cl. In another class of this embodiment, R^2 is halogen. In a subclass of this class, R^2 is selected from: F and Cl. In another subclass of this class, R^2 is Cl.

In another class of this embodiment, each R^1 and R^2 is independently selected from: halogen, aryl, aryl-C_{3-7}cycloalkyl, aryl-C_{2-10}cycloheteroalkyl, aryl-aryl, aryl-heteroaryl, and heteroaryl, wherein each cycloalkyl, cycloheteroalkyl, aryl and heteroaryl is unsubstituted or substituted with 1, 2, 3 or 4 substituents independently selected from R^a, provided that at least

one of and only one of R^1 and R^2 is selected from halogen. In a class of this embodiment, at least one of and only one of R^1 and R^2 is selected from: F and Cl. In another class of this embodiment, R^2 is halogen. In a subclass of this class, R^2 is selected from: F and Cl. In another subclass of this class, R^2 is Cl.

In another class of this embodiment, each R^1 and R^2 is independently selected from: halogen, phenyl, phenyl-cyclopropyl, phenyl-pyrrolidine, phenyl-piperazine, phenyl-piperidine, phenyl-oxetane, phenyl-thiamorpholine, phenyl-azetidine, biphenyl, phenyl-pyrazole, phenyl-dihydropyrrolopyrazole, phenyl-pyridine, and benzodioxole, wherein each cycloalkyl, cycloheteroalkyl, phenyl and heteroaryl is unsubstituted or substituted with 1, 2, 3 or 4 substituents independently selected from R^a, provided that at least one of and only one of R^1 and R^2 is selected from halogen. In a subclass of this class, at least one of and only one of R^1 and R^2 is selected from: F and Cl. In another class of this embodiment, R^2 is halogen. In a subclass of this class, R^2 is selected from: F and Cl. In another subclass of this class, R^2 is Cl.

In another subclass of this embodiment of the present invention, each R^1 and R^2 is independently selected from: aryl, aryl-C_{2-10}cycloheteroalkyl, aryl-aryl, and aryl-heteroaryl, wherein each cycloheteroalkyl, aryl and heteroaryl is unsubstituted or substituted with 1, 2, 3 or 4 substituents independently selected from R^a, provided that at least one of and only one of R^1 and R^2 is selected from halogen. In a subclass of this subclass, at least one of and only one of R^1 and R^2 is selected from: F and Cl. In another subclass of this class, R^2 is halogen. In another subclass of this class, R^2 is Cl.

In another embodiment of the present invention, each R^1 and R^2 is independently selected from: halogen, and aryl-aryl, wherein each aryl is unsubstituted or substituted with 1, 2, 3 or 4 substituents independently selected from R^a, provided that at least one of and only one of R^1 and R^2 is selected from halogen. In a subclass of this subclass, at least one of and only one of R^1 and R^2 is selected from: F and Cl. In another subclass of this class, R^2 is halogen. In another subclass of this class, R^2 is Cl.

In another embodiment of the present invention, each R^1 and R^2 is independently selected from: halogen and biphenyl, wherein each phenyl is unsubstituted or substituted with 1, 2, 3 or 4 substituents independently selected from R^a, provided that at least one of and only one of R^1 and R^2 is selected from halogen. In a subclass of this subclass, at least one of and only one of R^1 and R^2 is selected from: F and Cl. In another subclass of this class, R^2 is halogen. In another subclass of this class, R^2 is Cl.

In another subclass of this embodiment of the present invention, each R^1 and R^2 is independently selected from: phenyl, phenyl-pyrrolidine, biphenyl, and phenyl-pyridine, wherein each cycloheteroalkyl, phenyl, and heteroaryl is unsubstituted or substituted with 1, 2, 3 or 4 substituents independently selected from R^a, provided that at least one of and only one of R^1 and R^2 is selected from halogen. In a subclass of this subclass, at least one of and only one

of R^1 and R^2 is selected from: F and Cl. In another subclass of this class, R^2 is halogen. In another subclass of this class, R^2 is Cl,

In another embodiment of the present invention, each R^1 is independently selected from: hydrogen, halogen, CN, CF_3,-C_{1-6}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -$(CH_2)_pC_{3-10}$cycloalkyl, -$(CH_2)_pC_{3-7}$cycloalkyl-aryl, -$(CH_2)_pC_{3-7}$cycloalkyl-heteroaryl, -$(CH_2)_pC_{4-10}$cycloalkenyl, -$(CH_2)_pC_{4-7}$cycloalkenyl-aryl, -$(CH_2)_pC_{4-7}$cycloalkenyl-heteroaryl, -$(CH_2)_pC_{2-10}$cycloheteroalkyl, -$(CH_2)_pC_{2-10}$cycloheteroalkenyl, -$(CH_2)_p$aryl, -$(CH_2)_p$aryl-C_{1-8}alkyl, -$(CH_2)_p$aryl-C_{2-8}alkenyl, -$(CH_2)_p$aryl-C_{2-8}alkynyl-C_{1-8}alkyl, -$(CH_2)_p$aryl-C_{2-8}alkynyl-C_{3-7}cycloalkyl, -$(CH_2)_p$aryl-C_{2-8}alkynyl-C_{3-7}cycloalkenyl, -$(CH_2)_p$aryl-C_{2-8}alkynyl-C_{2-10}cycloheteroalkyl, -$(CH_2)_p$aryl-C_{2-8}alkynyl-C_{2-10}cycloheteroalkenyl, -$(CH_2)_p$aryl-C_{2-8}alkynyl-aryl, -$(CH_2)_p$aryl-C_{2-8}alkynyl-heteroaryl, -$(CH_2)_p$aryl-C_{3-7}cycloalkyl, -$(CH_2)_p$aryl-C_{2-10}cycloheteroalkyl, -$(CH_2)_p$aryl-C_{2-10}cycloheteroalkenyl, -$(CH_2)_p$aryl-aryl, -$(CH_2)_p$aryl-heteroaryl, -$(CH_2)_p$heteroaryl, -$(CH_2)_p$heteroaryl-C_{3-7}cycloalkyl, -$(CH_2)_p$heteroaryl-C_{2-10}cycloheteroalkyl -$(CH_2)_p$heteroaryl-C_{2-10}cycloheteroalkenyl, -$(CH_2)_p$heteroaryl-aryl, -$(CH_2)_p$heteroaryl-heteroaryl, -C_{2-6}alkenyl-alkyl, -C_{2-6}alkenyl-aryl, -C_{2-6}alkenyl-heteroaryl, -C_{2-6}alkenyl-C_{3-7}cycloalkyl, -C_{2-6}alkenyl-C_{3-7}cycloalkenyl, -C_{2-6}alkenyl-C_{2-7}cycloheteroalkyl, -C_{2-6}alkenyl-C_{2-7}cycloheteroalkenyl, -C_{2-6} alkynyl-$(CH_2)_{1-3}$-O-aryl, -C_{2-6}alkynyl-alkyl, -C_{2-6}alkynyl-aryl, -C_{2-6}alkynyl-heteroaryl, -C_{2-6}alkynyl-C_{3-7}cycloalkyl, -C_{2-6}alkynyl-C_{3-7}cycloalkenyl, -C_{2-6}alkynyl-C_{2-7}cycloheteroalkyl, -C_{2-6}alkynyl-C_{2-7}cycloheteroalkenyl, and –C(O)NH-$(CH_2)_{0-3}$phenyl, wherein each CH_2 is unsubstituted or substituted with 1 or 2 substituents selected from: halogen, CF_3, -OH, -NH_2, –C_{1-6}alkyl, -OC_{1-6}alkyl, –NHC_{1-6}alkyl, and –N$(C_{1-6}$alkyl$)_2$, and wherein each alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloheteroalkyl, cycloheteroalkenyl, phenyl, aryl and heteroaryl is unsubstituted or substituted with 1, 2, 3 or 4 substituents independently selected from R^a.

In another embodiment of the present invention, each R^1 is independently selected from: -$(CH_2)_pC_{3-10}$cycloalkyl, -$(CH_2)_pC_{3-7}$cycloalkyl-aryl, -$(CH_2)_pC_{3-7}$cycloalkyl-heteroaryl, -$(CH_2)_pC_{4-10}$cycloalkenyl, -$(CH_2)_pC_{4-7}$cycloalkenyl-aryl, -$(CH_2)_pC_{4-7}$cycloalkenyl-heteroaryl, -$(CH_2)_pC_{2-10}$cycloheteroalkyl, -$(CH_2)_pC_{2-10}$cycloheteroalkenyl, -$(CH_2)_p$aryl, -$(CH_2)_p$aryl-C_{1-8}alkyl, -$(CH_2)_p$aryl-C_{2-8}alkenyl, -$(CH_2)_p$aryl-C_{2-8}alkynyl-C_{1-8}alkyl, -$(CH_2)_p$aryl-C_{2-8}alkynyl-C_{3-7}cycloalkyl, -$(CH_2)_p$aryl-C_{2-8}alkynyl-C_{3-7}cycloalkenyl, -$(CH_2)_p$aryl-C_{2-8}alkynyl-C_{2-10}cycloheteroalkyl, -$(CH_2)_p$aryl-C_{2-8}alkynyl-C_{2-10}cycloheteroalkenyl, -$(CH_2)_p$aryl-C_{2-8}alkynyl-aryl, -$(CH_2)_p$aryl-C_{2-8}alkynyl-heteroaryl, -$(CH_2)_p$aryl-C_{3-7}cycloalkyl, -$(CH_2)_p$aryl-C_{2-10}cycloheteroalkyl, -$(CH_2)_p$aryl-C_{2-10}cycloheteroalkenyl, -$(CH_2)_p$aryl-aryl, -$(CH_2)_p$aryl-heteroaryl, -$(CH_2)_p$heteroaryl, -$(CH_2)_p$heteroaryl-C_{3-7}cycloalkyl, -$(CH_2)_p$heteroaryl-C_{2-10}cycloheteroalkyl -$(CH_2)_p$heteroaryl-C_{2-10}cycloheteroalkenyl, -$(CH_2)_p$heteroaryl-aryl, -$(CH_2)_p$heteroaryl-heteroaryl, -C_{2-6}alkenyl-alkyl, -C_{2-6}alkenyl-aryl, -C_{2-6}alkenyl-heteroaryl, -C_{2-6}alkenyl-C_{3-}

7cycloalkyl, -C_{2-6}alkenyl-C_{3-7}cycloalkenyl, -C_{2-6}alkenyl-C_{2-7}cycloheteroalkyl, -C_{2-6}alkenyl-C_{2-7}cycloheteroalkenyl, -C_{2-6} alkynyl-$(CH_2)_{1-3}$-O-aryl, -C_{2-6}alkynyl-alkyl, -C_{2-6}alkynyl-aryl, -C_{2-6}alkynyl-heteroaryl, -C_{2-6}alkynyl-C_{3-7}cycloalkyl, -C_{2-6}alkynyl-C_{3-7}cycloalkenyl, -C_{2-6}alkynyl-C_{2-7}cycloheteroalkyl, -C_{2-6}alkynyl-C_{2-7}cycloheteroalkenyl, and –C(O)NH-$(CH_2)_{0-3}$phenyl, wherein each CH_2 is unsubstituted or substituted with 1 or 2 substituents selected from: halogen, CF_3, -OH, -NH_2, –C_{1-6}alkyl, -OC_{1-6}alkyl, –NHC_{1-6}alkyl, and –N(C_{1-6}alkyl)$_2$, and wherein each alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloheteroalkyl, cycloheteroalkenyl, phenyl, aryl and heteroaryl is unsubstituted or substituted with 1, 2, 3 or 4 substituents independently selected from R^a.

In another class of this embodiment, each R^1 is independently selected from: aryl-C_{2-8}alkynyl-heteroaryl, -C_{2-6}alkynyl-aryl, aryl, aryl-C_{3-7}cycloalkyl, aryl-C_{2-10}cycloheteroalkyl, aryl-aryl, aryl-heteroaryl and heteroaryl, wherein each alkynyl, cycloalkyl, cycloheteroalkyl, aryl and heteroaryl is unsubstituted or substituted with 1, 2, 3 or 4 substituents independently selected from R^a.

In another class of this embodiment, each R^1 is independently selected from: aryl-C_2alkynyl-heteroaryl, -C_2alkynyl-aryl, aryl, aryl-C_{3-7}cycloalkyl, aryl-C_{2-10}cycloheteroalkyl, aryl-aryl, aryl-heteroaryl and heteroaryl, wherein each alkynyl, cycloalkyl, cycloheteroalkyl, aryl and heteroaryl is unsubstituted or substituted with 1, 2, 3 or 4 substituents independently selected from R^a.

In another class of this embodiment, each R^1 is independently selected from: phenyl-ethynyl-tetrazole, ethynyl-phenyl, phenyl, phenyl-cyclopropyl, phenyl-pyrrolidine, phenyl-piperazine, phenyl-piperidine, phenyl-oxetane, phenyl-thiamorpholine, phenyl-azetidine, biphenyl, phenyl-pyrazole, phenyl-dihydropyrrolopyrazole, phenyl-pyridine, and benzodioxole, wherein each ethynyl, cycloalkyl, cycloheteroalkyl, phenyl and heteroaryl is unsubstituted or substituted with 1, 2, 3 or 4 substituents independently selected from R^a.

In another class of this embodiment, each R^1 is independently selected from: aryl, aryl-C_{3-7}cycloalkyl, aryl-C_{2-10}cycloheteroalkyl, aryl-aryl, aryl-heteroaryl, and heteroaryl, wherein each cycloalkyl, cycloheteroalkyl, aryl and heteroaryl is unsubstituted or substituted with 1, 2, 3 or 4 substituents independently selected from R^a.

In another class of this embodiment, each R^1 is independently selected from: phenyl, phenyl-cyclopropyl, phenyl-pyrrolidine, phenyl-piperazine, phenyl-piperidine, phenyl-oxetane, phenyl-thiamorpholine, phenyl-azetidine, biphenyl, phenyl-pyrazole, phenyl-dihydropyrrolopyrazole, phenyl-pyridine, and benzodioxole, wherein each cycloalkyl, cycloheteroalkyl, phenyl and heteroaryl is unsubstituted or substituted with 1, 2, 3 or 4 substituents independently selected from R^a.

In another embodiment of the present invention, each R^1 is independently selected from: aryl-C_{2-8}alkynyl-heteroaryl, -C_{2-6}alkynyl-aryl, aryl, aryl-C_{3-7}cycloalkyl, aryl-C_{2-}

10cycloheteroalkyl, aryl-aryl, aryl-heteroaryl and heteroaryl, wherein each cycloalkyl, cycloheteroalkyl, aryl and heteroaryl is unsubstituted or substituted with 1, 2, 3 or 4 substituents independently selected from R^a.

In another embodiment of the present invention, each R^1 is independently selected from: aryl, aryl-C_{2-10}cycloheteroalkyl, aryl-aryl, and aryl-heteroaryl, wherein each cycloheteroalkyl, aryl and heteroaryl is unsubstituted or substituted with 1, 2, 3 or 4 substituents independently selected from R^a. In another embodiment of the present invention, each R^1 is independently selected from: aryl-aryl, wherein each aryl is unsubstituted or substituted with 1, 2, 3 or 4 substituents independently selected from R^a.

In another embodiment of the present invention, each R^1 is independently selected from: phenyl, phenyl-pyrrolidine, biphenyl, and phenyl-pyridine, wherein each cycloheteroalkyl, phenyl, and heteroaryl is unsubstituted or substituted with 1, 2, 3 or 4 substituents independently selected from R^a. In another embodiment of the present invention, each R^1 is independently selected from: biphenyl, wherein each phenyl is unsubstituted or substituted with 1, 2, 3 or 4 substituents independently selected from R^a.

In another embodiment of the present invention, each each R^1 is independently selected from: hydrogen, halogen, -CN, $-CF_3$, $-C_{1-6}$alkyl, $-C_{2-6}$alkenyl and $-C_{2-6}$alkynyl. In another embodiment of the present invention, each each R^1 is independently selected from: halogen. In another embodiment of the present invention, each R^1 is independently selected from: Cl and F. In a class of this embodiment, R^1 is Cl. In another class of this embodiment, R^1 is F.

In another embodiment of the present invention, R^2 is independently selected from: hydrogen, halogen, CN, CF_3,-C_{1-6}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -$(CH_2)_pC_{3-10}$cycloalkyl, -$(CH_2)_pC_{3-7}$cycloalkyl-aryl, -$(CH_2)_pC_{3-7}$cycloalkyl-heteroaryl, -$(CH_2)_pC_{4-10}$cycloalkenyl, -$(CH_2)_pC_{4-7}$cycloalkenyl-aryl, -$(CH_2)_pC_{4-7}$cycloalkenyl-heteroaryl, -$(CH_2)_pC_{2-10}$cycloheteroalkyl, -$(CH_2)_pC_{2-10}$cycloheteroalkenyl, -$(CH_2)_p$aryl, -$(CH_2)_p$aryl-C_{1-8}alkyl, -$(CH_2)_p$aryl-C_{2-8}alkenyl, -$(CH_2)_p$aryl-C_{2-8}alkynyl-C_{1-8}alkyl, -$(CH_2)_p$aryl-C_{2-8}alkynyl-C_{3-7}cycloalkyl, -$(CH_2)_p$aryl-C_{2-8}alkynyl-C_{3-7}cycloalkenyl, -$(CH_2)_p$aryl-C_{2-8}alkynyl-C_{2-10}cycloheteroalkyl, -$(CH_2)_p$aryl-C_{2-8}alkynyl-C_{2-10}cycloheteroalkenyl, -$(CH_2)_p$aryl-C_{2-8}alkynyl-aryl, -$(CH_2)_p$aryl-C_{2-8}alkynyl-heteroaryl, -$(CH_2)_p$aryl-C_{3-7}cycloalkyl, -$(CH_2)_p$aryl-C_{2-10}cycloheteroalkyl, -$(CH_2)_p$aryl-C_{2-10}cycloheteroalkenyl, -$(CH_2)_p$aryl-aryl, -$(CH_2)_p$aryl-heteroaryl, -$(CH_2)_p$heteroaryl, -$(CH_2)_p$heteroaryl-C_{3-7}cycloalkyl, -$(CH_2)_p$heteroaryl-C_{2-10}cycloheteroalkyl -$(CH_2)_p$heteroaryl-C_{2-10}cycloheteroalkenyl, -$(CH_2)_p$heteroaryl-aryl, -$(CH_2)_p$heteroaryl-heteroaryl, -C_{2-6}alkenyl-alkyl, -C_{2-6}alkenyl-aryl, -C_{2-6}alkenyl-heteroaryl, -C_{2-6}alkenyl-C_{3-7}cycloalkyl, -C_{2-6}alkenyl-C_{3-7}cycloalkenyl, -C_{2-6}alkenyl-C_{2-7}cycloheteroalkyl, -C_{2-6}alkenyl-C_{2-7}cycloheteroalkenyl, -C_{2-6} alkynyl-$(CH_2)_{1-3}$-O-aryl, -C_{2-6}alkynyl-alkyl, -C_{2-6}alkynyl-aryl, -C_{2-6}alkynyl-heteroaryl, -C_{2-6}alkynyl-C_{3-7}cycloalkyl, -C_{2-6}alkynyl-C_{3-7}cycloalkenyl, -C_{2-6}alkynyl-C_{2-7}cycloheteroalkyl, -C_{2-6}alkynyl-C_{2-}

7cycloheteroalkenyl, and –C(O)NH-$(CH_2)_{0-3}$phenyl, wherein each CH_2 is unsubstituted or substituted with 1 or 2 substituents selected from: halogen, CF_3, -OH, $-NH_2$, $-C_{1-6}$alkyl, $-OC_{1-6}$alkyl, $-NHC_{1-6}$alkyl, and $-N(C_{1-6}alkyl)_2$, and wherein each alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloheteroalkyl, cycloheteroalkenyl, phenyl, aryl and heteroaryl is unsubstituted or substituted with 1, 2, 3 or 4 substituents independently selected from R^a.

In another embodiment of the present invention, R^2 is independently selected from: -$(CH_2)_pC_{3-10}$cycloalkyl, -$(CH_2)_pC_{3-7}$cycloalkyl-aryl, -$(CH_2)_pC_{3-7}$cycloalkyl-heteroaryl, -$(CH_2)_pC_{4-10}$cycloalkenyl, -$(CH_2)_pC_{4-7}$cycloalkenyl-aryl, -$(CH_2)_pC_{4-7}$cycloalkenyl-heteroaryl, -$(CH_2)_pC_{2-10}$cycloheteroalkyl, -$(CH_2)_pC_{2-10}$cycloheteroalkenyl, -$(CH_2)_p$aryl, -$(CH_2)_p$aryl-C_{1-8}alkyl, -$(CH_2)_p$aryl-C_{2-8}alkenyl, -$(CH_2)_p$aryl-C_{2-8}alkynyl-C_{1-8}alkyl, -$(CH_2)_p$aryl-C_{2-8}alkynyl-C_{3-7}cycloalkyl, -$(CH_2)_p$aryl-C_{2-8}alkynyl-C_{3-7}cycloalkenyl, -$(CH_2)_p$aryl-C_{2-8}alkynyl-C_{2-10}cycloheteroalkyl, -$(CH_2)_p$aryl-C_{2-8}alkynyl-C_{2-10}cycloheteroalkenyl, -$(CH_2)_p$aryl-C_{2-8}alkynyl-aryl, -$(CH_2)_p$aryl-C_{2-8}alkynyl-heteroaryl, -$(CH_2)_p$aryl-C_{3-7}cycloalkyl, -$(CH_2)_p$aryl-C_{2-10}cycloheteroalkyl, -$(CH_2)_p$aryl-C_{2-10}cycloheteroalkenyl, -$(CH_2)_p$aryl-aryl, -$(CH_2)_p$aryl-heteroaryl, -$(CH_2)_p$heteroaryl, -$(CH_2)_p$heteroaryl-C_{3-7}cycloalkyl, -$(CH_2)_p$heteroaryl-C_{2-10}cycloheteroalkyl -$(CH_2)_p$heteroaryl-C_{2-10}cycloheteroalkenyl, -$(CH_2)_p$heteroaryl-aryl, -$(CH_2)_p$heteroaryl-heteroaryl, -C_{2-6}alkenyl-alkyl, -C_{2-6}alkenyl-aryl, -C_{2-6}alkenyl-heteroaryl, -C_{2-6}alkenyl-C_{3-7}cycloalkyl, -C_{2-6}alkenyl-C_{3-7}cycloalkenyl, -C_{2-6}alkenyl-C_{2-7}cycloheteroalkyl, -C_{2-6}alkenyl-C_{2-7}cycloheteroalkenyl, -C_{2-6} alkynyl-$(CH_2)_{1-3}$-O-aryl, -C_{2-6}alkynyl-alkyl, -C_{2-6}alkynyl-aryl, -C_{2-6}alkynyl-heteroaryl, -C_{2-6}alkynyl-C_{3-7}cycloalkyl, -C_{2-6}alkynyl-C_{3-7}cycloalkenyl, -C_{2-6}alkynyl-C_{2-7}cycloheteroalkyl, -C_{2-6}alkynyl-C_{2-7}cycloheteroalkenyl, and –C(O)NH-$(CH_2)_{0-3}$phenyl, wherein each CH_2 is unsubstituted or substituted with 1 or 2 substituents selected from: halogen, CF_3, -OH, $-NH_2$, $-C_{1-6}$alkyl, $-OC_{1-6}$alkyl, $-NHC_{1-6}$alkyl, and $-N(C_{1-6}alkyl)_2$, and wherein each alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloheteroalkyl, cycloheteroalkenyl, phenyl, aryl and heteroaryl is unsubstituted or substituted with 1, 2, 3 or 4 substituents independently selected from R^a.

In a class of this embodiment, each R^2 is independently selected from: aryl-C_{2-8}alkynyl-heteroaryl, -C_{2-6}alkynyl-aryl, aryl, aryl-C_{3-7}cycloalkyl, aryl-C_{2-10}cycloheteroalkyl, aryl-aryl, aryl-heteroaryl, and heteroaryl, wherein each alkynyl, cycloalkyl, cycloheteroalkyl, aryl and heteroaryl is unsubstituted or substituted with 1, 2, 3 or 4 substituents independently selected from R^a.

In another class of this embodiment, each R^2 is independently selected from: aryl-C_2alkynyl-heteroaryl, -C_2alkynyl-aryl, aryl, aryl-C_{3-7}cycloalkyl, aryl-C_{2-10}cycloheteroalkyl, aryl-aryl, aryl-heteroaryl, and heteroaryl, wherein each alkynyl, cycloalkyl, cycloheteroalkyl, aryl and heteroaryl is unsubstituted or substituted with 1, 2, 3 or 4 substituents independently selected from R^a.

In another class of this embodiment, each R^2 is independently selected from: phenyl-ethynyl-tetrazole, ethynyl-phenyl, phenyl, phenyl-cyclopropyl, phenyl-pyrrolidine, phenyl-piperazine, phenyl-piperidine, phenyl-oxetane, phenyl-thiamorpholine, phenyl-azetidine, biphenyl, phenyl-pyrazole, phenyl-dihydropyrrolopyrazole, phenyl-pyridine, and benzodioxole, wherein each ethynyl, cycloalkyl, cycloheteroalkyl, phenyl and heteroaryl is unsubstituted or substituted with 1, 2, 3 or 4 substituents independently selected from R^a.

In another class of this embodiment, each R^2 is independently selected from: aryl, aryl-C_{3-7}cycloalkyl, aryl-C_{2-10}cycloheteroalkyl, aryl-aryl, aryl-heteroaryl and heteroaryl, wherein each cycloalkyl, cycloheteroalkyl, aryl and heteroaryl is unsubstituted or substituted with 1, 2, 3 or 4 substituents independently selected from R^a.

In another class of this embodiment, each R^2 is independently selected from: phenyl, phenyl-cyclopropyl, phenyl-pyrrolidine, phenyl-piperazine, phenyl-piperidine, phenyl-oxetane, phenyl-thiamorpholine, phenyl-azetidine, biphenyl, phenyl-pyrazole, phenyl-dihydropyrrolopyrazole, phenyl-pyridine, and benzodioxole, wherein each cycloalkyl, cycloheteroalkyl, phenyl and heteroaryl is unsubstituted or substituted with 1, 2, 3 or 4 substituents independently selected from R^a.

In another embodiment of the present invention, R^2 is independently selected from: aryl, aryl-C_{2-10}cycloheteroalkyl, aryl-aryl, and aryl-heteroaryl, wherein each cycloheteroalkyl, aryl and heteroaryl is unsubstituted or substituted with 1, 2, 3 or 4 substituents independently selected from R^a. In another embodiment of the present invention, each R^2 is independently selected from: phenyl, phenyl-pyrrolidine, biphenyl, and phenyl-pyridine, wherein each cycloheteroalkyl, phenyl, and heteroaryl is unsubstituted or substituted with 1, 2, 3 or 4 substituents independently selected from R^a.

In another embodiment of the present invention, each R^2 is independently selected from: aryl-aryl, wherein each aryl is unsubstituted or substituted with 1, 2, 3 or 4 substituents independently selected from R^a.

In another embodiment of the present invention, each R^2 is independently selected from: biphenyl, wherein each phenyl is unsubstituted or substituted with 1, 2, 3 or 4 substituents independently selected from R^a.

In another embodiment of the present invention, each R^2 is independently selected from: hydrogen, halogen, -CN, -CF_3, -C_{1-6}alkyl, –C_{2-6}alkenyl and–C_{2-6}alkynyl. In another embodiment of the present invention, each R^2 is independently selected from: halogen. In another embodiment of the present invention, each R^2 is independently selected from: Cl and F. In a class of this embodiment, R^2 is Cl. In another class of this embodiment, R^2 is F.

In another embodiment of the present invention, R^3 and R^4 are each independently selected from: hydrogen, halogen, –C_{1-6}alkyl, –C_{2-6}alkenyl, –C_{2-6}alkynyl, –C_{3-10}cycloalkyl, –C_{3-10}cycloalkenyl, aryl, heteroaryl, –CN, –CF_3, –OH, -OC_{1-6}alkyl, –NH_2, –NHC_{1-6}alkyl, –

$N(C_{1-6}alkyl)_2$, $-SC_{1-6}alkyl$, $-SOC_{1-6}alkyl$, $-SO_2C_{1-6}alkyl$, $-NHSO_2C_{1-6}alkyl$, $-NHC(O)C_{1-6}alkyl$, $-SO_2NHC_{1-6}alkyl$, and $-C(O)NHC_{1-6}alkyl$.

In another embodiment of the present invention, each R^3 is independently selected from: hydrogen, halogen, $-C_{1-6}alkyl$, $-C_{2-6}alkenyl$, $-C_{2-6}alkynyl$, $-C_{3-10}cycloalkyl$, $-C_{3-10}cycloalkenyl$, aryl, heteroaryl, $-CN$, $-CF_3$, $-OH$, $-OC_{1-6}alkyl$, $-NH_2$, $-NHC_{1-6}alkyl$, $-N(C_{1-6}alkyl)_2$, $-SC_{1-6}alkyl$, $-SOC_{1-6}alkyl$, $-SO_2C_{1-6}alkyl$, $-NHSO_2C_{1-6}alkyl$, $-NHC(O)C_{1-6}alkyl$, $-SO_2NHC_{1-6}alkyl$, and $-C(O)NHC_{1-6}alkyl$.

In another embodiment of the present invention, R^3 is selected from hydrogen, halogen, and $-C_{1-6}alkyl$. In a class of this embodiment, R^3 is hydrogen. In a class of this embodiment, R^3 is halogen. In another class of this embodiment of the present invention, R^3 is absent.

In another embodiment of the present invention, each R^4 is absent or independently selected from: hydrogen, halogen, $-C_{1-6}alkyl$, $-C_{2-6}alkenyl$, $-C_{2-6}alkynyl$, $-C_{3-10}cycloalkyl$, $-C_{3-10}cycloalkenyl$, aryl, heteroaryl, $-CN$, $-CF_3$, $-OH$, $-OC_{1-6}alkyl$, $-NH_2$, $-NHC_{1-6}alkyl$, $-N(C_{1-6}alkyl)_2$, $-SC_{1-6}alkyl$, $-SOC_{1-6}alkyl$, $-SO_2C_{1-6}alkyl$, $-NHSO_2C_{1-6}alkyl$, $-NHC(O)C_{1-6}alkyl$, $-SO_2NHC_{1-6}alkyl$, and $-C(O)NHC_{1-6}alkyl$.

In another embodiment of the present invention, R^4 is selected from hydrogen, halogen, and $-C_{1-6}alkyl$. In a class of this embodiment, R^4 is hydrogen. In another class of this embodiment, R^4 is halogen. In another class of this embodiment of the present invention, R^4 is absent.

In another embodiment of the present invention, R^5 is selected from: hydrogen, $-C_{1-6}alkyl$, $-C_{1-6}alkenyl$, $-(CH_2)_uOH$, $-CH_2CO_2H$, and $-CH_2CO_2C_{1-6}alkyl$. In a class of this embodiment, R^5 is hydrogen.

In another embodiment of the present invention, each R^a is independently selected from the group consisting of: $-(CH_2)_m$-halogen, oxo, $-(CH_2)_mOH$, $-(CH_2)_mN(R^j)_2$, $-(CH_2)_mNO_2$, $-(CH_2)_mCN$, $-C_{1-6}alkyl$, $-(CH_2)_mCF_3$, $-(CH_2)_mOCF_3$, $-O-(CH_2)_m-OC_{1-6}$ alkyl, $-(CH_2)_mN(R^j)C(O)R^f$, $-(CH_2)_mN(R^j)CO_2R^f$, $-(CH_2)_mC(=N-OH)N(R^j)_2$, $-(CH_2)_mOC_{1-6}alkyl$, $-(CH_2)_mO-(CH_2)_m-C_{3-7}cycloalkyl$, $-(CH_2)_mO-(CH_2)_m-C_{2-7}cycloheteroalkyl$, $-(CH_2)_mO-(CH_2)_m$-aryl, $-(CH_2)_mO-(CH_2)_m$-heteroaryl, $-(CH_2)_mSC_{1-6}alkyl$, $-(CH_2)_mS(O)C_{1-6}alkyl$, $-(CH_2)_mSO_2C_{1-6}alkyl$, $-(CH_2)_mSO_2(CH_2)_m-C_{3-7}cycloalkyl$, $-(CH_2)_mSO_2(CH_2)_m-C_{2-7}cycloheteroalkyl$, $-(CH_2)_mSO_2(CH_2)_m$-aryl, $-(CH_2)_mSO_2(CH_2)_m$-heteroaryl, $-(CH_2)_mSO_2NH_2$, $-(CH_2)_mSO_2NHC_{1-6}alkyl$, $-(CH_2)_mSO_2NHC_{3-7}cycloalkyl$, $-(CH_2)_mSO_2NHC_{2-7}cycloheteroalkyl$, $-(CH_2)_mSO_2NH$-aryl, $-(CH_2)_mSO_2NH$-heteroaryl, $-(CH_2)_mNHSO_2C_{1-6}alkyl$, $-(CH_2)_mNHSO_2-C_{3-7}cycloalkyl$, $-(CH_2)_mNHSO_2-C_{2-7}cycloheteroalkyl$, $-(CH_2)_mNHSO_2$-aryl, $-(CH_2)_mNHSO_2NH$-heteroaryl, $-(CH_2)_mN(R^j)-C_{1-6}alkyl$, $-(CH_2)_mN(R^j)-C_{3-7}cycloalkyl$, $-(CH_2)_mN(R^j)-C_{2-7}cycloheteroalkyl$, $-(CH_2)_mN(R^j)-C_{2-7}cycloheteroalkenyl$, $-(CH_2)_mN(R^j)$-aryl, $-(CH_2)_mN(R^j)$-heteroaryl, $-(CH_2)_mC(O)R^f$, $-(CH_2)_mC(O)N(R^j)_2$, $-(CH_2)_mN(R^j)C(O)N(R^j)_2$, $-(CH_2)_mCO_2H$, $-(CH_2)_mOCOH$, -

$(CH_2)_mCO_2R^f$, $-(CH_2)_mOCOR^f$, $-(CH_2)_mC_{3-7}$cycloalkyl, $-(CH_2)_mC_{3-7}$cycloalkenyl, $-(CH_2)_mC_{2-6}$cycloheteroalkyl, $-(CH_2)_mC_{2-6}$cycloheteroalkenyl, $-(CH_2)_m$aryl, and $-(CH_2)_m$heteroaryl, wherein each CH_2 is unsubstituted or substituted with 1 or 2 substituents selected from: oxo, -OH, $-(CH_2)_{1-3}OH$, -CN, $-NH_2$, $-NH(C_{1-6}alkyl)$, $-N(C_{1-6}alkyl)_2$, oxo, $-C_{1-6}$alkyl, $-C_{1-6}$alkyl substituted with 1-5 OH, $-OC_{1-6}$alkyl, halogen, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CO_2H$, $-CO_2C_{1-6}$alkyl, $-C_{3-7}$cycloalkyl, phenyl, CH_2phenyl, heteroaryl and CH_2heteroaryl, and wherein alkyl, cycloalkyl, cycloalkenyl, cycloheteroalkyl, cycloheteroalkenyl, aryl and heteroaryl are unsubstituted or substituted with 1, 2, 3 or 4 substituents selected from: oxo, -OH, $-(CH_2)_{1-5}OH$, $-(CH_2)_{1-5}CN$, -CN, $-NH_2$, $-NH(C_{1-6}alkyl)$, $-N(C_{1-6}alkyl)_2$, $-C_{1-6}$alkyl, $-C_{1-6}$alkyl substituted with 1-5 OH, $-OC_{1-6}$alkyl, halogen, $-CH_2F$, $-CHF_2$, $-CF_3$, $-(CH_2)_{1-5}CF_3$ optionally substituted with 1, 2 or 3 -OH, $-CO_2H$, $-CO_2C_{1-6}$alkyl, $-SO_2C_{1-6}$alkyl, $-C_{3-7}$cycloalkyl, phenyl, CH_2phenyl, heteroaryl and CH_2heteroaryl.

In another embodiment of the present invention, each R^a is independently selected from the group consisting of: -halogen, oxo, $-(CH_2)_mOH$, $-(CH_2)_mN(R^j)_2$, -CN, $-C_{1-6}$alkyl, $-(CH_2)_mCF_3$, $-N(R^j)CO_2R^f$, $-OC_{1-6}$alkyl, $-O-C_{3-7}$cycloalkyl, $-O-C_{2-7}$cycloheteroalkyl, $-(CH_2)_mSO_2C_{1-6}$alkyl, $-SO_2-C_{3-7}$cycloalkyl, $-SO_2-C_{2-7}$cycloheteroalkyl, $-SO_2NH_2$, $-SO_2NHC_{1-6}$alkyl, $-SO_2NHC_{3-7}$cycloalkyl, $-N(R^j)-C_{1-6}$alkyl, $-C(O)R^f$, $-C(O)N(R^j)_2$, $-(CH_2)_mCO_2H$, $-CO_2R^f$, $-(CH_2)_mC_{2-6}$cycloheteroalkyl, and -heteroaryl, wherein each CH_2 is unsubstituted or substituted with 1 or 2 substituents selected from: oxo, -OH, $-(CH_2)_{1-3}OH$, -CN, $-NH_2$, $-NH(C_{1-6}alkyl)$, $-N(C_{1-6}alkyl)_2$, oxo, $-C_{1-6}$alkyl, $-C_{1-6}$alkyl substituted with 1-5 OH, $-OC_{1-6}$alkyl, halogen, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CO_2H$, $-CO_2C_{1-6}$alkyl, $-C_{3-7}$cycloalkyl, phenyl, CH_2phenyl, heteroaryl and CH_2heteroaryl, and wherein alkyl, cycloalkyl, cycloheteroalkyl and heteroaryl are unsubstituted or substituted with 1, 2, 3 or 4 substituents selected from: oxo, -OH, $-(CH_2)_{1-5}OH$, $-(CH_2)_{1-5}CN$, -CN, $-NH_2$, $-NH(C_{1-6}alkyl)$, $-N(C_{1-6}alkyl)_2$, $-C_{1-6}$alkyl, $-C_{1-6}$alkyl substituted with 1-5 OH, $-OC_{1-6}$alkyl, halogen, $-CH_2F$, $-CHF_2$, $-CF_3$, $-(CH_2)_{1-5}CF_3$ optionally substituted with 1, 2 or 3 -OH, $-CO_2H$, $-CO_2C_{1-6}$alkyl, and $-SO_2C_{1-6}$alkyl.

In another embodiment of the present invention, each R^a is independently selected from the group consisting of: -halogen, oxo, $-(CH_2)_mOH$, $-(CH_2)_mN(R^j)_2$, -CN, $-C_{1-6}$alkyl, $-(CH_2)_mCF_3$, $-N(R^j)CO_2R^f$, $-OC_{1-6}$alkyl, $-O-C_{3-7}$cycloalkyl, $-O-C_{2-7}$cycloheteroalkyl, $-(CH_2)_mSO_2C_{1-6}$alkyl, $-SO_2-C_{3-7}$cycloalkyl, $-SO_2-C_{2-7}$cycloheteroalkyl, $-SO_2NH_2$, $-SO_2NHC_{1-6}$alkyl, $-SO_2NHC_{3-7}$cycloalkyl, $-N(R^j)-C_{1-6}$alkyl, $-C(O)R^f$, $-C(O)N(R^j)_2$, $-(CH_2)_mCO_2H$, $-CO_2R^f$, $-(CH_2)_mC_{2-6}$cycloheteroalkyl, and -heteroaryl, wherein each CH_2 is unsubstituted or substituted with 1 or 2 substituents selected from: oxo, -OH, $-(CH_2)_{1-3}OH$, -CN, $-NH_2$, $-NH(C_{1-6}alkyl)$, $-N(C_{1-6}alkyl)_2$, oxo, $-C_{1-6}$alkyl, $-C_{1-6}$alkyl substituted with 1-5 OH, $-OC_{1-6}$alkyl, halogen, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CO_2H$, $-CO_2C_{1-6}$alkyl, $-C_{3-7}$cycloalkyl, phenyl, CH_2phenyl, heteroaryl and CH_2heteroaryl, and wherein alkyl, cycloalkyl,

cycloheteroalkyl, and heteroaryl are unsubstituted or substituted with 1, 2, 3 or 4 substituents selected from: oxo, -OH, -$(CH_2)_{1-5}OH$, -NH_2, -$N(C_{1-6}alkyl)_2$, -C_{1-6}alkyl, halogen, -CF_3, and -SO_2C_{1-6}alkyl.

In another embodiment of the present invention, each R^a is independently selected from the group consisting of: F, oxo, -OH, -CH_2OH, -CH_3, -$C(CH_3)_2CH_2OH$, -$C(CH_3)_2OH$, -$CF_2C(CH_3)_2OH$, -$CH_2C(CH_3)_2OH$, -CH(CF_3)NH-cyclopropyl, -$NHCO_2CH_3$, -CN, -CH_2F, -CH_2CF_3, -CH(NH_2)CF_3,-$NHCO_2CH_2CH(OH)CH_2OH$, -$NHCO_2(CH_2)_2$-imidazole, -$NHCO_2(CH_2)_2$-morpholine, -$NHCO_2(CH_2)_2N(CH_3)_2$, -OCH_2CH_3, -$OCH(CH_3)CH_2OH$, -O-cyclobutyl, -O-oxetane, -O-tetrahydrothiopyran, -SO_2CH_3, -$CH_2SO_2CH_3$, -$(CH_2)_2SO_2CH_3$, -$SO_2(CH_2)_2CH_3$, -$SO_2CH(CH_3)_2$, -$SO_2CH_2CH(CH_3)_2$, -$SO_2CH_2C(CH_3)_2OH$, -SO_2-cyclopropyl, -SO_2-cyclopentyl, -SO_2-oxetane, -SO_2CH_2-oxetane, -SO_2-azetidine, -SO_2-piperidine, -SO_2NH_2, -$SO_2NH(CH_2)_2OH$, -$SO_2NH(CH_2)_2N(CH_3)_2$, -SO_2NH-cyclopropyl, -$NHCH(CH_3)(CH_2)_2SO_2CH_3$, -C(O)pyrrolidine, -C(O)piperidine, -C(O)$NHCH_3$, -$CH_2CH(NH_2)CO_2H$, -$(CH_2)_3CO_2H$, -CO_2CH_3, -$CO_2CH(CH_3)_2$, -CH(CF_3)morpholine, pyrrolidine, pyrazole, triazole, triazole substituted with CH_3, pyrimidine, imidazole, oxadiazole and oxazole.

In another embodiment of the present invention, each R^a is independently selected from the group consisting of: -halogen, oxo, -$(CH_2)_mOH$, -$(CH_2)_mN(R^j)_2$, -CN, -C_{1-6}alkyl, -$(CH_2)_mCF_3$, -$N(R^j)CO_2R^f$, -OC_{1-6}alkyl, -O-C_{3-7}cycloalkyl, -O-C_{2-7}cycloheteroalkyl, -$(CH_2)_mSO_2C_{1-6}$alkyl, -SO_2-C_{3-7}cycloalkyl, -SO_2-C_{2-7}cycloheteroalkyl, -SO_2NH_2, -SO_2NHC_{1-6}alkyl, -SO_2NHC_{3-7}cycloalkyl, -$N(R^j)$-C_{1-6}alkyl, -C(O)R^f, -C(O)$N(R^j)_2$, -$(CH_2)_mCO_2H$, -CO_2R^f, -$(CH_2)_mC_{2-6}$cycloheteroalkyl, and -heteroaryl, wherein each CH_2 is unsubstituted or substituted with 1 or 2 substituents selected from: oxo, -OH, -$(CH_2)_{1-3}OH$, -CN, -NH_2, -NH(C_{1-6}alkyl), -$N(C_{1-6}alkyl)_2$, oxo, -C_{1-6}alkyl, -C_{1-6}alkyl substituted with 1-5 OH, -OC_{1-6}alkyl, halogen, -CH_2F, -CHF_2, -CF_3, -CO_2H, -CO_2C_{1-6}alkyl, -C_{3-7}cycloalkyl, phenyl, CH_2phenyl, heteroaryl and CH_2heteroaryl, and wherein alkyl, cycloalkyl, cycloheteroalkyl, and heteroaryl are unsubstituted or substituted with 1, 2, 3 or 4 substituents selected from: oxo, -OH, -$(CH_2)_{1-5}OH$, -NH_2, -$N(C_{1-6}alkyl)_2$, -C_{1-6}alkyl, halogen, -CF_3, and -SO_2C_{1-6}alkyl.

In another embodiment of the present invention, each R^a is independently selected from the group consisting of: F, oxo, -OH, -CH_2OH, -$C(CH_3)_2CH_2OH$, -$C(CH_3)_2OH$, -$CF_2C(CH_3)_2OH$, -$CH_2C(CH_3)_2OH$, -CH(CF_3)NH-cyclopropyl, -$NHCO_2CH_3$, -CN, -CH_2F, -CH_2CF_3, -CH(NH_2)CF_3,-$NHCO_2CH_2CH(OH)CH_2OH$, -$NHCO_2(CH_2)_2$-imidazole, -$NHCO_2(CH_2)_2$-morpholine, -$NHCO_2(CH_2)_2N(CH_3)_2$, -OCH_2CH_3, -$OCH(CH_3)CH_2OH$, -O-cyclobutyl, -O-oxetane, -O-tetrahydrothiopyran, -SO_2CH_3, -$CH_2SO_2CH_3$, -$(CH_2)_2SO_2CH_3$, -$SO_2(CH_2)_2CH_3$, -$SO_2CH(CH_3)_2$, -$SO_2CH_2CH(CH_3)_2$, -$SO_2CH_2C(CH_3)_2OH$, -SO_2-cyclopropyl, -SO_2-cyclopentyl, -SO_2-oxetane, -SO_2CH_2-oxetane, -SO_2-azetidine, -SO_2-

piperidine, -SO_2NH_2, -$SO_2NH(CH_2)_2OH$, -$SO_2NH(CH_2)_2N(CH_3)_2$, -SO_2NH-cyclopropyl, -$NHCH(CH_3)(CH_2)_2SO_2CH_3$, -C(O)pyrrolidine, -C(O)piperidine, -$C(O)NHCH_3$, -$CH_2CH(NH_2)CO_2H$, -$(CH_2)_3CO_2H$, -CO_2CH_3, -$CO_2CH(CH_3)_2$, -$CH(CF_3)$morpholine, pyrrolidine, -pyrazole, triazole, pyrimidine, imidazole, oxadiazole,and oxazole.

In another embodiment of the present invention, each R^a is independently selected from the group consisting of: -halogen, -OH, -OC_{1-6}alkyl, -SO_2C_{1-6}alkyl, -SO_2-C_{2-7}cycloheteroalkyl, -$C(O)R^f$, and heteroaryl, wherein each CH_2 is unsubstituted or substituted with 1 or 2 substituents selected from: -C_{1-6}alkyl.

In another embodiment of the present invention, each R^a is independently selected from the group consisting of: -F, -OH, -$OCH(CH_3)CH_2OH$, -SO_2CH_3, -SO_2-oxetane, -C(O)pyrrolidine and triazole.

In another embodiment of the present invention, each R^b is independently selected from: hydrogen, -C_{1-6}alkyl, -C_{1-6}alkenyl, -$(CH_2)_nC_{3-10}$cycloalkyl, -$(CH_2)_nC_{3-10}$cycloalkenyl, -$(CH_2)_nC_{2-10}$cycloheteroalkyl, -$(CH_2)_nC_{2-10}$cycloheteroalkenyl, -$(CH_2)_n$aryl, -$(CH_2)_n$heteroaryl, oxo, -$(CH_2)_nCF_3$, -$(CH_2)_n$CN, -$(CH_2)_t$-halogen, -$(CH_2)_s$-OH, -$(CH_2)_nNO_2$, -$(CH_2)_nNH_2$, -$(CH_2)_nNH(C_{1-6}$alkyl), -$(CH_2)_nN(C_{1-6}$alkyl$)_2$, -$(CH_2)_nNHCO_2H$, -$(CH_2)_nOC_{1-6}$alkyl, -$(CH_2)_nOC_{1-6}$alkenyl, -$(CH_2)_nCOC_{1-6}$alkyl, –$(CH_2)_nCO_2H$, -$(CH_2)_n$OCOH, -$(CH_2)_nCO_2R^i$, –$(CH_2)_nOC(O)R^i$, -$(CH_2)_qC(O)N(R^e)_2$, -$(CH_2)_qCO_2N(R^e)_2$, –$(CH_2)_nC(O)(CH_2)_nN(R^g)_2$, –$(CH_2)_nOC(O)(CH_2)_nN(R^g)_2$, -$(CH_2)_nN(R^e)C(O)C_{1-6}$alkyl, -$(CH_2)_nN(R^e)SO_2R^i$, –$(CH_2)_nSO_2C_{1-6}$alkyl, –$(CH_2)_nSO_2N(R^e)R^g$, -$(CH_2)_nSO_2N(R^e)C(O)R^i$, –$(CH_2)_nSO_2N(R^e)CO_2R^i$, –$(CH_2)_nSO_2N(R^e)CON(R^g)_2$, –$(CH_2)_nC(O)N(R^e)SO_2R^i$, –$(CH_2)_nN(R^e)C(O)N(R^g)_2$, =N(OH), and =N($OC_{1-6}$alkyl), wherein each CH_2 is unsubstituted or substituted with 1 or 2 substituents selected from: -C_{1-6}alkyl, -OH, halogen and -NH_2 wherein each NH is unsubstituted or substituted with 1 substituent selected from R^c, and wherein each alkyl, cycloalkyl, cycloalkenyl, cycloheteroalkyl, cycloheteroalkenyl, aryl and heteroaryl is unsubstituted or substituted with 1, 2, 3 or 4 substituents selected from R^c, or wherein two R^b substituents and the carbon to which they are attached may form a 3 to 6 membered cycloalkyl ring, a 3-6 membered cycloalkenyl ring, a 3-6 membered cycloheteroalkyl ring or a 3-6 membered cycloheteroalkenyl ring, wherein the ring is unsubstituted or substituted with 1, 2, 3 or 4 substituents selected from R^c. In a class of this embodiment, two R^b substituents and the carbon to which they are attached may form a 3-6 membered cycloheteroalkyl ring, wherein the ring is unsubstituted or substituted with 1, 2, 3 or 4 substituents selected from R^c.

In another embodiment of the present invention, each R^b is independently selected from: -C_{1-6}alkyl, -$(CH_2)_s$-OH, -OC_{1-6}alkyl and -CO_2H, wherein each CH_2 is unsubstituted or substituted with 1 or 2 substituents selected from: -C_{1-6}alkyl, -OH, halogen and -NH_2 wherein each NH is unsubstituted or substituted with 1 substituent selected from R^c, and wherein each

alkyl is unsubstituted or substituted with 1, 2, 3 or 4 substituents selected from R^c, or wherein two R^b substituents and the carbon to which they are attached may form a 3 to 6 membered cycloalkyl ring, a 3-6 membered cycloalkenyl ring, a 3-6 membered cycloheteroalkyl ring or a 3-6 membered cycloheteroalkenyl ring, wherein the ring is unsubstituted or substituted with 1, 2, 3 or 4 substituents selected from R^c. In a class of this embodiment, two R^b substituents and the carbon to which they are attached may form a 3-6 membered cycloheteroalkyl ring, wherein the ring is unsubstituted or substituted with 1, 2, 3 or 4 substituents selected from R^c.

In another embodiment of the present invention, each R^b is independently selected from: -C_{1-6}alkyl, -(CH_2)s-OH, and -OC_{1-6}alkyl, wherein each CH_2 is unsubstituted or substituted with 1 or 2 substituents selected from: -C_{1-6}alkyl, -OH, halogen and -NH_2 wherein each NH is unsubstituted or substituted with 1 substituent selected from R^c, and wherein each alkyl is unsubstituted or substituted with 1, 2, 3 or 4 substituents selected from R^c, or wherein two R^b substituents and the carbon to which they are attached may form a 3 to 6 membered cycloalkyl ring, a 3-6 membered cycloalkenyl ring, a 3-6 membered cycloheteroalkyl ring or a 3-6 membered cycloheteroalkenyl ring, wherein the ring is unsubstituted or substituted with 1, 2, 3 or 4 substituents selected from R^c. In a class of this embodiment, two R^b substituents and the carbon to which they are attached may form a 3-6 membered cycloheteroalkyl ring, wherein the ring is unsubstituted or substituted with 1, 2, 3 or 4 substituents selected from R^c.

In another embodiment of the present invention, each R^b is independently selected from: -C_{1-6}alkyl, -(CH_2)s-OH, and -OC_{1-6}alkyl, wherein each CH_2 is unsubstituted or substituted with 1 or 2 substituents selected from: -C_{1-6}alkyl, -OH, halogen and -NH_2 wherein each NH is unsubstituted or substituted with 1 substituent selected from R^c, and wherein each alkyl is unsubstituted or substituted with 1, 2, 3 or 4 substituents selected from R^c. In a class of this embodiment of the present invention, each R^b is independently selected from: -$C(CH_3)_2OH$, -OH, -CH_2OH, and -OCH_3.

In another embodiment of the present invention, each R^b is independently selected from: -C_{1-6}alkyl, and -(CH_2)s-OH, wherein each CH_2 is unsubstituted or substituted with 1 or 2 substituents selected from: -C_{1-6}alkyl, -OH, halogen and -NH_2 wherein each NH is unsubstituted or substituted with 1 substituent selected from R^c, and wherein each alkyl is unsubstituted or substituted with 1, 2, 3 or 4 substituents selected from R^c, or wherein two R^b substituents and the carbon to which they are attached may form a 3-6 membered cycloheteroalkyl ring, wherein the ring is unsubstituted or substituted with 1, 2, 3 or 4 substituents selected from R^c.

In another embodiment of the present invention, each R^b is independently selected from: -C_{1-6}alkyl, and -(CH_2)s-OH, wherein each CH_2 is unsubstituted or substituted with 1 or 2 substituents selected from: -C_{1-6}alkyl, -OH, halogen and -NH_2 wherein each NH is unsubstituted or substituted with 1 substituent selected from R^c, and wherein each alkyl is

unsubstituted or substituted with 1, 2, 3 or 4 substituents selected from R^c. In a class of this embodiment, each R^b is independently selected from: -C(CH3)2OH, -OH, and -CH2OH.

In another embodiment of the present invention, each R^c is independently selected from: halogen, oxo, -$(CH_2)_r$OH, -$(CH_2)_r$N(R^e)2, -$(CH_2)_r$CN, -C_{1-6}alkyl, -CF_3, -C_{1-6}alkyl-OH, -OCH_2OC_{1-6}alkyl, -$(CH_2)_rOC_{1-6}$alkyl, -OCH_2aryl, -$(CH_2)_rSC_{1-6}$alkyl, –$(CH_2)_rC(O)R^f$, –$(CH_2)_rC(O)N(R^e)_2$, -$(CH_2)_rCO_2H$, -$(CH_2)_rCO_2R^f$, -$(CH_2)_rC_{3-7}$cycloalkyl, -$(CH_2)_rC_{2-6}$cycloheteroalkyl, -$(CH_2)_r$aryl, and -$(CH_2)_r$heteroaryl, wherein each CH_2 is unsubstituted or substituted with 1 or 2 substituents selected from: oxo, –OH, -CN, -N(R^h)2, -C_{1-6}alkyl, -OC_{1-6}alkyl, halogen, -CH_2F, -CHF_2, -CF_3, -CO_2H, -CO_2C_{1-6}alkyl, -C_{3-7}cycloalkyl and heteroaryl, and wherein alkyl, cycloalkyl, cycloheteroalkyl, aryl and heteroaryl are unsubstituted or substituted with 1, 2, 3 or 4 substituents selected from: oxo, –OH, -CN, -N(R^h)2, -C_{1-6}alkyl, -OC_{1-6}alkyl, halogen, -CH_2F, -CHF_2, -CF_3, -CO_2H, -CO_2C_{1-6}alkyl, -C_{3-7}cycloalkyl and heteroaryl. In a class of this embodiment, each R^c is independently selected from: oxo, -$(CH_2)_r$OH, -$(CH_2)_rCO_2H$, and -$(CH_2)_rCO_2R^f$, wherein each CH_2 is unsubstituted or substituted with 1 or 2 substituents selected from: oxo, –OH, -CN, -N(R^h)2, -C_{1-6}alkyl, -OC_{1-6}alkyl, halogen, -CH_2F, -CHF_2, -CF_3, -CO_2H, -CO_2C_{1-6}alkyl, -C_{3-7}cycloalkyl and heteroaryl. In a subclass of this class, each R^c is independently selected from: oxo, -OH, -CO_2H and -CO_2R^f.

In another embodiment of the present invention, each R^c is independently selected from: halogen, oxo, -$(CH_2)_r$OH, -$(CH_2)_r$N(R^e)2, -$(CH_2)_r$CN, -C_{1-6}alkyl, -CF_3, -C_{1-6}alkyl-OH, -OCH_2OC_{1-6}alkyl, -$(CH_2)_rOC_{1-6}$alkyl, -OCH_2aryl, -$(CH_2)_rSC_{1-6}$alkyl, –$(CH_2)_rC(O)R^f$, –$(CH_2)_rC(O)N(R^e)_2$, -$(CH_2)_rCO_2H$, and -$(CH_2)_rCO_2R^f$, wherein each CH_2 is unsubstituted or substituted with 1 or 2 substituents selected from: oxo, –OH, -CN, -N(R^h)2, -C_{1-6}alkyl, -OC_{1-6}alkyl, halogen, -CH_2F, -CHF_2, -CF_3, -CO_2H, -CO_2C_{1-6}alkyl, -C_{3-7}cycloalkyl and heteroaryl, and wherein alkyl, cycloalkyl, cycloheteroalkyl, aryl and heteroaryl are unsubstituted or substituted with 1, 2, 3 or 4 substituents selected from: oxo, –OH, -CN, -N(R^h)2, -C_{1-6}alkyl, -OC_{1-6}alkyl, halogen, -CH_2F, -CHF_2, -CF_3, -CO_2H, and -CO_2C_{1-6}alkyl.

In another embodiment of the present invention, each R^c is independently selected from: halogen, oxo, -$(CH_2)_r$OH, -$(CH_2)_r$N(R^e)2, -$(CH_2)_r$CN, -C_{1-6}alkyl, -CF_3, and -C_{1-6}alkyl-OH.

In another embodiment of the present invention, each R^c is independently selected from: halogen, oxo, and -C_{1-6}alkyl. In another embodiment of the present invention, each R^c is -C_{1-6}alkyl.

In another embodiment of the present invention, each R^e, Rg and R^h is independently selected from: hydrogen, –C_{1-6}alkyl, and –O-C_{1-6}alkyl, wherein alkyl is unsubstituted or substituted with 1, 2, 3 or 4 substituents selected from: -OH, oxo, halogen, C_{1-6}alkyl, -OC_{1-6}alkyl, –NH_2, -NH(C_{1-6}alkyl), and -N(C_{1-6}alkyl)2.

In another embodiment of the present invention, each R^e is independently selected from:

hydrogen, –C_{1-6}alkyl, and –O-C_{1-6}alkyl, wherein alkyl is unsubstituted or substituted with 1, 2, 3 or 4 substituents selected from: -OH, oxo, halogen, C_{1-6}alkyl, -OC_{1-6}alkyl, –NH_2, -NH(C_{1-6}alkyl), and -N(C_{1-6}alkyl)$_2$.

In another embodiment of the present invention, each R^g is independently selected from: hydrogen, –C_{1-6}alkyl, and –O-C_{1-6}alkyl, wherein alkyl is unsubstituted or substituted with 1, 2, 3 or 4 substituents selected from: -OH, oxo, halogen, C_{1-6}alkyl, -OC_{1-6}alkyl, –NH_2, -NH(C_{1-6}alkyl), and -N(C_{1-6}alkyl)$_2$.

In another embodiment of the present invention, each R^h is independently selected from: hydrogen, –C_{1-6}alkyl, and –O-C_{1-6}alkyl, wherein alkyl is unsubstituted or substituted with 1, 2, 3 or 4 substituents selected from: -OH, oxo, halogen, C_{1-6}alkyl, -OC_{1-6}alkyl, –NH_2, -NH(C_{1-6}alkyl), and -N(C_{1-6}alkyl)$_2$.

In another embodiment of the present invention, each R^j is independently selected from: hydrogen, -C_{1-6}alkyl, -C_{3-6}cycloalkyl, –C(O)R^i, –CO_2R^i, and –SO_2R^i, wherein alkyl and cycloalkyl are unsubstituted or substituted with 1, 2, 3 or 4 substituents selected from: -OH, oxo, halogen, C_{1-6}alkyl, -OC_{1-6}alkyl, –NH_2, -NH(C_{1-6}alkyl), and -N(C_{1-6}alkyl)$_2$. In a class of this embodiment, each R^j is independently selected from: hydrogen, -C_{1-6}alkyl, -C_{3-6}cycloalkyl, and –CO_2R^i, wherein alkyl and cycloalkyl are unsubstituted or substituted with 1, 2, 3 or 4 substituents selected from: -OH, oxo, halogen, C_{1-6}alkyl, -OC_{1-6}alkyl, –NH_2, -NH(C_{1-6}alkyl), and -N(C_{1-6}alkyl)$_2$. In a subclass of this class, each R^j is independently selected from: hydrogen, -CH_3, -cyclopropyl and -CO_2CH_3.

In another embodiment of the present invention, each R^f and R^i is independently selected from: -C_{1-6}alkyl, -$(CH_2)_rC_{4-7}$cycloalkyl, -$(CH_2)_rC_{4-7}$cycloalkenyl, -$(CH_2)_rC_{3-7}$cycloheteroalkyl, -$(CH_2)_rC_{3-7}$cycloheteroalkenyl, -$(CH_2)_r$aryl, and -$(CH_2)_r$heteroaryl, wherein alkyl, cycloalkyl, cycloalkenyl, cycloheteroalkyl, cycloheteroalkenyl, aryl and heteroaryl are unsubstituted or substituted with 1, 2, 3 or 4 substituents selected from: oxo, -OH, -CN, -NH_2, -NH(C_{1-6}alkyl), -N(C_{1-6}alkyl)$_2$, -C_{1-6}alkyl, -OC_{1-6}alkyl, halogen, -CH_2F, -CHF_2, -CF_3, -CO_2H, -CO_2C_{1-6}alkyl, -C_{3-7}cycloalkyl, and heteroaryl. In a class of this embodiment, alkyl, cycloalkyl, cycloalkenyl, cycloheteroalkyl, cycloheteroalkenyl, aryl and heteroaryl are unsubstituted or substituted with 1, 2, 3 or 4 substituents selected from: oxo, -OH, -CN, -NH_2, -NH(C_{1-6}alkyl), -N(C_{1-6}alkyl)$_2$, -C_{1-6}alkyl, -OC_{1-6}alkyl, halogen, -CH_2F, -CHF_2, -CF_3, -CO_2H,and -CO_2C_{1-6}alkyl.

In another embodiment of the present invention, each R^f is independently selected from: -C_{1-6}alkyl, -$(CH_2)_rC_{4-7}$cycloalkyl, -$(CH_2)_rC_{4-7}$cycloalkenyl, -$(CH_2)_rC_{3-7}$cycloheteroalkyl, -$(CH_2)_rC_{3-7}$cycloheteroalkenyl, -$(CH_2)_r$aryl, and -$(CH_2)_r$heteroaryl, wherein alkyl, cycloalkyl, cycloalkenyl, cycloheteroalkyl, cycloheteroalkenyl, aryl and heteroaryl are unsubstituted or substituted with 1, 2, 3 or 4 substituents selected from: oxo, -OH, -CN, -NH_2, -NH(C_{1-6}alkyl), -N(C_{1-6}alkyl)$_2$, -C_{1-6}alkyl, -OC_{1-6}alkyl, halogen, -CH_2F, -CHF_2, -CF_3, -CO_2H, -CO_2C_{1-}

$_{6}$alkyl, -C$_{3-7}$cycloalkyl, and heteroaryl. In a class of this embodiment, alkyl, cycloalkyl, cycloalkenyl, cycloheteroalkyl, cycloheteroalkenyl, aryl and heteroaryl are unsubstituted or substituted with 1, 2, 3 or 4 substituents selected from: oxo, -OH, -CN, -NH$_2$, -NH(C$_{1-6}$alkyl), -N(C$_{1-6}$alkyl)$_2$, -C$_{1-6}$alkyl, -OC$_{1-6}$alkyl, halogen, -CH$_2$F, -CHF$_2$, -CF$_3$, -CO$_2$H,and -CO$_2$C$_{1-6}$alkyl.

In another embodiment of the present invention, each R^f is independently selected from: -C$_{1-6}$alkyl, and -(CH$_2$)$_r$C$_{3-7}$cycloheteroalkyl, wherein alkyl and cycloheteroalkyl are unsubstituted or substituted with 1, 2, 3 or 4 substituents selected from: oxo, -OH, -CN, -NH$_2$, -NH(C$_{1-6}$alkyl), -N(C$_{1-6}$alkyl)$_2$, -C$_{1-6}$alkyl, -OC$_{1-6}$alkyl, halogen, -CH$_2$F, -CHF$_2$, -CF$_3$, -CO$_2$H, -CO$_2$C$_{1-6}$alkyl, -C$_{3-7}$cycloalkyl, and heteroaryl. In a class of this embodiment, alkyl and cycloheteroalkyl are unsubstituted or substituted with 1, 2, 3 or 4 substituents selected from: oxo, -OH, -CN, -NH$_2$, -NH(C$_{1-6}$alkyl), -N(C$_{1-6}$alkyl)$_2$, -C$_{1-6}$alkyl, -OC$_{1-6}$alkyl, halogen, -CH$_2$F, -CHF$_2$, -CF$_3$, -CO$_2$H,and -CO$_2$C$_{1-6}$alkyl.

In another embodiment of the present invention, each R^f is independently selected from: -CH$_3$,-CH(CH$_3$)$_2$, CH$_2$CH(OH)CH$_2$OH, -(CH$_2$)$_2$N(CH$_3$)$_2$, pyrrolidine, piperidine, -(CH$_2$)$_2$-imidazole, and -(CH$_2$)$_2$-morpholine, wherein alkyl and cycloheteroalkyl are unsubstituted or substituted with 1, 2, 3 or 4 substituents selected from: oxo, -OH, -CN, -NH$_2$, -NH(C$_{1-6}$alkyl), -N(C$_{1-6}$alkyl)$_2$, -C$_{1-6}$alkyl, -OC$_{1-6}$alkyl, halogen, -CH$_2$F, -CHF$_2$, -CF$_3$, -CO$_2$H,and -CO$_2$C$_{1-6}$alkyl.

In another embodiment of the present invention, each R^f is independently selected from: -C$_{3-7}$cycloheteroalkyl, wherein cycloheteroalkyl are unsubstituted or substituted with 1, 2, 3 or 4 substituents selected from: oxo, -OH, -CN, -NH$_2$, -NH(C$_{1-6}$alkyl), -N(C$_{1-6}$alkyl)$_2$, -C$_{1-6}$alkyl, -OC$_{1-6}$alkyl, halogen, -CH$_2$F, -CHF$_2$, -CF$_3$, -CO$_2$H, and -CO$_2$C$_{1-6}$alkyl. In a class of this embodiment, each R^f is independently selected from: pyrrolidine, piperidine, -(CH$_2$)$_2$-imidazole, and -(CH$_2$)$_2$-morpholine, wherein each cycloheteroalkyl are unsubstituted or substituted with 1, 2, 3 or 4 substituents selected from: oxo, -OH, -CN, -NH$_2$, -NH(C$_{1-6}$alkyl), -N(C$_{1-6}$alkyl)$_2$, -C$_{1-6}$alkyl, -OC$_{1-6}$alkyl, halogen, -CH$_2$F, -CHF$_2$, -CF$_3$, -CO$_2$H, and -CO$_2$C$_{1-6}$alkyl. In another class of this embodiment, each R^f is pyrrolidine, unsubstituted or substituted with 1, 2, 3 or 4 substituents selected from: oxo, -OH, -CN, -NH$_2$, -NH(C$_{1-6}$alkyl), -N(C$_{1-6}$alkyl)$_2$, -C$_{1-6}$alkyl, -OC$_{1-6}$alkyl, halogen, -CH$_2$F, -CHF$_2$, -CF$_3$, -CO$_2$H, and -CO$_2$C$_{1-6}$alkyl. In another class of this embodiment, each R^f is pyrrolidine, unsubstituted or substituted with 1, 2, 3 or 4 substituents selected from: -OH.

In another embodiment of the present invention, each R^i is independently selected from: -C$_{1-6}$alkyl, -(CH$_2$)$_r$C$_{4-7}$cycloalkyl, -(CH$_2$)$_r$C$_{4-7}$cycloalkenyl, -(CH$_2$)$_r$C$_{3-7}$cycloheteroalkyl, -(CH$_2$)$_r$C$_{3-7}$cycloheteroalkenyl, -(CH$_2$)$_r$aryl, and -(CH$_2$)$_r$heteroaryl, wherein alkyl, cycloalkyl, cycloalkenyl, cycloheteroalkyl, cycloheteroalkenyl, aryl and heteroaryl are unsubstituted or substituted with 1, 2, 3 or 4 substituents selected from: oxo, -OH, -CN, -NH$_2$, -NH(C$_{1-6}$alkyl), -

$N(C_{1-6}alkyl)_2$, $-C_{1-6}alkyl$, $-OC_{1-6}alkyl$, halogen, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CO_2H$, $-CO_2C_{1-6}alkyl$, $-C_{3-7}cycloalkyl$, and heteroaryl. In a class of this embodiment, alkyl, cycloalkyl, cycloalkenyl, cycloheteroalkyl, cycloheteroalkenyl, aryl and heteroaryl are unsubstituted or substituted with 1, 2, 3 or 4 substituents selected from: oxo, -OH, -CN, $-NH_2$, $-NH(C_{1-6}alkyl)$, $-N(C_{1-6}alkyl)_2$, $-C_{1-6}alkyl$, $-OC_{1-6}alkyl$, halogen, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CO_2H$,and $-CO_2C_{1-6}alkyl$. In another class of this embodiment, each R^i is independently selected from $C_{1-6}alkyl$. In another class of this embodiment, R^i is CH_3.

In another embodiment of the present invention, n is 0, 1, 2, 3 or 4. In a class of this embodiment, n is 1, 2 or 3. In another class of this embodiment, n is 0, 1 or 2. In another class of this embodiment, n is 0. In another class of this embodiment, n is 1. In another class of this embodiment, n is 2.

In another embodiment of the present invention, m is 0, 1, 2, 3, or 4. In a class of this embodiment, m is 0, 1, 2 or 3. In another class of this embodiment, m is 1, 2 or 3. In another class of this embodiment, m is 0, 1 or 2. In another class of this embodiment, m is 0 or 1. In another class of this embodiment, m is 0. In another class of this embodiment, m is 1.

In another embodiment of the present invention, p is 0, 1, 2 or 3. In a class of this embodiment, p is 1, 2 or 3. In another class of this embodiment, p is 0, 1 or 2. In another class of this embodiment, p is 0 or 2. In another class of this embodiment, p is 0. In another class of this embodiment, p is 1. In another class of this embodiment, p is 2.

In another embodiment of the present invention, q is 0, 1, 2, 3 or 4. In a class of this embodiment, q is 1, 2 or 3. In another class of this embodiment, q is 0, 1 or 2. In another class of this embodiment, q is 1 or 2. In another class of this embodiment, q is 0. In another class of this embodiment, q is 1. In another class of this embodiment, q is 2.

In another embodiment of the present invention, r is 0, 1 or 2. In a class of this embodiment, r is 0 or 1. In another class of this embodiment, r is 0. In another class of this embodiment, r is 1. In another class of this embodiment, r is 2.

In another embodiment of the present invention, s is 0, 1, 2, 3 or 4. In a class of this embodiment, s is 0, 1, 2 or 3. In a class of this embodiment, s is 0, 1 or 2. In another class of this embodiment, s is 0 or 1. In another class of this embodiment, s is 1 or 2. In another class of this embodiment, s is 0 or 2. In another class of this embodiment, s is 0. In another class of this embodiment, s is 1. In another class of this embodiment, s is 2. In another class of this embodiment, s is 3.

In another embodiment of the present invention, t is 0, 1, 2, 3 or 4. In a class of this embodiment, t is 0, 1, 2 or 3. In a class of this embodiment, t is 0, 1 or 2. In another class of this embodiment, t is 0 or 1. In another class of this embodiment, t is 1 or 2. In another class of this embodiment, t is 0 or 2. In another class of this embodiment, t is 0. In another class of this embodiment, t is 1. In another class of this embodiment, t is 2. In another class of this

embodiment, t is 3.

In another embodiment of the present invention, u is 0, 1, 2, 3 or 4. In a class of this embodiment, u is 0, 1, 2 or 3. In a class of this embodiment, u is 0, 1 or 2. In another class of this embodiment, u is 0 or 1. In another class of this embodiment, u is 1 or 2. In another class of this embodiment, u is 0 or 2. In another class of this embodiment, u is 0. In another class of this embodiment, u is 1. In another class of this embodiment, u is 2. In another class of this embodiment, u is 3. In another class of this embodiment, u is 4.

Another embodiment of the present invention relates to compounds of structural formula I wherein:

T is N;

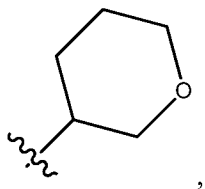
U is $-CR^1-$;

V is $-CR^2-$;

W is $-CR^4-$;

X is -O-;

Y is:



,

wherein Y is unsubstituted or substituted with 1, 2, 3, 4 or 5 substituents selected from R^b;

Z is NR^5;

each R^1 is independently selected from:

(1) aryl-C_{2-8}alkynyl-heteroaryl,

(2) -C_{2-6}alkynyl-aryl,

(3) aryl,

(4) aryl-C_{3-7}cycloalkyl,

(5) aryl-C_{2-10}cycloheteroalkyl,

(6) aryl-aryl,

(7) aryl-heteroaryl, and

(8) heteroaryl,

wherein each alkynyl, cycloalkyl, cycloheteroalkyl, aryl and heteroaryl is unsubstituted or substituted with 1, 2, 3 or 4 substituents independently selected from R^a;

R^2 is halogen;

R^4 is hydrogen; and

R^5 is hydrogen;

or a pharmaceutically acceptable salt thereof.

Another embodiment of the present invention relates to compounds of structural formula I wherein:

T is N;

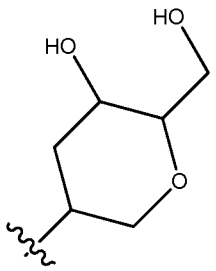
U is –CR^1-;

V is -CR^2-;

W is -CR^4-;

X is -O-;

Y is:



,

wherein Y is unsubstituted or substituted with 1, 2 or 3 substituents selected from R^b;

Z is NR^5;

each R^1 is independently selected from:

(1) aryl,

(2) aryl-C_{2-10}cycloheteroalkyl,

(3) aryl-aryl, and

(4) aryl-heteroaryl,

wherein each cycloheteroalkyl, aryl and heteroaryl is unsubstituted or substituted with 1, 2, 3 or 4 substituents independently selected from R^a,

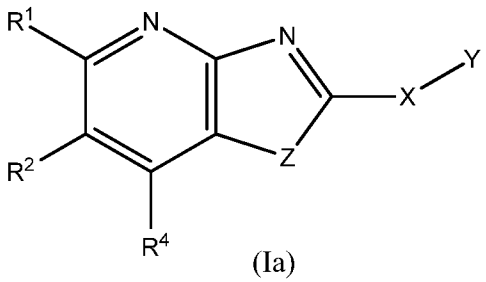
R^2 is halogen;

R^4 is hydrogen; and

R^5 is hydrogen;

or a pharmaceutically acceptable salt thereof.

In another embodiment of the present invention, the invention relates to compounds of structural formula Ia:

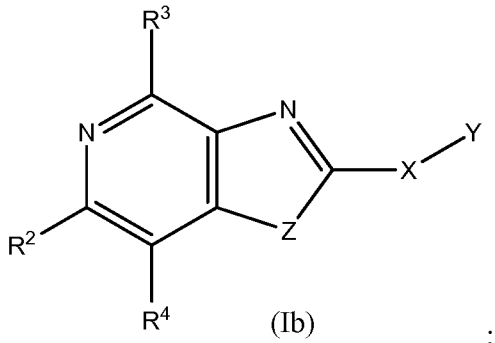


(Ia)

;

or a pharmaceutically acceptable salt thereof.

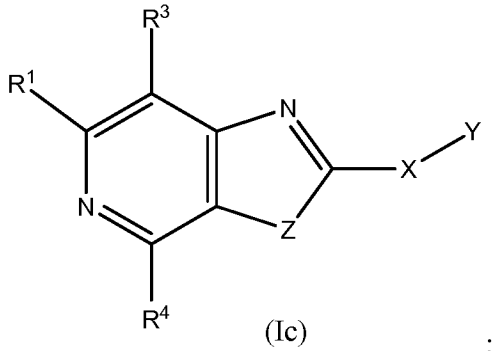
In another embodiment of the present invention, the invention relates to compounds of structural formula Ib:



(Ib) ;

or a pharmaceutically acceptable salt thereof.

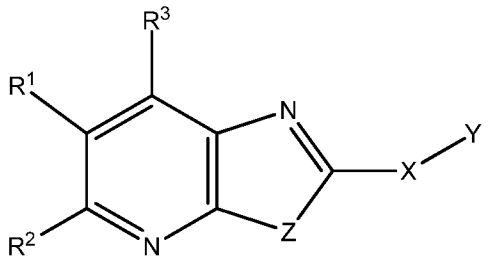
In another embodiment of the present invention, the invention relates to compounds of structural formula Ic:



(Ic) ;

or a pharmaceutically acceptable salt thereof.

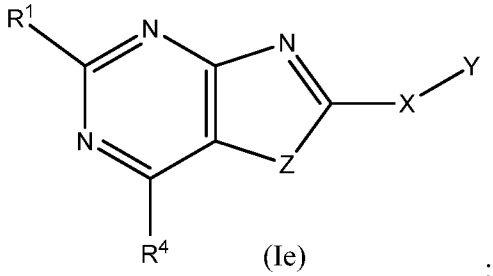
In another embodiment of the present invention, the invention relates to compounds of structural formula Id:



(Id) ;

or a pharmaceutically acceptable salt thereof.

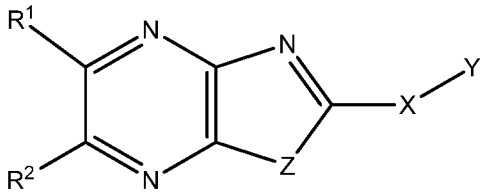
In another embodiment of the present invention, the invention relates to compounds of structural formula Ie:



(Ie) ;

or a pharmaceutically acceptable salt thereof.

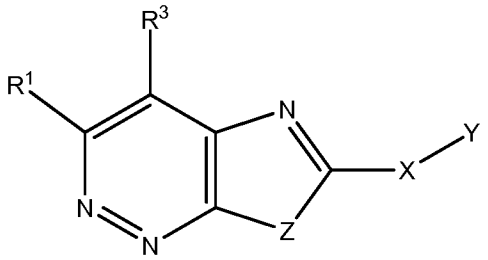
In another embodiment of the present invention, the invention relates to compounds of structural formula If:



(If) ;

or a pharmaceutically acceptable salt thereof.

In another embodiment of the present invention, the invention relates to compounds of structural formula Ig:

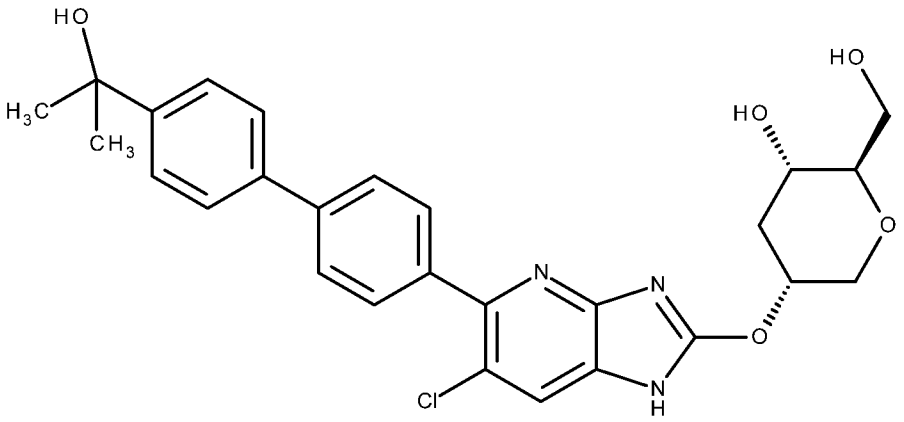


(Ig) ;

or a pharmaceutically acceptable salt thereof.

The compound of structural formula I, includes the compounds of structural formulas Ia, Ib, Ic, Id, Ie, If and Ig and pharmaceutically acceptable salts, hydrates and solvates thereof.

Illustrative, but non-limiting, examples of the compounds of the present invention that are useful as activators of AMP-protein kinase are the following compounds:



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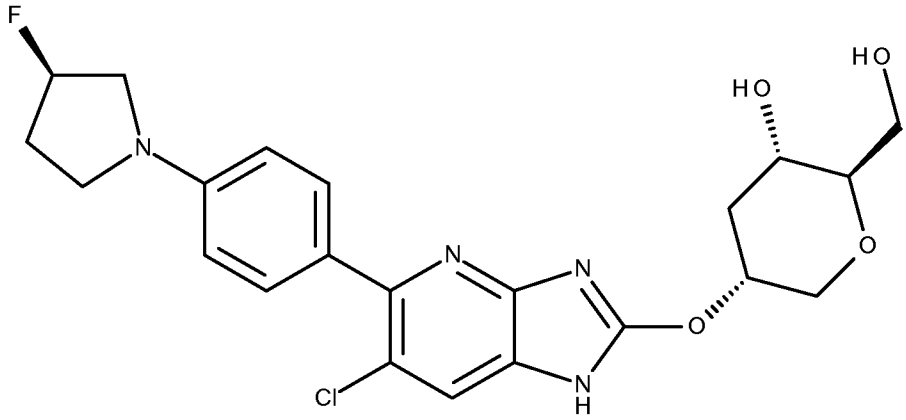

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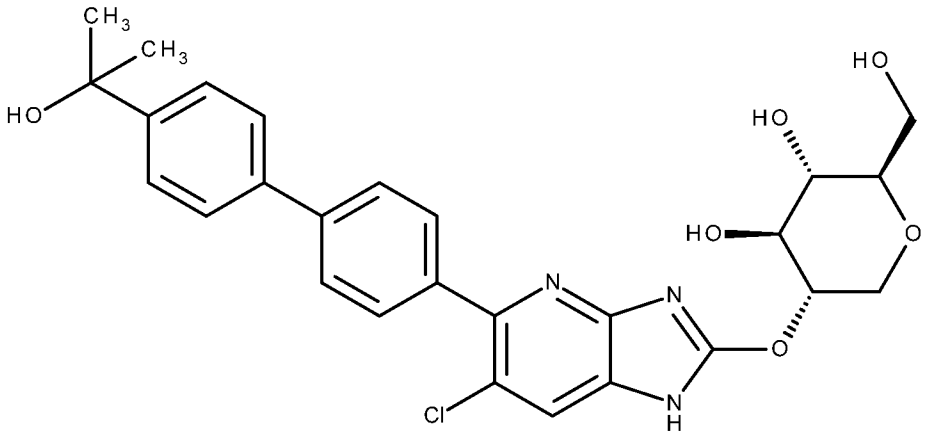

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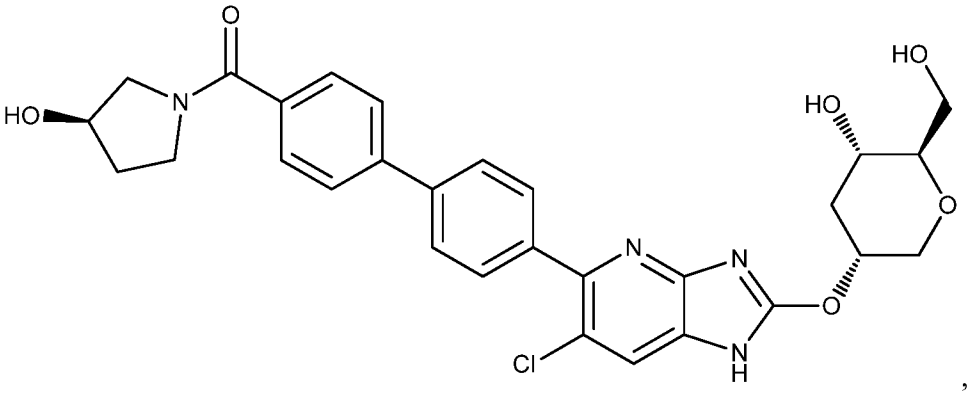

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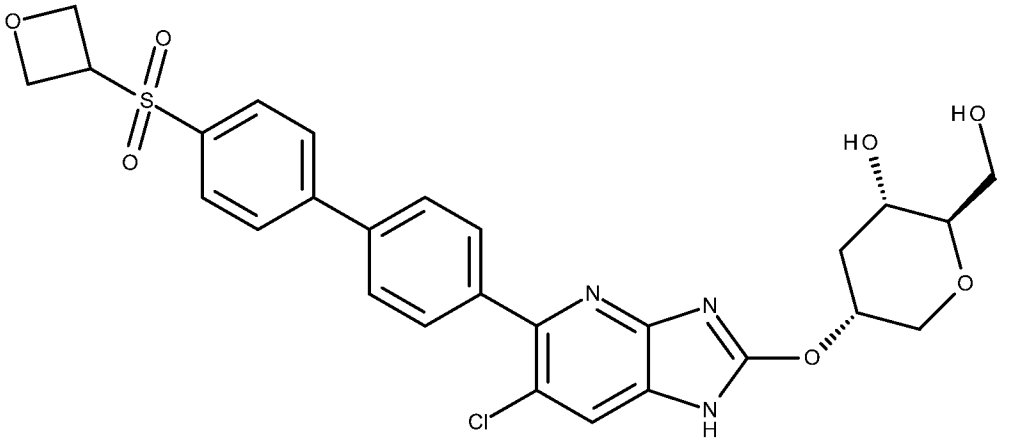

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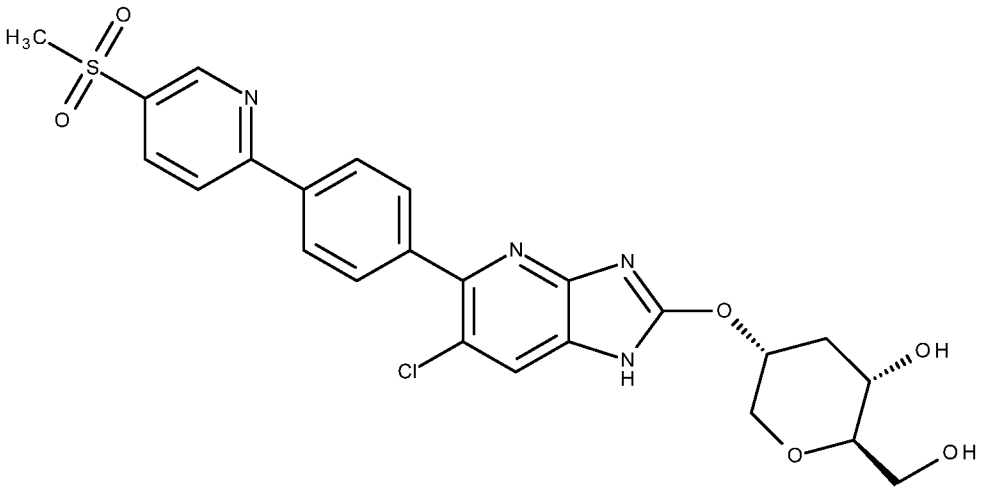

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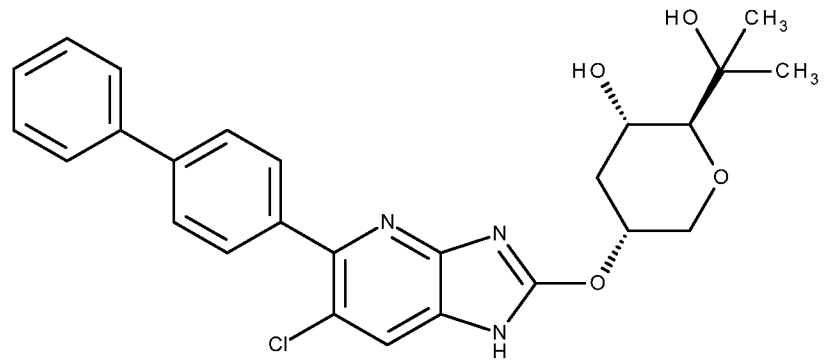

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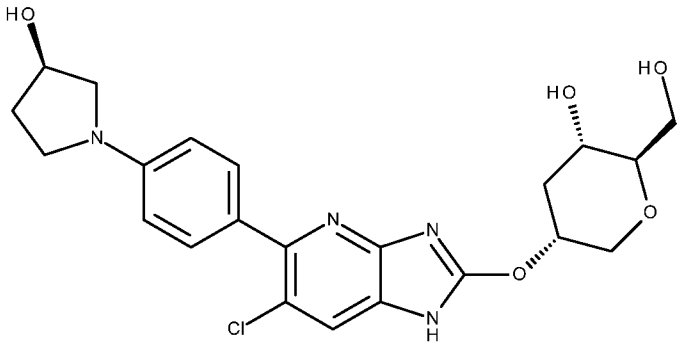

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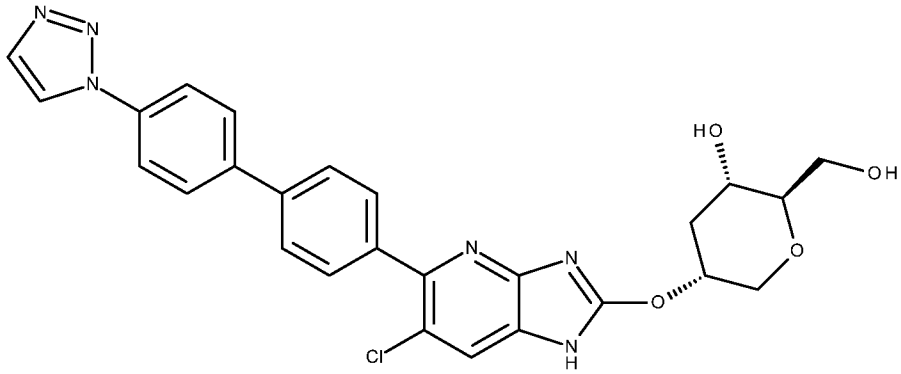

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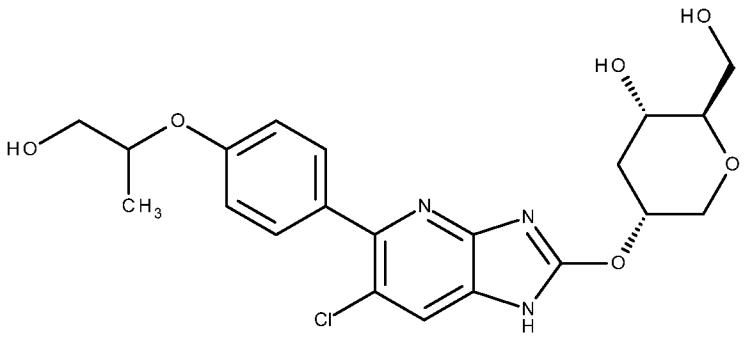

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and pharmaceutically acceptable salts thereof.

"Alkyl", as well as other groups having the prefix "alk", such as alkoxy, alkanoyl, means

carbon chains of up to 10 carbons which may be linear or branched or combinations thereof. Examples of alkyl groups include methyl, ethyl, n-propyl, isopropyl, butyl, isobutyl, *sec*- and *tert*-butyl, pentyl, hexyl, heptyl, octyl, nonyl, and the like.

"Alkenyl" means carbon chains up to 10 carbons which contain at least one carbon-carbon double bond, and which may be linear or branched or combinations thereof. Examples of alkenyl include vinyl, allyl, isopropenyl, pentenyl, hexenyl, heptenyl, 1-propenyl, 2-butenyl, 2-methyl-2-butenyl, and the like. In one embodiment of the present invention, alkenyl is vinyl.

"Alkynyl" means carbon chains up to 10 carbons which contain at least one carbon-carbon triple bond, and which may be linear or branched or combinations thereof. In one embodiment, C_{2-8}alkynyl means a carbon chain with 2 to 8 carbons that contains one carbon-carbon triple bond. Examples of alkynyl include ethynyl, propargyl, 3-methyl-1-pentynyl, 2-heptynyl and the like. In one embodiment of the present invention, alkynyl is ethynyl. In another embodiment, alkynyl is propargyl.

"Cycloalkyl" means mono- or bicyclic, spiro or bridged saturated carbocyclic rings, each having from 3 to 14 carbon atoms. Examples of cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, and decahydronaphthyl, and the like. In one embodiment of the present invention, cycloalkyl is selected from cyclopentyl and cyclohexyl. In another embodiment of the present invention, cycloalkyl is selected from cyclopropyl, cyclopentyl, and cyclohexyl. In another embodiment, C_{3-7}cycloalkyl is cyclopropyl In another embodiment, C_{3-7}cycloalkyl is cyclobutyl In another embodiment, -C_{3-7}cycloalkyl is cyclopropyl and cyclopentyl.

"Cycloalkenyl" means nonaromatic, mono- or bicyclic, spiro or bridged carbocyclic rings, each having from 3 to 14 carbon atoms and containing at least one double bond. Examples of cycloalkyl include cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooxtenyl, decahydronaphthyl, bicyclo[2.2.1]hept-5-en-2-yl, and the like.

"Cycloheteroalkyl" means nonaromatic, monocyclic, bicyclic, spiro or bridged saturated carbocyclic rings, each having from 2 to 14 carbon atoms and containing 1, 2, 3, 4 or 5 heteroatoms selected from N, NH, O and S. In one embodiment, C_{2-10}cycloheteroalkyl means non-aromatic, mono- or bicyclic, spiro or bridged saturated carbocyclic rings, having from 2 to 10 carbon atoms and containing, 1, 2, 3, 4 or 5 heteroatoms selected from N, NH, O and S. In another embodiment, C_{3-6}cycloheteroalkyl means non-aromatic, mono- or bicyclic, spiro or bridged saturated carbocyclic rings, having from 3 to 6 carbon atoms and containing, 1, 2, 3, 4 or 5 heteroatoms selected from N, NH, O and S. In another embodiment, C_{3-7}cycloheteroalkyl means non-aromatic, mono- or bicyclic, spiro or bridged saturated carbocyclic rings, having from 3 to 7 carbon atoms and containing, 1, 2, 3, 4 or 5 heteroatoms selected from N, NH, O and S. Examples of cycloheteroalkyl include tetrahydrofuranyl, azetidinyl, perhydroazepinyl, dihydrofuranyl, dioxanyl, oxanyl, morpholinyl, 1,4-dithianyl, piperazinyl, piperidinyl, 1,3-

dioxolanyl, imidazolidinyl, imidazolinyl, pyrrolinyl, pyrrolidinyl, pyranyl, tetrahydropyranyl, dihydropyranyl, oxathiolanyl, dithiolanyl, 1,3-dithianyl, oxathianyl, thiomorpholinyl, dioxidoisothiazolidinyl, azacycloheptyl, diazobicyclo[3.2.1]-octane, and hexahydroindazolyl. The cycloheteroalkyl ring may be substituted on the ring carbons and/or the ring nitrogens. In one embodiment of the present invention, cycloheteroalkyl is selected from piperidine, pyrrolidine, oxazolidine, 1,3-oxazolidine-2,4-dione, thiazolidine, 1,3-thiazolidine-2,4-dione, imidazolidine, and hydantoin, and the like. In another embodiment of the present invention cycloheteroalkyl is selected from: morpholine, pyrrolidine, piperazine, and piperidine. In another embodiment of the present invention, cycloheteroalkyl is pyrrolidine.

In another embodiment, C_{2-10}cycloheteroalkyl is a non-aromatic monocyclic, bicyclic, spiro or bridged carbocyclic ring having from 2 to 10 carbon atoms, and containing 1 or 2 heteroatoms selected from O. In another embodiment of the present invention, cycloheteroalkyl is dianhydro-mannitol. In another embodiment of the present invention, cycloheteroalkyl is 1, 4:3, 6-dianhydro-mannitol. In another embodiment of the present invention, cycloheteroalkyl is 1, 4:3, 6-dianhydro-D-mannitol. In another embodiment of the present invention, cycloheteroalkyl is hexahydrofuro[3,2-b]furan. In a class of this embodiment, cycloheteroalkyl is 2,3,3a,5,6,6a-hexahydrofuro[3,2-b]furan. In another embodiment, C_{2-10}cycloheteroalkyl is pyrrolidine, piperazine, piperidine, oxetane, thiamorpholine, and azetidine. In another embodiment, C_{3-7}cycloheteroalkyl is pyrrolidine, piperidine, imidazole, and morpholine. In another embodiment, C_{2-7}cycloheteroalkyl is oxetane, and tetrahydrothiopyran. In another embodiment, C_{2-7}cycloheteroalkyl is oxetane, azetidine, and piperidine. In another embodiment, cycloheteroalkyl is pyrrolidine and piperidine. In another embodiment, C_{2-6}cycloheteroalkyl is morpholine and pyrrolidine,

"Cycloheteroalkenyl" means aromatic monocyclic, bicyclic, spiro or bridged rings each having from 2 to 14 carbon atoms containing at least one double bond and containing 1, 2, 3, 4 or 5 heteroatoms selected from N, NH, O and S. Examples of cycloheteroalkenyl include 1,2,4-oxadiazol-5-one, 1,2,4-thiadiazol-5-one, 1,2,4-triazol-3-one, and 1,2,3,6-tetrahydropyridine, dihydro-1,3,4-oxadiazole, and [1,6]-dihydropyridine and the like. In one embodiment of the present invention, cycloheteroalkenyl is dihydro-1,3,4-oxadiazole. In another embodiment of the present invention, cycloheteroalkenyl is [1,6]-dihydropyridine.

In another embodiment, C_{2-10}cycloheteroalkenyl is a non-aromatic, bicyclic carbocyclic ring having from 2 to 10 carbon atoms, and containing 1, 2 or 3 heteroatoms selected from N, and NH. In a class of this embodiment, cycloheteroalkenyl is dihydropyrrolo[3,4-c]pyrazole. In another class of this embodiment, cycloheteroalkenyl is 4,6-dihydropyrrolo[3,4-c]pyrazole.

In another embodiment, C_{2-6}cycloheteroalkenyl is a non-aromatic, bicyclic carbocyclic ring having from 2 to 6 carbon atoms, and containing 1 or 2 heteroatoms selected from N, and NH. In a class of this embodiment, cycloheteroalkenyl is dihydroimidazole or

tetrahydropyrimidine. In another class of this embodiment, cycloheteroalkenyl is 2,5 dihydro-1H-imidazole or 1,4,5,6-tetrahydropyrimidine. In another class of this embodiment, cycloheteroalkenyl is dihydroimidazole. In another class of this embodiment, cycloheteroalkenyl is 2,5 dihydro-1H-imidazole. In another class of this embodiment, cycloheteroalkenyl is tetrahydropyrimidine. In another class of this embodiment, cycloheteroalkenyl is 1,4,5,6-tetrahydropyrimidine.

"Aryl" means a monocyclic, bicyclic or tricyclic ring system containing 5-14 carbon atoms, wherein at least one of the rings is aromatic. Aryl thus includes ring systems in which an aromatic ring is fused to a non-aromatic ring, such as a cycloalkyl or cycloalkenyl ring. Examples of aryl include phenyl, naphthalene, biphenyl, indane and 5,6,7,8-tetrahydronaphthalene, and the like. In one embodiment of the present invention, aryl is phenyl, naphthalene, biphenyl, indane, and 5,6,7,8-tetrahydronaphthalene. In another embodiment of the present invention, aryl is phenyl, naphthalene, indane and 5,6,7,8-tetrahydronaphthalene. In one class of this embodiment, aryl is phenyl and naphthalene. In another embodiment, aryl is phenyl. In another embodiment, aryl is naphthalene.

"Heteroaryl" means a monocyclic, bicyclic or tricyclic ring system containing 5-14 carbon atoms and containing 1, 2, 3, 4 or 5 heteroatoms selected from N, NH, O and S wherein at least one of the heteroatom containing rings is aromatic. Heteroaryl thus includes ring systems in which an aromatic heteroatom containing ring is fused to a non-aromatic ring, such as a cycloalkyl, cycloalkenyl, cycloheteroalkyl or cycloheteroalkenyl ring, and also includes ring systems in which an aryl ring is fused to a non-aromatic heteroatom containing ring, such as acycloheteroalkyl or cycloheteroalkenyl ring. Examples of heteroaryls include: pyrazole, pyridine, pyrazine, pyrimidine, thiazole, thiophene, benzoimidazole, quinoline, isoquinoline, indole, indazole, carbazole, benzotriazole, benzofuran, benzothiazole, benzothiophene, benzoisooxazole, oxazole, furan, benzoxazole, isoxazole, indoline, isoindoline, tetrazole, imidazole, oxadiazole, thiadiazole, triazole, benzothiazole, bernzopyrazole, imidazopyridine, benzodioxole, dihydropyridine, dihydropyrrolopyridine, dihydrobenzooxazine, benzodioxole, benzodioxine, pyrrolopyridine, triazolopyridine, dihydropyridooxazine, dihydrobenzoxazine, dihydroindole, dihydroisoindole, dihydrobenzoimidazole, dihydroquinoline, tetrahydroisoquinoline, tetrahydrocyclopentaindole, tetrahydroquinoxaline, and tetrahydropyridine. In one embodiment of the present invention, heteroaryl is selected from: imidazole, pyrazole, pyridine, pyrazine, pyrimidine, thiazole, thiophene, benzoimidazole, quinoline, isoquinoline, indole, indazole, carbazole, benzotriazole, benzofuran, benzothiazole, benzo[b]thiophene, benzo[d]isooxazole, 3,4-dihydro-2H-benzo[1,4]oxazine, benzo[1,3]dioxole, benzo[1,4]dioxine, 1H-pyrrolo[2,3-b]pyridine, 1,6-dihydro-pyridine, [1,2,4]triazolo[4,3-a]pyridine, 3,4 dihydropyrido [3,2-b][1,4]oxazine, 3,4-dihydro-2H-1,4-benzoxazine, 2,3-dihydro-1H-indole, 2,3-dihydro-1H-isoindole, 2,3-dihydrobenzoimidazole, 1,2-

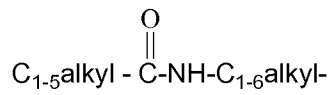
dihydroquinoline, 1,2,3,4-tetrahydroisoquinoline, 1,2,3,4-tetrahydrocyclopenta[b]indole, 1,2,3,4-tetrahydroquinoxaline, and 1,2,3,6-tetrahydropyridine. In another embodiment of the present invention, heteroaryl is tetrazole. In another embodiment, heteroaryl is selected from: pyrazole, pyridine, pyrimidine, isoxazole, imidazole, oxazole, triazole, tetrazole, oxadiazole, thiazole, thiadiazole, and benzoxazole. In another embodiment of this invention, heteroaryl is tetrazole. In another embodiment, heteroaryl is pyrazole, dihydropyrrolopyrazole and pyridine. In another embodiment, heteroaryl is benzodioxole. In another embodiment, heteroaryl is pyrazole, triazole, pyrimidine, imidazole, oxadiazole, and oxazole.

In another embodiment of the present invention, dihydropyrrolopyrazole is 4,6-dihydropyrrolo[3,4-c]pyrazole. In another embodiment of the present invention, dihydroimidazole is 4,5-dihydro-1*H*-imidazole.

"Halogen" includes fluorine, chlorine, bromine and iodine. In one embodiment of the present invention, halogen is selected from fluorine, chlorine, and bromine. In another embodiment of the present invention, halogen is selected from fluorine, and chlorine. In another embodiment of the present invention, halogen is fluorine. In another embodiment of the present invention, halogen is chlorine.

When any variable (e.g., R^1, R^a, etc.) occurs more than one time in any constituent or in formula I, its definition on each occurrence is independent of its definition at every other occurrence. Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds. A squiggly line across a bond in a substituent variable represents the point of attachment.

Under standard nomenclature used throughout this disclosure, the terminal portion of the designated side chain is described first, followed by the adjacent functionality toward the point of attachment. For example, a C_{1-5} alkylcarbonylamino C_{1-6} alkyl substituent is equivalent to:



In choosing compounds of the present invention, one of ordinary skill in the art will recognize that the various substituents, i.e. R^1, R^2, etc., are to be chosen in conformity with well-known principles of chemical structure connectivity and stability.

The term "substituted" shall be deemed to include multiple degrees of substitution by a named substitutent. Where multiple substituent moieties are disclosed or claimed, the substituted compound can be independently substituted by one or more of the disclosed or claimed substituent moieties, singly or plurally. By independently substituted, it is meant that the (two or more) substituents can be the same or different.

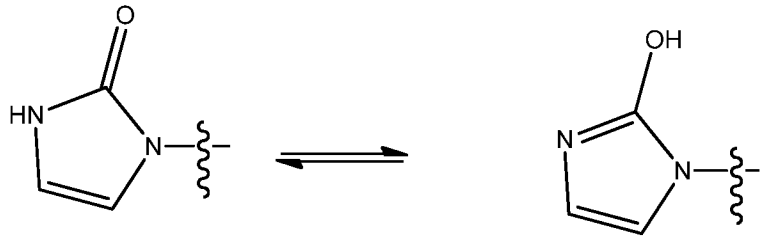
Compounds of Formula I may contain one or more asymmetric centers and can thus occur as racemates and racemic mixtures, single enantiomers, diastereomeric mixtures and individual diastereomers. The present invention is meant to comprehend all such isomeric forms

of the compounds of Formula I.

Some of the compounds described herein contain olefinic double bonds, and unless specified otherwise, are meant to include both E and Z geometric isomers.

Tautomers are defined as compounds that undergo rapid proton shifts from one atom of the compound to another atom of the compound. Some of the compounds described herein may exist as tautomers with different points of attachment of hydrogen. Such an example may be a ketone and its enol form known as keto-enol tautomers. The individual tautomers as well as mixture thereof are encompassed with compounds of Formula I.

Examples of tautomers include, but are not limited to:



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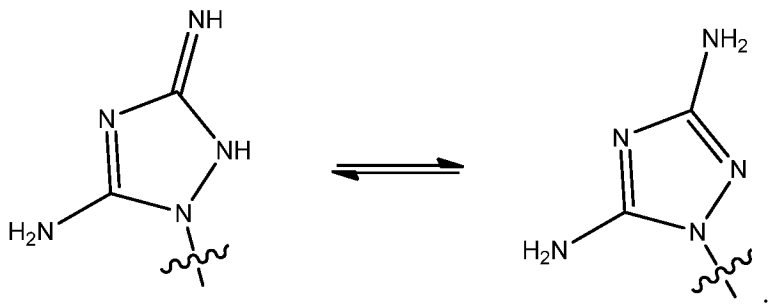

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In the compounds of general formula I, the atoms may exhibit their natural isotopic abundances, or one or more of the atoms may be artificially enriched in a particular isotope having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number predominately found in nature. The present invention is meant to include all suitable isotopic variations of the compounds of structural formula I. For example, different isotopic forms of hydrogen (H) include protium (^{1}H) and deuterium (^{2}H). Protium is the predominant hydrogen isotope found in nature. Enriching for deuterium may afford certain therapeutic advantages, such as increasing in vivo half-life or reducing dosage requirements, or may provide a compound useful as a standard for characterization of biological samples. Isotopically-enriched compounds within structural formula I, can be prepared without undue experimentation by conventional techniques well known to those skilled in the art or by processes analogous to those described in the Schemes and Examples herein using appropriate isotopically-enriched reagents and/or intermediates.

Compounds of the Formula I may be separated into diastereoisomeric pairs of enantiomers by, for example, fractional crystallization from a suitable solvent, for example

MeOH or ethyl acetate or a mixture thereof. The pair of enantiomers thus obtained may be separated into individual stereoisomers by conventional means, for example by the use of an optically active amine as a resolving agent or on a chiral HPLC column.

Alternatively, any enantiomer of a compound of the general Formula I may be obtained by stereospecific synthesis using optically pure starting materials or reagents of known configuration.

Furthermore, some of the crystalline forms for compounds of the present invention may exist as polymorphs and as such are intended to be included in the present invention. In addition, some of the compounds of the instant invention may form solvates with water or common organic solvents. Such solvates are encompassed within the scope of this invention.

It is generally preferable to administer compounds of the present invention as enantiomerically pure formulations. Racemic mixtures can be separated into their individual enantiomers by any of a number of conventional methods. These include chiral chromatography, derivatization with a chiral auxiliary followed by separation by chromatography or crystallization, and fractional crystallization of diastereomeric salts.

The term “pharmaceutically acceptable salts” refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids including inorganic or organic bases and inorganic or organic acids. Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc, and the like. Particularly preferred are the ammonium, calcium, magnesium, potassium, and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, and basic ion exchange resins, such as arginine, betaine, caffeine, choline, N,N’-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethyl-morpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine, and the like. The term "pharmaceutically acceptable salt" further includes all acceptable salts such as acetate, trifluoroacetate, lactobionate, benzenesulfonate, laurate, benzoate, malate, bicarbonate, maleate, bisulfate, mandelate, bitartrate, mesylate, borate, methylbromide, bromide, methylnitrate, calcium edetate, methylsulfate, camsylate, mucate, carbonate, napsylate, chloride, nitrate, clavulanate, N-methylglucamine, citrate, ammonium salt, dihydrochloride, oleate, edetate, oxalate, edisylate, pamoate (embonate), estolate, palmitate, esylate, pantothenate, fumarate, phosphate/diphosphate, gluceptate, polygalacturonate, gluconate, salicylate, glutamate, stearate, glycollylarsanilate, sulfate, hexylresorcinate, subacetate, hydrabamine, succinate, hydrobromide, tannate, hydrochloride, tartrate, hydroxynaphthoate, teoclate, iodide, tosylate,

isothionate, triethiodide, lactate, panoate, valerate, and the like which can be used as a dosage form for modifying the solubility or hydrolysis characteristics or can be used in sustained release or pro-drug formulations.

It will be understood that, as used herein, references to the compounds of Formula I are meant to also include the pharmaceutically acceptable salts.

Compounds of the present invention are activators of the AMP-activated protein kinase. The methods of treatment of this invention comprise a method of activating AMPK-activated protein kinase and treating AMPK-activated protein kinase mediated diseases by administering to a patient in need of such treatment a non-toxic therapeutically effective amount of a compound of this invention that activate AMPK-activated protein kinase.

AMP-activated protein kinase (AMPK) is a heterotrimeric enzyme composed of a catalytic α subunit and regulatory β and γ subunits. There are two genes encoding isoforms of both the α and β subunits ($\alpha1$, $\alpha2$, $\beta1$ and $\beta2$) and three genes encoding isoforms of the γ subunit ($\gamma1$, $\gamma2$ and $\gamma3$) leading to 12 possible heterotrimeric combinations. The $\alpha2$ isoform is predominately found in skeletal and cardiac muscle AMPK; both the $\alpha1$ and $\alpha2$ isoforms are found in hepatic AMPK; while in pancreatic islet β-cells the $\alpha1$ isoform AMPK predominates. In particular, the compounds of structural formula I are activators of at least one heterotrimeric isoform of AMP-activated protein kinase.

An "activator" is a compound that either increases the activity (phosphorylation of downstream substrates) of fully phosphorylated AMPK or that increases the phosphorylation of AMPK.

The compounds of the present invention are efficacious in the treatment and prevention of diseases, disorders and conditions that are responsive to the activation of AMP-activated protein kinase. As AMPK activators, the compounds of the present invention may be useful for the treatment of Type 2 diabetes, insulin resistance, hyperglycemia, obesity, hyperinsulinemia, glucose intolerance, atherosclerosis, Metabolic Syndrome, hypertension, high hepatic glucose output, high blood glucose concentrations, nonalcoholic steatohepatitis, protection against ischemia and reperfusion damage, and lipid disorders, such as dyslipidemia, elevated levels of plasma triglycerides, elevated levels of free fatty acids, elevated levels of cholesterol, high levels of low density lipoprotein (LDL) and low levels of high density lipoprotein (HDL). The compounds of the present invention may also be useful for the treatment of cancer, hypoxia and glucocorticoid-induced apoptosis. The compounds of the present invention may also be useful for the treatment of sarcopenia by treating or preventing the loss of skeletal muscle mass, including but not limited to a loss of skeletal muscle mass due to aging.

One or more of the following diseases may be treated by the administration of a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof, to a patient in need of treatment or prevention of: (1) non-insulin dependent

diabetes mellitus (Type 2 diabetes); (2) hyperglycemia; (3) Metabolic Syndrome; (4) obesity; (5) hypercholesterolemia; (6) hypertriglyceridemia (elevated levels of triglyceride-rich-lipoproteins); (7) mixed or diabetic dyslipidemia; (8) low HDL cholesterol; (9) high LDL cholesterol; (10) atherosclerosis; (11) atherosclerosis, (12) hypertension, and (13) sarcopenia.

In one embodiment of the present invention, the compounds of Formula I may be useful for the treatment of one or more of the following diseases by administering a therapeutically effective amount to a patient in need of treatment: (1) Type 2 diabetes; (2) hyperglycemia; (3) Metabolic Syndrome; (4) obesity; (5) hypercholesterolemia; and (6) hypertension.

The compounds of structural Formula I may also be used for manufacturing a medicament for use in the treatment of one or more of the above diseases.

The compounds may also be effective in lowering glucose and lipids in diabetic patients and in non-diabetic patients who have impaired glucose tolerance and/or are in a pre-diabetic condition. The compounds may ameliorate hyperinsulinemia, which often occurs in diabetic or pre-diabetic patients, by modulating the swings in the level of serum glucose that often occurs in these patients. The compounds may also be effective in treating or reducing insulin resistance. The compounds may be effective in treating or preventing gestational diabetes.

The compounds, compositions, methods and medicaments as described herein may also be effective in: a) reducing the risks of adverse sequelae associated with metabolic syndrome, b) reducing the risk of developing atherosclerosis, c) delaying the onset of atherosclerosis, and/or d) reducing the risk of sequelae of atherosclerosis. Sequelae of atherosclerosis include angina, claudication, heart attack, stroke, and others. By keeping hyperglycemia under control, the compounds may also be effective in delaying or preventing vascular restenosis and diabetic retinopathy.

The compounds of this invention may also have utility in improving or restoring β-cell function, and may be useful in treating type 1 diabetes, and in delaying or preventing a patient with Type 2 diabetes from needing insulin therapy.

Other possible outcomes of treatment with the compounds of the present invention may be: 1) a decrease in fatty acid synthesis; 2) an increase in fatty acid oxidation and ketogenesis; 3) a decrease in cholesterol synthesis, lipogenesis, and triglyceride synthesis; 4) a decrease in blood glucose levels and concentration; 5) an improvement in glucose homeostasis; 6) a normalization of glucose metabolism; 7) a decrease in blood pressure; 8) an increase in HDL; 9) a decrease in LDL; 10) a decrease in plasma triglycerides; 11) a decrease in free fatty acids; 12) a decrease in hepatic glucose output; 13) an improvement in insulin action; 14) a decrease in blood pressure; 15) an improvement in insulin sensitivity; 16) a suppression of hepatic glucose output; 17) an inhibition of de novo lipogenesis; 18) stimulation of muscle glucose uptake; 19) modulation of insulin secretion by pancreatic β cells; 20) a decrease in body weight; 21) an increase in skeletal muscle mass; and 22) a prevention in the loss of skeletal

muscle mass.

The compounds of the present invention may be efficacious in treating one or more of the following diseases: (1) Type 2 diabetes (also known as non-insulin dependent diabetes mellitus, or NIDDM), (2) hyperglycemia, (3) impaired glucose tolerance, (4) insulin resistance, (5) obesity, (6) lipid disorders, (7) dyslipidemia, (8) hyperlipidemia, (9) hypertriglyceridemia, (10) hypercholesterolemia, (11) low HDL levels, (12) high LDL levels, (13) atherosclerosis and its sequelae, (14) vascular restenosis, (15) abdominal obesity, (16) retinopathy, (17) metabolic syndrome, (18) high blood pressure (hypertension), and (19) insulin resistance.

One aspect of the invention provides potential methods for the treatment and control of mixed or diabetic dyslipidemia, hypercholesterolemia, atherosclerosis, low HDL levels, high LDL levels, hyperlipidemia, and/or hypertriglyceridemia, which comprises administering to a patient in need of such treatment a therapeutically effective amount of a compound of formula I alone or with a cholesterol biosynthesis inhibitor, particularly an HMG-CoA reductase inhibitor such as lovastatin, simvastatin, rosuvastatin, pravastatin, fluvastatin, atorvastatin, rivastatin, itavastatin, or ZD-4522. The compound of formula I may also be used advantageously in combination with other lipid lowering drugs such as cholesterol absorption inhibitors (for example stanol esters, sterol glycosides such as tiqueside, and azetidinones such as ezetimibe), ACAT inhibitors (such as avasimibe), CETP inhibitors (for example anacetrapib, torcetrapib, and those described in published applications WO2005/100298, WO2006/014413, and WO2006/014357), niacin and niacin receptor agonists, bile acid sequestrants, microsomal triglyceride transport inhibitors, and bile acid reuptake inhibitors. These combination treatments may be effective for the treatment or control of one or more related conditions selected from the group consisting of hypercholesterolemia, atherosclerosis, hyperlipidemia, hypertriglyceridemia, dyslipidemia, high LDL, and low HDL.

The present invention also provides potential methods and medicaments for the treatment, control, or prevention of Type 2 diabetes by administering the compounds and pharmaceutical compositions of the present invention alone or in combination with a therapeutically effective amount of another agent known to be useful to treat the condition. The present invention also relates to potential methods and medicaments for the treatment, control, or prevention of diabetes related disorders by administering the compounds and pharmaceutical compositions of the present invention alone, or in combination. The present invention also relates to potential methods and medicaments for the treatment and prevention of diabetes in pre-diabetic subject by administering the compounds and pharmaceutical compositions of the present invention alone, or in combination.

The present invention also relates to potential methods and medicaments for the treatment, control, or prevention of obesity by administering the compounds and pharmaceutical compositions of the present invention, alone or in combination with a therapeutically effective

amount of another agent known to be useful to treat the condition. The present invention also relates to potential methods and medicaments for the treatment, control, or prevention of obesity related disorders by administering the compounds and pharmaceutical compositions of the present invention alone, or in combination. The present invention also relates to potential methods and medicaments for the treatment and prevention of obesity in overweight subject by administering the compounds and pharmaceutical compositions of the present invention alone, or in combination. The compounds may also be useful for the treatment of obesity related disorders.

The present invention also relates to potential methods and medicaments for the treatment, control, or prevention of hyperglycemia by administering the compounds and pharmaceutical compositions of the present invention, alone or in combination with a therapeutically effective amount of another agent known to be useful to treat the condition.

The present invention also relates to potential methods and medicaments for the treatment, control, or prevention of insulin resistance by administering the compounds and pharmaceutical compositions of the present invention, alone or in combination with a therapeutically effective amount of another agent known to be useful to treat the condition.

The present invention also relates to potential methods and medicaments for the treatment, control, or prevention of lipid disorders by administering the compounds and pharmaceutical compositions of the present invention, alone or in combination with a therapeutically effective amount of another agent known to be useful to treat the condition. The present invention also relates to potential methods and medicaments for the treatment, control, or prevention of dyslipidemia related disorders and lipid disorder-related disorders by administering the compounds and pharmaceutical compositions of the present invention alone, or in combination.

The present invention also relates to potential methods and medicaments for the treatment, control, or prevention of atherosclerosis by administering the compounds and pharmaceutical compositions of the present invention, alone or in combination with a therapeutically effective amount of another agent known to be useful to treat the condition.

The present invention also relates to potential methods and medicaments for the treatment, control, or prevention of hypertension by administering the compounds and pharmaceutical compositions of the present invention, alone or in combination with a therapeutically effective amount of another agent known to be useful to treat the condition. The present invention also relates to potential methods and medicaments for the treatment and prevention of hypertension in pre-hypertensive subject by administering the compounds and pharmaceutical compositions of the present invention alone, or in combination.

The present invention also relates to potential methods and medicaments for the treatment, control, or prevention of Metabolic Syndrome by administering the compounds and

pharmaceutical compositions of the present invention, alone or in combination with a therapeutically effective amount of another agent known to be useful to treat the condition.

The compounds of the present invention wherein Y is a tetrahydropyran derivative have the unexpected benefit of reduced inhibition of recombinant CYP2C9 or CYP2C8 isozymes, compared to analogous compounds wherein Y is phenyl. In particular, the compounds of the present invention wherein Y is a tetrahydropyran derivative have the unexpected benefit of reduced inhibition of recombinant CYP2C9 or CYP2C8 isozymes, compared to analogous compounds wherein Y is benzoic acid.

Inhibition of a recombinant CYP isozyme is measured by using a probe substrate, which upon oxidation by human liver microsome, is converted to a metabolite which is monitored by LC-MS/MS. NADPH or NADPH regenerating system are used as electron donors for the microsome catalytic cycle. Control incubations containing no inhibitors performed to evaluate the 100% activities. The activity of the enzyme is evaluated in the presence of various concentrations of test compounds. Standard specific enzyme inhibitors are used as positive controls. Inhibition curves are generated and IC50 values are calculated for tested compounds.

Co-administration of CYP inhibitors with pharmaceutical agents that are metabolized by the enzyme can result in elevated circulating concentrations of the pharmaceutical agents. This can lead to adverse events.

Additionally, the compounds of the present invention wherein at least one of T, U, V and W is N or N-oxide have the unexpected benefit of reduced binding to human plasma proteins compared to compounds wherein T is CR^3, U is CR^1-, V is CR^2 and W is CR^4. Pharmacological activity in vivo is associated with the concentration of drug unbound to plasma proteins. Plasma proteins, by virtue of their high concentration, control the concentration of drug unbound to plasma proteins in plasma and in compartments in equilibrium with plasma, thereby, effectively attenuating drug potency in vivo (See Trainor, G.L. (2007), Expert Opin. Drug Discov. 2(1), 51-64). A higher concentration of drug unbound to plasma proteins results in an increase in pharmacological activity in vivo. Due to their increased potency and their higher unbound fraction in plasma, the compounds of the present invention are expected to exhibit glucose lowering efficacy at reduced plasma exposures.

The term "diabetes," as used herein, includes both insulin-dependent diabetes mellitus (i.e., IDDM, also known as type 1 diabetes) and non-insulin-dependent diabetes mellitus (i.e., NIDDM, also known as Type 2 diabetes). Type 1 diabetes, or insulin-dependent diabetes, is the result of an absolute deficiency of insulin, the hormone which regulates glucose utilization. Type 2 diabetes, or insulin-independent diabetes (i.e., non-insulin-dependent diabetes mellitus), often occurs in the face of normal, or even elevated levels of insulin and appears to be the result of the inability of tissues to respond appropriately to insulin. Most of the Type 2 diabetics are also obese. The compositions of the present invention may be useful for treating both Type 1

and Type 2 diabetes. The term “diabetes associated with obesity” refers to diabetes caused by obesity or resulting from obesity. The compositions may be especially effective for treating Type 2 diabetes. The compositions of the present invention may also be useful for treating and/or preventing gestational diabetes mellitus.

Diabetes is characterized by a fasting plasma glucose level of greater than or equal to 126 mg/dl. A diabetic subject has a fasting plasma glucose level of greater than or equal to 126 mg/dl. A pre diabetic subject is someone suffering from prediabetes. Prediabetes is characterized by an impaired fasting plasma glucose (FPG) level of greater than or equal to 110 mg/dl and less than 126 mg/dl; or impaired glucose tolerance; or insulin resistance. A prediabetic subject is a subject with impaired fasting glucose (a fasting plasma glucose (FPG) level of greater than or equal to 110 mg/dl and less than 126 mg/dl); or impaired glucose tolerance (a 2 hour plasma glucose level of $\geq$140 mg/dl and <200 mg/dl); or insulin resistance, resulting in an increased risk of developing diabetes.

Treatment of diabetes mellitus refers to the administration of a compound or combination of the present invention to treat a diabetic subject. One outcome of treatment may be decreasing the glucose level in a subject with elevated glucose levels. Another outcome of treatment may be decreasing insulin levels in a subject with elevated insulin levels. Another outcome of treatment may be decreasing plasma triglycerides in a subject with elevated plasma triglycerides. Another outcome of treatment is decreasing LDL cholesterol in a subject with high LDL cholesterol levels. Another outcome of treatment may be increasing HDL cholesterol in a subject with low HDL cholesterol levels. Another outcome of treatment is increasing insulin sensivity. Another outcome of treatment may be enhancing glucose tolerance in a subject with glucose intolerance. Yet another outcome of treatment may be decreasing insulin resistance in a subject with increased insulin resistance or elevated levels of insulin. Prevention of diabetes mellitus, in particular diabetes associated with obesity, refers to the administration of a compound or combination of the present invention to prevent the onset of diabetes in a subject in need thereof. A subject in need of preventing diabetes is a prediabetic subject that is overweight or obese.

The term "diabetes related disorders" should be understood to mean disorders that are associated with, caused by, or result from diabetes. Examples of diabetes related disorders include retinal damage, kidney disease, and nerve damage.

The term “atherosclerosis” as used herein encompasses vascular diseases and conditions that are recognized and understood by physicians practicing in the relevant fields of medicine. Atherosclerotic cardiovascular disease, coronary heart disease (also known as coronary artery disease or ischemic heart disease), cerebrovascular disease and peripheral vessel disease are all clinical manifestations of atherosclerosis and are therefore encompassed by the terms "atherosclerosis" and "atherosclerotic disease." The combination comprised of a therapeutically

effective amount of an anti-obesity agent in combination with a therapeutically effective amount of an anti-hypertensive agent may be administered to prevent or reduce the risk of occurrence, or recurrence where the potential exists, of a coronary heart disease event, a cerebrovascular event, or intermittent claudication. Coronary heart disease events are intended to include CHD death, myocardial infarction (i.e., a heart attack), and coronary revascularization procedures. Cerebrovascular events are intended to include ischemic or hemorrhagic stroke (also known as cerebrovascular accidents) and transient ischemic attacks. Intermittent claudication is a clinical manifestation of peripheral vessel disease. The term "atherosclerotic disease event" as used herein is intended to encompass coronary heart disease events, cerebrovascular events, and intermittent claudication. It is intended that persons who have previously experienced one or more non-fatal atherosclerotic disease events are those for whom the potential for recurrence of such an event exists. The term "atherosclerosis related disorders" should be understood to mean disorders associated with, caused by, or resulting from atherosclerosis.

The term “hypertension” as used herein includes essential, or primary, hypertension wherein the cause is not known or where hypertension is due to greater than one cause, such as changes in both the heart and blood vessels; and secondary hypertension wherein the cause is known. Causes of secondary hypertension include, but are not limited to obesity; kidney disease; hormonal disorders; use of certain drugs, such as oral contraceptives, corticosteroids, cyclosporin, and the like. The term “hypertension” encompasses high blood pressure, in which both the systolic and diastolic pressure levels are elevated ($\geq$140 mmHg/$\geq$90 mmHg), and isolated systolic hypertension, in which only the systolic pressure is elevated to greater than or equal to 140 mm Hg, while the diastolic pressure is less than 90 mm Hg. Normal blood pressure may be defined as less than 120 mmHg systolic and less than 80 mmHg diastolic. A hypertensive subject is a subject with hypertension. A pre-hypertensive subject is a subject with a blood pressure that is between 120 mmHg over 80 mmHg and 139 mmHg over 89 mmHg. One outcome of treatment is decreasing blood pressure in a subject with high blood pressure. Treatment of hypertension refers to the administration of the compounds and combinations of the present invention to treat hypertension in a hypertensive subject. Treatment of hypertension-related disorder refers to the administration of a compound or combination of the present invention to treat the hypertension-related disorder. Prevention of hypertension, or a hypertension related disorder, refers to the administration of the combinations of the present invention to a pre-hypertensive subject to prevent the onset of hypertension or a hypertension related disorder. The hypertension-related disorders herein are associated with, caused by, or result from hypertension. Examples of hypertension-related disorders include, but are not limited to: heart disease, heart failure, heart attack, kidney failure, and stroke.

Dyslipidemias and lipid disorders are disorders of lipid metabolism including various conditions characterized by abnormal concentrations of one or more lipids (i.e. cholesterol and

triglycerides), and/or apolipoproteins (i.e., apolipoproteins A, B, C and E), and/or lipoproteins (i.e., the macromolecular complexes formed by the lipid and the apolipoprotein that allow lipids to circulate in blood, such as LDL, VLDL and IDL). Hyperlipidemia is associated with abnormally high levels of lipids, LDL and VLDL cholesterol, and/or triglycerides. Treatment of dyslipidemia refers to the administration of the combinations of the present invention to a dyslipidemic subject. Prevention of dyslipidemia refers to the administration of the combinations of the present invention to a pre-dyslipidemic subject. A pre-dyslipidemic subject is a subject with higher than normal lipid levels, that is not yet dyslipidemic.

The terms "dyslipidemia related disorders" and "lipid disorder related disorders" should be understood to mean disorders associated with, caused by, or resulting from dyslipidemia or lipid disorders. Examples of dylipidemia related disorder and lipid disorder related disorders include, but are not limited to: hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, low high density lipoprotein (HDL) levels, high plasma low density lipoprotein (LDL) levels, atherosclerosis and its sequelae, coronary artery or carotid artery disease, heart attack, and stroke.

The term “obesity” as used herein is a condition in which there is an excess of body fat. The operational definition of obesity is based on the Body Mass Index (BMI), which is calculated as body weight per height in meters squared (kg/m^2). “Obesity” refers to a condition whereby an otherwise healthy subject has a Body Mass Index (BMI) greater than or equal to 30 kg/m^2, or a condition whereby a subject with at least one co-morbidity has a BMI greater than or equal to 27 kg/m^2. An “obese subject” is an otherwise healthy subject with a Body Mass Index (BMI) greater than or equal to 30 kg/m^2 or a subject with at least one co-morbidity with a BMI greater than or equal to 27 kg/m^2. An overweight subject is a subject at risk of obesity. A “subject at risk of obesity” is an otherwise healthy subject with a BMI of 25 kg/m^2 to less than 30 kg/m^2 or a subject with at least one co-morbidity with a BMI of 25 kg/m^2 to less than 27 kg/m^2.

The increased risks associated with obesity occur at a lower Body Mass Index (BMI) in Asians. In Asian countries, including Japan, “obesity” refers to a condition whereby a subject with at least one obesity-induced or obesity-related co-morbidity, that requires weight reduction or that would be improved by weight reduction, has a BMI greater than or equal to 25 kg/m^2. In Asian countries, including Japan, an “obese subject” refers to a subject with at least one obesity-induced or obesity-related co-morbidity that requires weight reduction or that would be improved by weight reduction, with a BMI greater than or equal to 25 kg/m^2. In Asia-Pacific, a “subject at risk of obesity” is a subject with a BMI of greater than 23 kg/m^2 to less than 25 kg/m^2.

As used herein, the term “obesity” is meant to encompass all of the above definitions of obesity.

Obesity-induced or obesity-related co-morbidities include, but are not limited to, diabetes mellitus, non-insulin dependent diabetes mellitus - type 2, diabetes associated with obesity, impaired glucose tolerance, impaired fasting glucose, insulin resistance syndrome, dyslipidemia, hypertension, hypertension associated with obesity, hyperuricacidemia, gout, coronary artery disease, myocardial infarction, angina pectoris, sleep apnea syndrome, Pickwickian syndrome, fatty liver; cerebral infarction, cerebral thrombosis, transient ischemic attack, orthopedic disorders, arthritis deformans, lumbodynia, emmeniopathy, and infertility. In particular, co-morbidities include: hypertension, hyperlipidemia, dyslipidemia, glucose intolerance, cardiovascular disease, sleep apnea, and other obesity-related conditions.

Treatment of obesity and obesity-related disorders refers to the administration of the compounds of the present invention to reduce or maintain the body weight of an obese subject. One outcome of treatment may be reducing the body weight of an obese subject relative to that subject's body weight immediately before the administration of the compounds of the present invention. Another outcome of treatment may be preventing body weight regain of body weight previously lost as a result of diet, exercise, or pharmacotherapy. Another outcome of treatment may be decreasing the occurrence of and/or the severity of obesity-related diseases. The treatment may suitably result in a reduction in food or calorie intake by the subject, including a reduction in total food intake, or a reduction of intake of specific components of the diet such as carbohydrates or fats; and/or the inhibition of nutrient absorption; and/or the inhibition of the reduction of metabolic rate; and in weight reduction in patients in need thereof. The treatment may also result in an alteration of metabolic rate, such as an increase in metabolic rate, rather than or in addition to an inhibition of the reduction of metabolic rate; and/or in minimization of the metabolic resistance that normally results from weight loss.

Prevention of obesity and obesity-related disorders refers to the administration of the compounds of the present invention to reduce or maintain the body weight of a subject at risk of obesity. One outcome of prevention may be reducing the body weight of a subject at risk of obesity relative to that subject's body weight immediately before the administration of the compounds of the present invention. Another outcome of prevention may be preventing body weight regain of body weight previously lost as a result of diet, exercise, or pharmacotherapy. Another outcome of prevention may be preventing obesity from occurring if the treatment is administered prior to the onset of obesity in a subject at risk of obesity. Another outcome of prevention may be decreasing the occurrence and/or severity of obesity-related disorders if the treatment is administered prior to the onset of obesity in a subject at risk of obesity. Moreover, if treatment is commenced in already obese subjects, such treatment may prevent the occurrence, progression or severity of obesity-related disorders, such as, but not limited to, arteriosclerosis, Type II diabetes, polycystic ovarian disease, cardiovascular diseases, osteoarthritis, dermatological disorders, hypertension, insulin resistance, hypercholesterolemia,

hypertriglyceridemia, and cholelithiasis.

The obesity-related disorders herein are associated with, caused by, or result from obesity. Examples of obesity-related disorders include overeating and bulimia, hypertension, diabetes, elevated plasma insulin concentrations and insulin resistance, dyslipidemias, hyperlipidemia, endometrial, breast, prostate and colon cancer, osteoarthritis, obstructive sleep apnea, cholelithiasis, gallstones, heart disease, abnormal heart rhythms and arrythmias, myocardial infarction, congestive heart failure, coronary heart disease, sudden death, stroke, polycystic ovarian disease, craniopharyngioma, the Prader-Willi Syndrome, Frohlich's syndrome, GH-deficient subjects, normal variant short stature, Turner's syndrome, and other pathological conditions showing reduced metabolic activity or a decrease in resting energy expenditure as a percentage of total fat-free mass, e.g, children with acute lymphoblastic leukemia. Further examples of obesity-related disorders are metabolic syndrome, also known as syndrome X, insulin resistance syndrome, sexual and reproductive dysfunction, such as infertility, hypogonadism in males and hirsutism in females, gastrointestinal motility disorders, such as obesity-related gastro-esophageal reflux, respiratory disorders, such as obesity-hypoventilation syndrome (Pickwickian syndrome), cardiovascular disorders, inflammation, such as systemic inflammation of the vasculature, arteriosclerosis, hypercholesterolemia, hyperuricaemia, lower back pain, gallbladder disease, gout, and kidney cancer.

The compounds of formula I may also be useful for treating or preventing obesity and obesity-related disorders in cats and dogs. As such, the term "mammal" includes companion animals such as cats and dogs.

The term "metabolic syndrome", also known as syndrome X, is defined in the Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III, or ATP III), National Institutes of Health, 2001, NIH Publication No. 01-3670. E.S. Ford et al., JAMA, vol. 287 (3), Jan. 16, 2002, pp 356-359. Briefly, a person is defined as having metabolic syndrome if the person has three or more of the following disorders: abdominal obesity, hypertriglyceridemia, low HDL cholesterol, high blood pressure, and high fasting plasma glucose. The criteria for these are defined in ATP-III. Treatment of metabolic syndrome refers to the administration of the combinations of the present invention to a subject with metabolic syndrome. Prevention of metabolic syndrome refers to the administration of the combinations of the present invention to a subject with two of the disorders that define metabolic syndrome. A subject with two of the disorders that define metabolic syndrome is a subject that has developed two of the disorders that define metabolic syndrome, but has not yet developed three or more of the disorders that define metabolic syndrome.

The terms "administration of" and or "administering a" compound should be understood to mean providing a compound of the invention or a prodrug of a compound of the invention to

the individual or mammal in need of treatment.

The administration of the compound of structural formula I in order to practice the present methods of therapy is carried out by administering an effective amount of the compound of structural formula I to the mammal in need of such treatment or prophylaxis. The need for a prophylactic administration according to the methods of the present invention is determined via the use of well known risk factors. The effective amount of an individual compound is determined, in the final analysis, by the physician or veterinarian in charge of the case, but depends on factors such as the exact disease to be treated, the severity of the disease and other diseases or conditions from which the patient suffers, the chosen route of administration other drugs and treatments which the patient may concomitantly require, and other factors in the physician's judgment.

The usefulness of the present compounds in these diseases or disorders may be demonstrated in animal disease models that have been reported in the literature.

The magnitude of prophylactic or therapeutic dose of a compound of Formula I will, of course, vary with the nature of the severity of the condition to be treated and with the particular compound of Formula I and its route of administration. It will also vary according to the age, weight and response of the individual patient. In general, the daily dose range lie within the range of from about 0.001 mg to about 100 mg per kg body weight of a mammal, preferably 0.01 mg to about 50 mg per kg, and most preferably 0.1 to 10 mg per kg, in single or divided doses. On the other hand, it may be necessary to use dosages outside these limits in some cases.

For use where a composition for intravenous administration is employed, a suitable dosage range is from about 0.001 mg to about 100 mg in one embodiment from about 0.01 mg to about 50 mg, and in another embodiment from 0.1 mg to 10 mg of a compound of Formula I per kg of body weight per day.

In the case where an oral composition is employed, a suitable dosage range is, e.g. from about 0.01 mg to about 1000 mg of a compound of Formula I per day. In one embodiment, the range is from about 0.1 mg to about 10 mg per day. For oral administration, the compositions are preferably provided in the form of tablets containing from 0.01 to 1,000 mg, preferably 0.01, 0.05, 0.1, 0.5, 1, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, 10, 12, 12.5, 15, 20, 25, 30, 40, 50, 100, 250, 500, 750 or 1000 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated.

Another aspect of the present invention provides pharmaceutical compositions which comprises a compound of Formula I and a pharmaceutically acceptable carrier. The term "composition", as in pharmaceutical composition, is intended to encompass a product comprising the active ingredient(s), and the inert ingredient(s) (pharmaceutically acceptable excipients) that make up the carrier, as well as any product which results, directly or indirectly, from combination, complexation or aggregation of any two or more of the ingredients, or from

dissociation of one or more of the ingredients, or from other types of reactions or interactions of one or more of the ingredients. Accordingly, the pharmaceutical compositions of the present invention encompass any composition made by admixing a compound of Formula I, additional active ingredient(s), and pharmaceutically acceptable excipients.

Any suitable route of administration may be employed for providing a mammal, particularly a human or a companion animal such as a dog or cat, with an effective dosage of a compound of the present invention. For example, oral, rectal, topical, parenteral, ocular, pulmonary, and nasal routes of administration, and the like may be employed. Dosage forms include tablets, troches, dispersions, suspensions, solutions, capsules, creams, ointments, aerosols, and the like.

The pharmaceutical compositions of the present invention comprise a compound of Formula I as an active ingredient or a pharmaceutically acceptable salt thereof, and may also contain a pharmaceutically acceptable carrier and optionally other therapeutic ingredients. By "pharmaceutically acceptable" it is meant the carrier, diluent or excipient must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof. The compositions include compositions suitable for oral, rectal, topical, parenteral (including subcutaneous, intramuscular, and intravenous), ocular (ophthalmic), pulmonary (aerosol inhalation), or nasal administration, although the most suitable route in any given case will depend on the nature and severity of the conditions being treated and on the nature of the active ingredient. They may be conveniently presented in unit dosage form and prepared by any of the methods well-known in the art of pharmacy.

For administration by inhalation, the compounds of the present invention are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or nebulizers, or as powders which may be formulated and the powder composition may be inhaled with the aid of an insufflation powder inhaler device. The preferred delivery systems for inhalation are metered dose inhalation (MDI) aerosol, which may be formulated as a suspension or solution of a compound of Formula I in suitable propellants, such as fluorocarbons or hydrocarbons and dry powder inhalation (DPI) aerosol, which may be formulated as a dry powder of a compound of Formula I with or without additional excipients.

Suitable topical formulations of a compound of formula I include transdermal devices, aerosols, creams, solutions, ointments, gels, lotions, dusting powders, and the like. The topical pharmaceutical compositions containing the compounds of the present invention ordinarily include about 0.005% to 5% by weight of the active compound in admixture with a pharmaceutically acceptable vehicle. Transdermal skin patches useful for administering the compounds of the present invention include those known to those of ordinary skill in that art.

In practical use, the compounds of Formula I can be combined as the active ingredient in intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical

compounding techniques. The carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g., oral or parenteral (including intravenous). In preparing the compositions for oral dosage form, any of the usual pharmaceutical media may be employed, such as, for example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like in the case of oral liquid preparations, such as, for example, suspensions, elixirs and solutions; or carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents and the like in the case of oral solid preparations such as, for example, powders, capsules and tablets, with the solid oral preparations being preferred over the liquid preparations. Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit form in which case solid pharmaceutical carriers are obviously employed. If desired, tablets may be coated by standard aqueous or nonaqueous techniques.

In addition to the common dosage forms set out above, the compounds of Formula I may also be administered by controlled release means and/or delivery devices such as those described in U.S. Patent Nos. 3,845,770; 3,916,899; 3,536,809; 3,598,123; 3,630,200 and 4,008,719.

Pharmaceutical compositions of the present invention suitable for oral administration may be presented as discrete units such as capsules (including timed release and sustained release formulations), pills, cachets, powders, granules or tablets each containing a predetermined amount of the active ingredient, as a powder or granules or as a solution or a suspension in an aqueous liquid, a non-aqueous liquid, an oil-in-water emulsion or a water-in-oil liquid emulsion, including elixirs, tinctures, solutions, suspensions, syrups and emulsions. Such compositions may be prepared by any of the methods of pharmacy but all methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product into the desired presentation. For example, a tablet may be prepared by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine, the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine, a mixture of the powdered compound moistened with an inert liquid diluent. Desirably, each tablet cachet or capsule contains from about 0.01 to 1,000 mg, particularly 0.01, 0.05, 0.1, 0.5, 1.0, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, 10, 12, 15, 25, 30, 40, 50, 75, 100, 125, 150, 175, 180, 200, 225, 250, 500, 750 and 1,000 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated.

Additional suitable means of administration of the compounds of the present invention include injection, intravenous bolus or infusion, intraperitoneal, subcutaneous, intramuscular,

intranasal, and topical, with or without occlusion.

Exemplifying the invention is a pharmaceutical composition comprising any of the compounds described above and a pharmaceutically acceptable carrier. Also exemplifying the invention is a pharmaceutical composition made by combining any of the compounds described above and a pharmaceutically acceptable carrier. An illustration of the invention is a process for making a pharmaceutical composition comprising combining any of the compounds described above and a pharmaceutically acceptable carrier.

The dose 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. Furthermore, based on the properties of the individual compound selected for administration, the dose may be administered less frequently, e.g., weekly, twice weekly, monthly, etc. The unit dosage will, of course, be correspondingly larger for the less frequent administration.

When administered via intranasal routes, transdermal routes, by rectal or vaginal suppositories, or through a continual intravenous solution, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen.

The following are examples of representative pharmaceutical dosage forms for the compounds of Formula I:

Injectable Suspension (I.M.)	mg/mL	Tablet	mg/tablet
Compound of Formula I	10	Compound of Formula I	25
Methylcellulose	5.0	Microcrystalline Cellulose	415
Tween 80	0.5	Povidone	14.0
Benzyl alcohol	9.0	Pregelatinized Starch	43.5
Benzalkonium chloride	1.0	Magnesium Stearate	2.5
Water for injection to a total volume of 1 mL			500

Capsule	mg/capsule	Aerosol	Per canister
Compound of Formula I	25	Compound of Formula I	24 mg
Lactose Powder	573.5	Lecithin, NF Liq. Conc.	1.2 mg
Magnesium Stearate	1.5	Trichlorofluoromethane, NF	4.025 g
	600	Dichlorodifluoromethane, NF	12.15 g

Compounds of Formula I may be used in combination with other drugs that are used in the treatment/prevention/suppression or amelioration of the diseases, disorders or conditions for which compounds of Formula I may be useful. Such other drugs may be administered, by a route and in an amount commonly used therefor, contemporaneously or sequentially with a compound of Formula I. When a compound of Formula I is used contemporaneously with one or more other drugs, a pharmaceutical composition containing such other drugs in addition to the compound of Formula I is preferred. Accordingly, the pharmaceutical compositions of the

present invention include those that also contain one or more other active ingredients, in addition to a compound of Formula I. Examples of other active ingredients that may be combined with a compound of Formula I include, but are not limited to: other anti-diabetic agents, anti-dylipidemic agents, and anti-hypertensive agents, anti-obesity agents, and anorectic agents, which may be administered separately or in the same pharmaceutical compositions.

The present invention also provides a method for the treatment or prevention of an AMPK-activated protein kinase (AMPK) mediated disease, which method comprises administration to a patient in need of such treatment or at risk of developing an AMPK mediated disease of an amount of an AMPK activator and an amount of one or more active ingredients, such that together they give effective relief.

In a further aspect of the present invention, there is provided a pharmaceutical composition comprising an AMPK activator and one or more active ingredients, together with at least one pharmaceutically acceptable carrier or excipient.

Thus, according to a further aspect of the present invention there is provided the use of an AMPK activator and one or more active ingredients for the manufacture of a medicament for the treatment or prevention of an AMPK mediated disease. In a further or alternative aspect of the present invention, there is provided a product comprising an AMPK activator and one or more active ingredients as a combined preparation for simultaneous, separate or sequential use in the treatment or prevention of an AMPK mediated disease. Such a combined preparation may be, for example, in the form of a twin pack.

It will be appreciated that for the potential treatment or prevention of diabetes, obesity, hypertension, Metabolic Syndrome, dyslipidemia, cancer, atherosclerosis, and related disorders thereof, a compound of the present invention may be used in conjunction with another pharmaceutical agent effective to treat that disorder.

The present invention also provides a potential method for the treatment or prevention of diabetes, obesity, hypertension, Metabolic Syndrome, dyslipidemia, cancer, atherosclerosis, and related disorders thereof, which method comprises administration to a patient in need of such treatment an amount of a compound of the present invention and an amount of another pharmaceutical agent effective to threat that disorder, such that together they give effective relief.

The present invention also provides a potential method for the treatment or prevention of diabetes, obesity, hypertension, Metabolic Syndrome, dyslipidemia, cancer, atherosclerosis, and related disorders thereof, which method comprises administration to a patient in need of such treatment an amount of a compound of the present invention and an amount of another pharmaceutical agent useful in treating that particular condition, such that together they give effective relief.

Examples of other active ingredients that may be administered separately or in the same

pharmaceutical composition in combination with a compound of the formulas described herein include, but are not limited to:

(1) dipeptidyl peptidase-IV (DPP-4) inhibitors (e.g., sitagliptin, alogliptin, linagliptin, vildagliptin, saxagliptin, teneligliptin, omarigliptin);

(2) insulin sensitizers, including (i) PPARγ agonists, such as the glitazones (e.g. pioglitazone, AMG 131, MBX2044, mitoglitazone, lobeglitazone, IDR-105, rosiglitazone, and balaglitazone), and other PPAR ligands, including (1) PPARα/γ dual agonists (e.g., ZYH2, ZYH1, GFT505, chiglitazar, muraglitazar, aleglitazar, sodelglitazar, and naveglitazar); (2) PPARα agonists such as fenofibric acid derivatives (e.g., gemfibrozil, clofibrate, ciprofibrate, fenofibrate, bezafibrate), (3) selective PPARγ modulators (SPPARγM's), (e.g., such as those disclosed in WO 02/060388, WO 02/08188, WO 2004/019869, WO 2004/020409, WO 2004/020408, and WO 2004/066963); and (4) PPARγ partial agonists; (ii) biguanides, such as metformin and its pharmaceutically acceptable salts, in particular, metformin hydrochloride, and extended-release formulations thereof, such as Glumetza™, Fortamet™, and GlucophageXR™; and (iii) protein tyrosine phosphatase-1B (PTP-1B) inhibitors (e.g., ISIS-113715 and TTP814);

(3) insulin or insulin analogs (e.g., insulin detemir, insulin glulisine, insulin degludec, insulin glargine, insulin lispro, SBS1000 and oral and inhalable formulations of insulin and insulin analogs);

(4) leptin and leptin derivatives and agonists;

(5) amylin and amylin analogs (e.g., pramlintide);

(6) sulfonylurea and non-sulfonylurea insulin secretagogues (e.g., tolbutamide, glyburide, glipizide, glimepiride, mitiglinide, meglitinides, nateglinide and repaglinide);

(7) α-glucosidase inhibitors (e.g., acarbose, voglibose and miglitol);

(8) glucagon receptor antagonists (e.g., NOXG15, LY2409021);

(9) incretin mimetics, such as GLP-1, GLP-1 analogs, derivatives, and mimetics; and GLP-1 receptor agonists (e.g., dulaglutide, semaglutide, albiglutide, exenatide, liraglutide, lixisenatide, taspoglutide, GSK2374697, ADX72231, RG7685, NN9924, ZYOG1, CJC-1131, and BIM-51077, including intranasal, transdermal, and once-weekly formulations thereof), and oxyntomodulin and oxyntomodulin analogs and derivatives;

(10) LDL cholesterol lowering agents such as (i) HMG-CoA reductase inhibitors (e.g., simvastatin, lovastatin, pravastatin, crivastatin, fluvastatin, atorvastatin, pitavastatin and rosuvastatin), (ii) bile acid sequestering agents (e.g., colestilan, colestimide, colesevalam hydrochloride, colestipol, cholestyramine, and dialkylaminoalkyl derivatives of a cross-linked dextran), (iii) inhibitors of cholesterol absorption, (e.g., ezetimibe), and (iv) acyl CoA:cholesterol acyltransferase inhibitors, (e.g., avasimibe);

(11) HDL-raising drugs, (e.g., niacin and nicotinic acid receptor agonists, and extended-release versions thereof; MK-524A, which is a combination of niacin extended-release and the

DP-1 antagonist MK-524);

(12) antiobesity compounds;

(13) agents intended for use in inflammatory conditions, such as aspirin, non-steroidal anti-inflammatory drugs or NSAIDs, glucocorticoids, and selective cyclooxygenase-2 or COX-2 inhibitors;

(14) antihypertensive agents, such as ACE inhibitors (e.g.,lisinopril, enalapril, ramipril, captopril, quinapril, and tandolapril), A-II receptor blockers (e.g., losartan, candesartan, irbesartan, olmesartan medoxomil, valsartan, telmisartan, and eprosartan), renin inhibitors (e.g., aliskiren), beta blockers, and calcium channel blockers;

(15) glucokinase activators (GKAs) (e.g., AZD6370);

(16) inhibitors of 11β-hydroxysteroid dehydrogenase type 1, (e.g., such as those disclosed in U.S. Patent No. 6,730,690, and LY-2523199);

(17) CETP inhibitors (e.g., anacetrapib, evacetrapib and torcetrapib);

(18) inhibitors of fructose 1,6-bisphosphatase, (e.g., such as those disclosed in U.S. Patent Nos. 6,054,587; 6,110,903; 6,284,748; 6,399,782; and 6,489,476);

(19) inhibitors of acetyl CoA carboxylase-1 or 2 (ACC1 or ACC2);

(20) AMP-activated Protein Kinase (AMPK) activators, such as MB1055, ETC 1002;

(21) other agonists of the G-protein-coupled receptors: (i) GPR-109, (ii) GPR-119 (e.g., MBX2982, APD597, GSK1292263, HM47000, and PSN821), and (iii) GPR-40 (e.g., TAK875, MR 1704, TUG 469, TUG499, ASP 4178);

(22) SSTR3 antagonists (e.g., such as those disclosed in WO 2009/001836);

(23) neuromedin U receptor agonists (e.g., such as those disclosed in WO 2009/042053, including, but not limited to, neuromedin S (NMS));

(24) SCD inhibitors;

(25) GPR-105 antagonists (e.g., such as those disclosed in WO 2009/000087);

(26) SGLT inhibitors (e.g., ASP1941, SGLT-3, empagliflozin, dapagliflozin, canagliflozin, BI-10773, PF-04971729, remogloflozin, TS-071, tofogliflozin, ipragliflozin, and LX-4211);

(27) inhibitors of acyl coenzyme A:diacylglycerol acyltransferase 1 and 2 (DGAT-1 and DGAT-2);

(28) inhibitors of fatty acid synthase;

(29) inhibitors of acyl coenzyme A:monoacylglycerol acyltransferase 1 and 2 (MGAT-1 and MGAT-2);

(30) agonists of the TGR5 receptor (also known as GPBAR1, BG37, GPCR19, GPR131, and M-BAR);

(31) ileal bile acid transporter inhibitors;

(32) PACAP, PACAP mimetics, and PACAP receptor 3 agonists;

(33) PPAR agonists;

(34) protein tyrosine phosphatase-1B (PTP-1B) inhibitors;

(35) IL-1b antibodies, (e.g., XOMA052 and canakinumab);

(36) bromocriptine mesylate and rapid-release formulations thereof;

(37) GPR 120 agonists (such as KDT501.

Other suitable pharmaceutical agents of use in combination with a compound of the present invention, include, but are not limited to:

(a) anti-diabetic agents such as (1) PPARγ agonists such as glitazones (e.g. ciglitazone; darglitazone; englitazone; isaglitazone (MCC-555); pioglitazone (ACTOS); rosiglitazone (AVANDIA); troglitazone; rivoglitazone, BRL49653; CLX-0921; 5-BTZD, GW-0207, LG-100641, R483, and LY-300512, and the like and compounds disclosed in WO97/10813, 97/27857, 97/28115, 97/28137, 97/27847, 03/000685, and 03/027112 and SPPARMS (selective PPAR gamma modulators) such as T131 (Amgen), FK614 (Fujisawa), netoglitazone, and metaglidasen; (2) biguanides such as buformin; metformin; and phenformin, and the like; (3) protein tyrosine phosphatase-1B (PTP-1B) inhibitors such as ISIS 113715, A-401674, A-364504, IDD-3, IDD 2846, KP-40046, KR61639, MC52445, MC52453, C7, OC-060062, OC-86839, OC29796, TTP-277BC1, and those agents disclosed in WO 04/041799, 04/050646, 02/26707, 02/26743, 04/092146, 03/048140, 04/089918, 03/002569, 04/065387, 04/127570, and US 2004/167183; (4) sulfonylureas such as acetohexamide; chlorpropamide; diabinese; glibenclamide; glipizide; glyburide; glimepiride; gliclazide; glipentide; gliquidone; glisolamide; tolazamide; and tolbutamide, and the like; (5) meglitinides such as repaglinide, metiglinide (GLUFAST) and nateglinide, and the like; (6) alpha glucoside hydrolase inhibitors such as acarbose; adiposine; camiglibose; emiglitate; miglitol; voglibose; pradimicin-Q; salbostatin; CKD-711; MDL-25,637; MDL-73,945; and MOR 14, and the like; (7) alpha-amylase inhibitors such as tendamistat, trestatin, and Al-3688, and the like; (8) insulin secreatagogues such as linogliride nateglinide, mitiglinide (GLUFAST), ID1101 A-4166, and the like; (9) fatty acid oxidation inhibitors, such as clomoxir, and etomoxir, and the like; (10) A2 antagonists, such as midaglizole; isaglidole; deriglidole; idazoxan; earoxan; and fluparoxan, and the like; (11) insulin or insulin mimetics, such as biota, LP-100, novarapid, insulin detemir, insulin lispro, insulin glargine, insulin zinc suspension (lente and ultralente); Lys-Pro insulin, GLP-1 (17-36), GLP-1 (73-7) (insulintropin); GLP-1 (7-36)-NH_2) exenatide/Exendin-4, Exenatide LAR, Linaglutide, AVE0010, CJC 1131, BIM51077, CS 872, THO318, BAY-694326, GP010, ALBUGON (GLP-1 fused to albumin), HGX-007 (Epac agonist), S-23521, and compounds disclosed in WO 04/022004, WO 04/37859, and the like; (12) non-thiazolidinediones such as JT-501, and farglitazar (GW-2570/GI-262579), and the like; (13) PPARα/γ dual agonists such as AVE 0847, CLX-0940, GW-1536, GW1929, GW-2433, KRP-297, L-796449, LBM 642, LR-90, LY510919, MK-0767, ONO 5129, SB 219994, TAK-559, TAK-654, 677954 (GlaxoSmithkline), E-3030

(Eisai), LY510929 (Lilly), AK109 (Asahi), DRF2655 (Dr. Reddy), DRF8351 (Dr. Reddy), MC3002 (Maxocore), TY51501 (ToaEiyo), farglitazar, naveglitazar, muraglitazar, peliglitazar, tesaglitazar (GALIDA), reglitazar (JT-501), chiglitazar, and those disclosed in WO 99/16758, WO 99/19313, WO 99/20614, WO 99/38850, WO 00/23415, WO 00/23417, WO 00/23445, WO 00/50414, WO 01/00579, WO 01/79150, WO 02/062799, WO 03/033481, WO 03/033450, WO 03/033453; and (14), insulin, insulin mimetics and other insulin sensitizing drugs; (15) VPAC2 receptor agonists; (16) GLK modulators, such as PSN105, RO 281675, RO 274375 and those disclosed in WO 03/015774, WO 03/000262, WO 03/055482, WO 04/046139, WO 04/045614, WO 04/063179, WO 04/063194, WO 04/050645, and the like; (17) retinoid modulators such as those disclosed in WO 03/000249; (18) GSK 3beta/GSK 3 inhibitors such as 4-[2-(2-bromophenyl)-4-(4-fluorophenyl-1H-imidazol-5-yl]pyridine, CT21022, CT20026, CT-98023, SB-216763, SB410111, SB-675236, CP-70949, XD4241 and those compounds disclosed in WO 03/037869, 03/03877, 03/037891, 03/024447, 05/000192, 05/019218 and the like; (19) glycogen phosphorylase (HGLPa) inhibitors, such as AVE 5688, PSN 357, GPi-879, those disclosed in WO 03/037864, WO 03/091213, WO 04/092158, WO 05/013975, WO 05/013981, US 2004/0220229, and JP 2004-196702, and the like; (20) ATP consumption promotors such as those disclosed in WO 03/007990; (21) fixed combinations of PPAR γ agonists and metformin such as AVANDAMET; (22) PPAR pan agonists such as GSK 677954; (23) GPR40 (G-protein coupled receptor 40) also called SNORF 55 such as BG 700, and those disclosed in WO 04/041266, 04/022551, 03/099793; (24) GPR119 (G-protein coupled receptor 119, also called RUP3; SNORF 25) such as RUP3, HGPRBMY26, PFI 007, SNORF 25; (25) adenosine receptor 2B antagonists such as ATL-618, ATl-802, E3080, and the like; (26) carnitine palmitoyl transferase inhibitors such as ST 1327, and ST 1326, and the like; (27) Fructose 1,6-bisphospohatase inhibitors such as CS-917, MB7803, and the like; (28) glucagon antagonists such as AT77077, BAY 694326, GW 4123X, NN2501, and those disclosed in WO 03/064404, WO 05/00781, US 2004/0209928, US 2004/029943, and the like; (30) glucose-6-phosphase inhibitors; (31) phosphoenolpyruvate carboxykinase (PEPCK) inhibitors; (32) pyruvate dehydrogenase kinase (PDK) activators; (33) RXR agonists such as MC1036, CS00018, JNJ 10166806, and those disclosed in WO 04/089916, US 6759546, and the like; (34) SGLT inhibitors such as AVE 2268, KGT 1251, T1095/RWJ 394718; (35) BLX-1002; (36) alpha glucosidase inhibitors; (37) glucagon receptor agonists; (38) glucokinase activators; 39) GIP-1; 40) insulin secretagogues; 41) GPR-40 agonists, such as TAK-875, 5-[4-[[(1R)-4-[6-(3-hydroxy-3-methylbutoxy)-2-methylpyridine-3-yl]-2,3-dihydro-1H-indene-1-yl]oxy]phenyl]isothiazole-3-ol 1-oxide, 5-(4-((3-(2,6-dimethyl-4-(3-(methylsulfonyl)propoxy)phenyl)phenyl)methoxy)phenyl)iso, 5-(4-((3-(2-methyl-6-(3-hydroxypropoxy)pyridine-3-yl)-2-methylphenyl)methoxy)phenyl)isothiazole-3-ol 1-oxide, and 5-[4-[[3-[4-(3-aminopropoxy)-2,6-dimethylphenyl]phenyl]methoxy]phenyl]isothiazole-3-ol 1-

oxide), and those disclosed in WO 11/078371.

(b) anti-dyslipidemic agents such as (1) bile acid sequestrants such as, cholestyramine, colesevelem, colestipol, dialkylaminoalkyl derivatives of a cross-linked dextran; Colestid®; LoCholest®; and Questran®, and the like; (2) HMG-CoA reductase inhibitors such as atorvastatin, itavastatin, pitavastatin, fluvastatin, lovastatin, pravastatin, rivastatin, simvastatin, rosuvastatin (ZD-4522), and other statins, particularly simvastatin; (3) HMG-CoA synthase inhibitors; (4) cholesterol absorption inhibitors such as FMVP4 (Forbes Medi-Tech), KT6-971 (Kotobuki Pharmaceutical), FM-VA12 (Forbes Medi-Tech), FM-VP-24 (Forbes Medi-Tech), stanol esters, beta-sitosterol, sterol glycosides such as tiqueside; and azetidinones such as ezetimibe, and those disclosed in WO 04/005247 and the like; (5) acyl coenzyme A -cholesterol acyl transferase (ACAT) inhibitors such as avasimibe, eflucimibe, pactimibe (KY505), SMP 797 (Sumitomo), SM32504 (Sumitomo), and those disclosed in WO 03/091216, and the like; (6) CETP inhibitors such as anacetrapib, JTT 705 (Japan Tobacco), torcetrapib, CP 532,632, BAY63-2149 (Bayer), SC 591, SC 795, and the like; (7) squalene synthetase inhibitors; (8) anti-oxidants such as probucol, and the like; (9) PPARα agonists such as beclofibrate, bezafibrate, ciprofibrate, clofibrate, etofibrate, fenofibrate, gemcabene, and gemfibrozil, GW 7647, BM 170744 (Kowa), LY518674 (Lilly), GW590735 (GlaxoSmithkline), KRP-101 (Kyorin), DRF10945 (Dr. Reddy), NS-220/R1593 (Nippon Shinyaku/Roche, ST1929 (Sigma Tau) MC3001/MC3004 (MaxoCore Pharmaceuticals, gemcabene calcium, other fibric acid derivatives, such as Atromid®, Lopid® and Tricor®, and those disclosed in US 6,548,538, and the like; (10) FXR receptor modulators such as GW 4064 (GlaxoSmithkline), SR 103912, QRX401, LN-6691 (Lion Bioscience), and those disclosed in WO 02/064125, WO 04/045511, and the like; (11) LXR receptor modulators such as GW 3965 (GlaxoSmithkline), T9013137, and XTCO179628 (X-Ceptor Therapeutics/Sanyo), and those disclosed in WO 03/031408, WO 03/063796, WO 04/072041, and the like; (12) lipoprotein synthesis inhibitors such as niacin; (13) renin angiotensin system inhibitors; (14) PPAR δ partial agonists, such as those disclosed in WO 03/024395; (15) bile acid reabsorption inhibitors, such as BARI 1453, SC435, PHA384640, S8921, AZD7706, and the like; and bile acid sequesterants such as colesevelam (WELCHOL/ CHOLESTAGEL), colestipol, cholestyramine, and dialkylaminoalkyl derivatives of a cross-linked dextran, (16) PPARδ agonists such as GW 501516 (Ligand, GSK), GW 590735, GW-0742 (GlaxoSmithkline), T659 (Amgen/Tularik), LY934 (Lilly), NNC610050 (Novo Nordisk) and those disclosed in WO97/28149, WO 01/79197, WO 02/14291, WO 02/46154, WO 02/46176, WO 02/076957, WO 03/016291, WO 03/033493, WO 03/035603, WO 03/072100, WO 03/097607, WO 04/005253, WO 04/007439, and JP10237049, and the like; (17) triglyceride synthesis inhibitors; (18) microsomal triglyceride transport (MTTP) inhibitors, such as implitapide, LAB687, JTT130 (Japan Tobacco), CP346086, and those disclosed in WO 03/072532, and the like; (19) transcription modulators; (20) squalene epoxidase inhibitors; (21)

low density lipoprotein (LDL) receptor inducers; (22) platelet aggregation inhibitors; (23) 5-LO or FLAP inhibitors; and (24) niacin receptor agonists including HM74A receptor agonists; (25) PPAR modulators such as those disclosed in WO 01/25181, WO 01/79150, WO 02/79162, WO 02/081428, WO 03/016265, WO 03/033453; (26) niacin-bound chromium, as disclosed in WO 03/039535; (27) substituted acid derivatives disclosed in WO 03/040114; (28) infused HDL such as LUV/ETC-588 (Pfizer), APO-A1 Milano/ETC216 (Pfizer), ETC-642 (Pfizer), ISIS301012, D4F (Bruin Pharma), synthetic trimeric ApoA1, Bioral Apo A1 targeted to foam cells, and the like; (29) IBAT inhibitors such as BARI143/HMR145A/ HMR1453 (Sanofi-Aventis, PHA384640E (Pfizer), S8921 (Shionogi) AZD7806 (AstrZeneca), AK105 (Asah Kasei), and the like; (30) Lp-PLA2 inhibitors such as SB480848 (GlaxoSmithkline), 659032 (GlaxoSmithkline), 677116 (GlaxoSmithkline), and the like; (31) other agents which affect lipic composition including ETC1001/ESP31015 (Pfizer), ESP-55016 (Pfizer), AGI1067 (AtheroGenics), AC3056 (Amylin), AZD4619 (AstrZeneca); and

(c) anti-hypertensive agents such as (1) diuretics, such as thiazides, including chlorthalidone, chlorthiazide, dichlorophenamide, hydroflumethiazide, indapamide, and hydrochlorothiazide; loop diuretics, such as bumetanide, ethacrynic acid, furosemide, and torsemide; potassium sparing agents, such as amiloride, and triamterene; and aldosterone antagonists, such as spironolactone, epirenone, and the like; (2) beta-adrenergic blockers such as acebutolol, atenolol, betaxolol, bevantolol, bisoprolol, bopindolol, carteolol, carvedilol, celiprolol, esmolol, indenolol, metaprolol, nadolol, nebivolol, penbutolol, pindolol, propanolol, sotalol, tertatolol, tilisolol, and timolol, and the like; (3) calcium channel blockers such as amlodipine, aranidipine, azelnidipine, barnidipine, benidipine, bepridil, cinaldipine, clevidipine, diltiazem, efonidipine, felodipine, gallopamil, isradipine, lacidipine, lemildipine, lercanidipine, nicardipine, nifedipine, nilvadipine, nimodepine, nisoldipine, nitrendipine, manidipine, pranidipine, and verapamil, and the like; (4) angiotensin converting enzyme (ACE) inhibitors such as benazepril; captopril; cilazapril; delapril; enalapril; fosinopril; imidapril; losinopril; moexipril; quinapril; quinaprilat; ramipril; perindopril; perindropril; quanipril; spirapril; tenocapril; trandolapril, and zofenopril, and the like; (5) neutral endopeptidase inhibitors such as omapatrilat, cadoxatril and ecadotril, fosidotril, sampatrilat, AVE7688, ER4030, and the like; (6) endothelin antagonists such as tezosentan, A308165, and YM62899, and the like; (7) vasodilators such as hydralazine, clonidine, minoxidil, and nicotinyl alcohol, nicotinic acid or salt thereof, and the like; (8) angiotensin II receptor antagonists such as candesartan, eprosartan, irbesartan, losartan, pratosartan, tasosartan, telmisartan, valsartan, and EXP-3137, FI6828K, and RNH6270, and the like; (9) α/β adrenergic blockers as nipradilol, arotinolol and amosulalol, and the like; (10) alpha 1 blockers, such as terazosin, urapidil, prazosin, bunazosin, trimazosin, doxazosin, naftopidil, indoramin, WHIP 164, and XEN010, and the like; (11) alpha 2 agonists such as lofexidine, tiamenidine, moxonidine, rilmenidine and guanobenz, and the like; (12)

aldosterone inhibitors, and the like; (13) angiopoietin-2-binding agents such as those disclosed in WO 03/030833; and

(d) anti-obesity agents, such as (1) 5HT (serotonin) transporter inhibitors, such as paroxetine, fluoxetine, fenfluramine, fluvoxamine, sertraline, and imipramine, and those disclosed in WO 03/00663, as well as serotonin/noradrenaline re uptake inhibitors such as sibutramine (MERIDIA/REDUCTIL) and dopamine uptake inhibitor/Norepenephrine uptake inhibitors such as radafaxine hydrochloride, 353162 (GlaxoSmithkline), and the like; (2) NE (norepinephrine) transporter inhibitors, such as GW 320659, despiramine, talsupram, and nomifensine; (3) CB1 (cannabinoid-1 receptor) antagonist/inverse agonists, such as taranabant, rimonabant (ACCOMPLIA Sanofi Synthelabo), SR-147778 (Sanofi Synthelabo), AVE1625 (Sanofi-Aventis), BAY 65-2520 (Bayer), SLV 319 (Solvay), SLV326 (Solvay), CP945598 (Pfizer), E-6776 (Esteve), O1691 (Organix), ORG14481 (Organon), VER24343 (Vernalis), NESS0327 (Univ of Sassari/Univ of Cagliari), and those disclosed in US Patent Nos. 4,973,587, 5,013,837, 5,081,122, 5,112,820, 5,292,736, 5,532,237, 5,624,941, 6,028,084, and 6,509367; and WO 96/33159, WO97/29079, WO98/31227, WO 98/33765, WO98/37061, WO98/41519, WO98/43635, WO98/43636, WO99/02499, WO00/10967, WO00/10968, WO 01/09120, WO 01/58869, WO 01/64632, WO 01/64633, WO 01/64634, WO 01/70700, WO 01/96330, WO 02/076949, WO 03/006007, WO 03/007887, WO 03/020217, WO 03/026647, WO 03/026648, WO 03/027069, WO 03/027076, WO 03/027114, WO 03/037332, WO 03/040107, WO 04/096763, WO 04/111039, WO 04/111033, WO 04/111034, WO 04/111038, WO 04/013120, WO 05/000301, WO 05/016286, WO 05/066126 and EP-658546 and the like; (4) ghrelin agonists/antagonists, such as BVT81-97 (BioVitrum), RC1291 (Rejuvenon), SRD-04677 (Sumitomo), unacylated ghrelin (TheraTechnologies), and those disclosed in WO 01/87335, WO 02/08250, WO 05/012331, and the like; (5) H3 (histamine H3) antagonist/inverse agonists, such as thioperamide, 3-(1H-imidazol-4-yl)propyl N-(4-pentenyl)carbamate), clobenpropit, iodophenpropit, imoproxifan, GT2394 (Gliatech), and A331440, and those disclosed in WO 02/15905; and O-[3-(1H-imidazol-4-yl)propanol]carbamates (Kiec-Kononowicz, K. et al., Pharmazie, 55:349-55 (2000)), piperidine-containing histamine H3-receptor antagonists (Lazewska, D. et al., Pharmazie, 56:927-32 (2001), benzophenone derivatives and related compounds (Sasse, A. et al., Arch. Pharm.(Weinheim) 334:45-52 (2001)), substituted N-phenylcarbamates (Reidemeister, S. et al., Pharmazie, 55:83-6 (2000)), and proxifan derivatives (Sasse, A. et al., J. Med. Chem.. 43:3335-43 (2000)) and histamine H3 receptor modulators such as those disclosed in WO 03/024928 and WO 03/024929; (6) melanin-concentrating hormone 1 receptor (MCH1R) antagonists, such as T-226296 (Takeda), T71 (Takeda/Amgen), AMGN-608450, AMGN-503796 (Amgen), 856464 (GlaxoSmithkline), A224940 (Abbott), A798 (Abbott), ATC0175/AR224349 (Arena Pharmaceuticals), GW803430 (GlaxoSmithkine), NBI-1A (Neurocrine Biosciences), NGX-1 (Neurogen), SNP-7941 (Synaptic), SNAP9847 (Synaptic),

T-226293 (Schering Plough), TPI-1361-17 (Saitama Medical School/University of California Irvine), and those disclosed WO 01/21169, WO 01/82925, WO 01/87834, WO 02/051809, WO 02/06245, WO 02/076929, WO 02/076947, WO 02/04433, WO 02/51809, WO 02/083134, WO 02/094799, WO 03/004027, WO 03/13574, WO 03/15769, WO 03/028641, WO 03/035624, WO 03/033476, WO 03/033480, WO 04/004611, WO 04/004726, WO 04/011438, WO 04/028459, WO 04/034702, WO 04/039764, WO 04/052848, WO 04/087680; and Japanese Patent Application Nos. JP 13226269, JP 1437059, JP2004315511, and the like; (7) MCH2R (melanin concentrating hormone 2R) agonist/antagonists; (8) NPY1 (neuropeptide Y Y1) antagonists, such as BMS205749, BIBP3226, J-115814, BIBO 3304, LY-357897, CP-671906, and GI-264879A; and those disclosed in U.S. Patent No. 6,001,836; and WO 96/14307, WO 01/23387, WO 99/51600, WO 01/85690, WO 01/85098, WO 01/85173, and WO 01/89528; (9) NPY5 (neuropeptide Y Y5) antagonists, such as 152,804, S2367 (Shionogi), E-6999 (Esteve), GW-569180A, GW-594884A (GlaxoSmithkline), GW-587081X, GW-548118X; FR 235,208; FR226928, FR 240662, FR252384; 1229U91, GI-264879A, CGP71683A, C-75 (Fasgen) LY-377897, LY366377, PD-160170, SR-120562A, SR-120819A,S2367 (Shionogi), JCF-104, and H409/22; and those compounds disclosed in U.S. Patent Nos. 6,140,354, 6,191,160, 6,258,837, 6,313,298, 6,326,375, 6,329,395, 6,335,345, 6,337,332, 6,329,395, and 6,340,683 ; and EP-01010691, EP-01044970, and FR252384; and PCT Publication Nos. WO 97/19682, WO 97/20820, WO 97/20821, WO 97/20822, WO 97/20823, WO 98/27063, WO 00/107409, WO 00/185714, WO 00/185730, WO 00/64880, WO 00/68197, WO 00/69849, WO 01/09120, WO 01/14376, WO 01/85714, WO 01/85730, WO 01/07409, WO 01/02379, WO 01/02379, WO 01/23388, WO 01/23389, WO 01/44201, WO 01/62737, WO 01/62738, WO 01/09120, WO 02/20488, WO 02/22592, WO 02/48152, WO 02/49648, WO 02/051806, WO 02/094789, WO 03/009845, WO 03/014083, WO 03/022849, WO 03/028726, WO 05/014592, WO 05/01493; and Norman et al., J. Med. Chem. 43:4288-4312 (2000); (10) leptin, such as recombinant human leptin (PEG-OB, Hoffman La Roche) and recombinant methionyl human leptin (Amgen); (11) leptin derivatives, such as those disclosed in Patent Nos. 5,552,524; 5,552,523; 5,552,522; 5,521,283; and WO 96/23513; WO 96/23514; WO 96/23515; WO 96/23516; WO 96/23517; WO 96/23518; WO 96/23519; and WO 96/23520; (12) opioid antagonists, such as nalmefene (Revex ®), 3-methoxynaltrexone, naloxone, and naltrexone; and those disclosed in WO 00/21509; (13) orexin antagonists, such as SB-334867-A (GlaxoSmithkline); and those disclosed in WO 01/96302, 01/68609, 02/44172, 02/51232, 02/51838, 02/089800, 02/090355, 03/023561, 03/032991, 03/037847, 04/004733, 04/026866, 04/041791, 04/085403, and the like; (14) BRS3 (bombesin receptor subtype 3) agonists; (15) CCK-A (cholecystokinin-A) agonists, such as AR-R 15849, GI 181771, JMV-180, A-71378, A-71623, PD170292, PD 149164, SR146131, SR125180, butabindide, and those disclosed in US 5,739,106; (16) CNTF (ciliary neurotrophic factors), such as GI-181771 (Glaxo-SmithKline); SR146131 (Sanofi Synthelabo); butabindide;

and PD170,292, PD 149164 (Pfizer); (17) CNTF derivatives, such as axokine (Regeneron); and those disclosed in WO 94/09134, WO 98/22128, and WO 99/43813; (18) GHS (growth hormone secretagogue receptor) agonists, such as NN703, hexarelin, MK-0677, SM-130686, CP-424,391, L-692,429 and L-163,255, and those disclosed in U.S. Patent No. 6358951, U.S. Patent Application Nos. 2002/049196 and 2002/022637; and WO 01/56592, and WO 02/32888; (19) 5HT2c (serotonin receptor 2c) agonists, such as APD3546/AR10A (Arena Pharmaceuticals), ATH88651 (Athersys), ATH88740 (Athersys), BVT933 (Biovitrum/GSK), DPCA37215 (BMS), IK264; LY448100 (Lilly), PNU 22394; WAY 470 (Wyeth), WAY629 (Wyeth), WAY161503 (Biovitrum), R-1065, VR1065 (Vernalis/Roche) YM 348; and those disclosed in U.S. Patent No. 3,914,250; and PCT Publications 01/66548, 02/36596, 02/48124, 02/10169, 02/44152; 02/51844, 02/40456, 02/40457, 03/057698, 05/000849, and the like; (20) Mc3r (melanocortin 3 receptor) agonists; (21) Mc4r (melanocortin 4 receptor) agonists, such as CHIR86036 (Chiron), CHIR915 (Chiron); ME-10142 (Melacure), ME-10145 (Melacure), HS-131 (Melacure), NBI72432 (Neurocrine Biosciences), NNC 70-619 (Novo Nordisk), TTP2435 (Transtech)and those disclosed in PCT Publications WO 99/64002, 00/74679, 01/991752, 01/0125192, 01/52880, 01/74844, 01/70708, 01/70337, 01/91752, 01/010842, 02/059095, 02/059107, 02/059108, 02/059117, 02/062766, 02/069095, 02/12166, 02/11715, 02/12178, 02/15909, 02/38544, 02/068387, 02/068388, 02/067869, 02/081430, 03/06604, 03/007949, 03/009847, 03/009850, 03/013509, 03/031410, 03/094918, 04/028453, 04/048345, 04/050610, 04/075823, 04/083208, 04/089951, 05/000339, and EP 1460069, and US 2005049269, and JP2005042839, and the like; (22) monoamine reuptake inhibitors, such as sibutratmine (Meridia ®/Reductil®) and salts thereof, and those compounds disclosed in U.S. Patent Nos. 4,746,680, 4,806,570, and 5,436,272, and U.S. Patent Publication No. 2002/0006964, and WO 01/27068, and WO 01/62341; (23) serotonin reuptake inhibitors, such as dexfenfluramine, fluoxetine, and those in U.S. Patent No. 6,365,633, and WO 01/27060, and WO 01/162341; (24) GLP-1 (glucagon-like peptide 1) agonists; (25) Topiramate (Topimax®); (26) phytopharm compound 57 (CP 644,673); (27) ACC2 (acetyl-CoA carboxylase-2) inhibitors; (28) β3 (beta adrenergic receptor 3) agonists, such as rafebergron/AD9677/TAK677 (Dainippon/ Takeda), CL-316,243, SB 418790, BRL-37344, L-796568, BMS-196085, BRL-35135A, CGP12177A, BTA-243, GRC1087 (Glenmark Pharmaceuticals) GW 427353 (solabegron hydrochloride), Trecadrine, Zeneca D7114, N-5984 (Nisshin Kyorin), LY-377604 (Lilly), KT07924 (Kissei), SR 59119A, and those disclosed in US Patent Nos. 5,705,515, US 5,451,677; and WO94/18161, WO95/29159, WO97/46556, WO98/04526 WO98/32753, WO 01/74782, WO 02/32897, WO 03/014113, WO 03/016276, WO 03/016307, WO 03/024948, WO 03/024953, WO 03/037881, WO 04/108674, and the like; (29) DGAT1 (diacylglycerol acyltransferase 1) inhibitors; (30) DGAT2 (diacylglycerol acyltransferase 2)inhibitors; (31) FAS (fatty acid synthase) inhibitors, such as Cerulenin and C75; (32) PDE (phosphodiesterase) inhibitors, such as theophylline,

pentoxifylline, zaprinast, sildenafil, amrinone, milrinone, cilostamide, rolipram, and cilomilast, as well as those described in WO 03/037432, WO 03/037899; (33) thyroid hormone β agonists, such as KB-2611 (KaroBioBMS), and those disclosed in WO 02/15845; and Japanese Patent Application No. JP 2000256190; (34) UCP-1 (uncoupling protein 1), 2, or 3 activators, such as phytanic acid, 4-[(E)-2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-napthalenyl)-1-propenyl]benzoic acid (TTNPB), and retinoic acid; and those disclosed in WO 99/00123; (35) acyl-estrogens, such as oleoyl-estrone, disclosed in del Mar-Grasa, M. et al., Obesity Research, 9:202-9 (2001); (36) glucocorticoid receptor antagonists, such as CP472555 (Pfizer), KB 3305, and those disclosed in WO 04/000869, WO 04/075864, and the like; (37) 11β HSD-1 (11-beta hydroxy steroid dehydrogenase type 1) inhibitors, such as BVT 3498 (AMG 331), BVT 2733, 3-(1-adamantyl)-4-ethyl-5-(ethylthio)-4H-1,2,4-triazole, 3-(1-adamantyl)-5-(3,4,5-trimethoxyphenyl)-4-methyl-4H-1,2,4-triazole, 3-adamantanyl-4,5,6,7,8,9,10,11,12,3a-decahydro-1,2,4-triazolo[4,3-a][11]annulene, and those compounds disclosed in WO 01/90091, 01/90090, 01/90092, 02/072084, 04/011410, 04/033427, 04/041264, 04/027047, 04/056744, 04/065351, 04/089415, 04/037251, and the like; (38) SCD-1 (stearoyl-CoA desaturase-1) inhibitors; (39) dipeptidyl peptidase IV (DPP-4) inhibitors, such as isoleucine thiazolidide, valine pyrrolidide, sitagliptin (Januvia), saxagliptin, alogliptin, NVP-DPP728, LAF237 (vildagliptin), P93/01, TSL 225, TMC-2A/2B/2C, FE 999011, P9310/K364, VIP 0177, SDZ 274-444, GSK 823093, E 3024, SYR 322, TS021, SSR 162369, GRC 8200, K579, NN7201, CR 14023, PHX 1004, PHX 1149, PT-630, SK-0403; and the compounds disclosed in WO 02/083128, WO 02/062764, WO 02/14271, WO 03/000180, WO 03/000181, WO 03/000250, WO 03/002530, WO 03/002531, WO 03/002553, WO 03/002593, WO 03/004498, WO 03/004496, WO 03/005766, WO 03/017936, WO 03/024942, WO 03/024965, WO 03/033524, WO 03/055881, WO 03/057144, WO 03/037327, WO 04/041795, WO 04/071454, WO 04/0214870, WO 04/041273, WO 04/041820, WO 04/050658, WO 04/046106, WO 04/067509, WO 04/048532, WO 04/099185, WO 04/108730, WO 05/009956, WO 04/09806, WO 05/023762, US 2005/043292, and EP 1 258 476; (40) lipase inhibitors, such as tetrahydrolipstatin (orlistat/XENICAL), ATL962 (Alizyme/Takeda), GT389255 (Genzyme/Peptimmune)Triton WR1339, RHC80267, lipstatin, teasaponin, and diethylumbelliferyl phosphate, FL-386, WAY-121898, Bay-N-3176, valilactone, esteracin, ebelactone A, ebelactone B, and RHC 80267, and those disclosed in WO 01/77094, WO 04/111004, and U.S. Patent Nos. 4,598,089, 4,452,813, 5,512,565, 5,391,571, 5,602,151, 4,405,644, 4,189,438, and 4,242,453, and the like; (41) fatty acid transporter inhibitors; (42) dicarboxylate transporter inhibitors; (43) glucose transporter inhibitors; and (44) phosphate transporter inhibitors; (45) anorectic bicyclic compounds such as 1426 (Aventis) and 1954 (Aventis), and the compounds disclosed in WO 00/18749, WO 01/32638, WO 01/62746, WO 01/62747, and WO 03/015769; (46) peptide YY and PYY agonists such as PYY336

(Nastech/Merck), AC162352 (IC Innovations/Curis/Amylin), TM30335/TM30338 (7TM Pharma), PYY336 (Emisphere Tehcnologies), pegylated peptide YY3-36, those disclosed in WO 03/026591, 04/089279, and the like; (47) lipid metabolism modulators such as maslinic acid, erythrodiol, ursolic acid uvaol, betulinic acid, betulin, and the like and compounds disclosed in WO 03/011267; (48) transcription factor modulators such as those disclosed in WO 03/026576; (49) Mc5r (melanocortin 5 receptor) modulators, such as those disclosed in WO 97/19952, WO 00/15826, WO 00/15790, US 20030092041, and the like; (50) Brain derived neutotropic factor (BDNF), (51) Mc1r (melanocortin 1 receptor modulators such as LK-184 (Proctor & Gamble), and the like; (52) 5HT6 antagonists such as BVT74316 (BioVitrum), BVT5182c (BioVitrum), E-6795 (Esteve), E-6814 (Esteve), SB399885 (GlaxoSmithkline), SB271046 (GlaxoSmithkline), RO-046790 (Roche), and the like; (53) fatty acid transport protein 4 (FATP4); (54) acetyl-CoA carboxylase (ACC) inhibitors such as CP640186, CP610431, CP640188 (Pfizer); (55) C-terminal growth hormone fragments such as AOD9604 (Monash Univ/Metabolic Pharmaceuticals), and the like; (56) oxyntomodulin; (57) neuropeptide FF receptor antagonists such as those disclosed in WO 04/083218, and the like; (58) amylin agonists such as Symlin/pramlintide/AC137 (Amylin); (59) Hoodia and trichocaulon extracts; (60) BVT74713 and other gut lipid appetite suppressants; (61) dopamine agonists such as bupropion (WELLBUTRIN/GlaxoSmithkline); (62) zonisamide (ZONEGRAN/Dainippon/Elan), and the like; and

(e) anorectic agents suitable for use in combination with a compound of the present invention include, but are not limited to, aminorex, amphechloral, amphetamine, benzphetamine, chlorphentermine, clobenzorex, cloforex, clominorex, clortermine, cyclexedrine, dexfenfluramine, dextroamphetamine, diethylpropion, diphemethoxidine, N-ethylamphetamine, fenbutrazate, fenfluramine, fenisorex, fenproporex, fludorex, fluminorex, furfurylmethylamphetamine, levamfetamine, levophacetoperane, mazindol, mefenorex, metamfepramone, methamphetamine, norpseudoephedrine, pentorex, phendimetrazine, phenmetrazine, phentermine, phenylpropanolamine, picilorex and sibutramine; and pharmaceutically acceptable salts thereof. A particularly suitable class of anorectic agent are the halogenated amphetamine derivatives, including chlorphentermine, cloforex, clortermine, dexfenfluramine, fenfluramine, picilorex and sibutramine; and pharmaceutically acceptable salts thereof. Particular halogenated amphetamine derivatives of use in combination with a compound of the present invention include: fenfluramine and dexfenfluramine, and pharmaceutically acceptable salts thereof.

Specific compounds of use in combination with a compound of the present invention include: simvastatin, mevastatin, ezetimibe, atorvastatin, sitagliptin, metformin, sibutramine, orlistat, Qnexa, topiramate, naltrexone, bupriopion, phentermine, and losartan, losartan with hydrochlorothiazide. Specific CB1 antagonists/inverse agonists of use in combination with a

compound of the present invention include: those described in WO03/077847, including: N-[3-(4-chlorophenyl)-2(S)-phenyl-1(S)-methylpropyl]-2-(4-trifluoromethyl-2-pyrimidyloxy)-2-methylpropanamide, N-[3-(4-chlorophenyl)-2-(3-cyanophenyl)-1-methylpropyl]-2-(5-trifluoromethyl-2-pyridyloxy)-2-methylpropanamide, N-[3-(4-chlorophenyl)-2-(5-chloro-3-pyridyl)-1-methylpropyl]-2-(5-trifluoromethyl-2-pyridyloxy)-2-methylpropanamide, and pharmaceutically acceptable salts thereof; as well as those in WO05/000809, which includes the following: 3-{1-[bis(4-chlorophenyl)methyl]azetidin-3-ylidene}-3-(3,5-difluorophenyl)-2,2-dimethylpropanenitrile, 1-{1-[1-(4-chlorophenyl)pentyl]azetidin-3-yl}-1-(3,5-difluorophenyl)-2-methylpropan-2-ol. 3-((S)-(4-chlorophenyl){3-[(1S)-1-(3,5-difluorophenyl)-2-hydroxy-2-methylpropyl]azetidin-1-yl}methyl)benzonitrile, 3-((S)-(4-chlorophenyl){3-[(1S)-1-(3,5-difluorophenyl)-2-fluoro-2-methylpropyl]azetidin-1-yl}methyl)benzonitrile, 3-((4-chlorophenyl){3-[1-(3,5-difluorophenyl)-2,2-dimethylpropyl]azetidin-1-yl}methyl)benzonitrile, 3-((1S)-1-{1-[(S)-(3-cyanophenyl)(4-cyanophenyl)methyl]azetidin-3-yl}-2-fluoro-2-methylpropyl)-5-fluorobenzonitrile, 3-[(S)-(4-chlorophenyl)(3-{(1S)-2-fluoro-1-[3-fluoro-5-(4H-1,2,4-triazol-4-yl)phenyl]-2-methylpropyl}azetidin-1-yl)methyl]benzonitrile, and 5-((4-chlorophenyl){3-[(1S)-1-(3,5-difluorophenyl)-2-fluoro-2-methylpropyl]azetidin-1-yl}methyl)thiophene-3-carbonitrile, and pharamecueitcally acceptable salts thereof; as well as: 3-[(S)-(4-chlorophenyl)(3-{(1S)-2-fluoro-1-[3-fluoro-5-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)phenyl]-2-methylpropyl}azetidin-1-yl)methyl]benzonitrile, 3-[(S)-(4-chlorophenyl)(3-{(1S)-2-fluoro-1-[3-fluoro-5-(1,3,4-oxadiazol-2-yl)phenyl]-2-methylpropyl}azetidin-1-yl)methyl]benzonitrile, 3-[(S)-(3-{(1S)-1-[3-(5-amino-1,3,4-oxadiazol-2-yl)-5-fluorophenyl]-2-fluoro-2-methylpropyl} azetidin-1-yl)(4-chlorophenyl)methyl]benzonitrile, 3-[(S)-(4-cyanophenyl)(3-{(1S)-2-fluoro-1-[3-fluoro-5-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)phenyl]-2-methylpropyl}azetidin-1-yl)methyl]benzonitrile, 3-[(S)-(3-{(1S)-1-[3-(5-amino-1,3,4-oxadiazol-2-yl)-5-fluorophenyl]-2-fluoro-2-methylpropyl} azetidin-1-yl)(4-cyanophenyl)methyl]benzonitrile, 3-[(S)-(4-cyanophenyl)(3-{(1S)-2-fluoro-1-[3-fluoro-5-(1,3,4-oxadiazol-2-yl)phenyl]-2-methylpropyl}azetidin-1-yl)methyl]benzonitrile, 3-[(S)-(4-chlorophenyl)(3-{(1S)-2-fluoro-1-[3-fluoro-5-(1,2,4-oxadiazol-3-yl)phenyl]-2-methylpropyl}azetidin-1-yl)methyl]benzonitrile, 3-[(1S)-1-(1-{(S)-(4-cyanophenyl)[3-(1,2,4-oxadiazol-3-yl)phenyl]-methyl}azetidin-3-yl)-2-fluoro-2-methylpropyl]-5-fluorobenzonitrile, 5-(3-{1-[1-(diphenylmethyl)azetidin-3-yl]-2-fluoro-2-methylpropyl}-5-fluorophenyl)-1H-tetrazole, 5-(3-{1-[1-(diphenylmethyl)azetidin-3-yl]-2-fluoro-2-methylpropyl}-5-fluorophenyl)-1-methyl-1H-tetrazole, 5-(3-{1-[1-(diphenylmethyl)azetidin-3-yl]-2-fluoro-2-methylpropyl}-5-fluorophenyl)-2-methyl-2H-tetrazole, 3-[(4-chlorophenyl)(3-{2-fluoro-1-[3-fluoro-5-(2-methyl-2H-tetrazol-5-yl)phenyl]-2-methylpropyl}azetidin-1-yl)methyl]benzonitrile, 3-[(4-chlorophenyl)(3-{2-fluoro-1-[3-fluoro-5-(1-methyl-1H-tetrazol-5-yl)phenyl]-2-methylpropyl}azetidin-1-yl)methyl]benzonitrile, 3-[(4-cyanophenyl)(3-{2-fluoro-1-[3-fluoro-5-

(1-methyl-1H-tetrazol-5-yl)phenyl]-2-methylpropyl}azetidin-1-yl)methyl]benzonitrile, 3-[(4-cyanophenyl)(3-{2-fluoro-1-[3-fluoro-5-(2-methyl-2H-tetrazol-5-yl)phenyl]-2-methylpropyl}azetidin-1-yl)methyl]benzonitrile, 5-{3-[(S)-{3-[(1S)-1-(3-bromo-5-fluorophenyl)-2-fluoro-2-methylpropyl]azetidin-1-yl}(4-chlorophenyl)methyl]phenyl}-1,3,4-oxadiazol-2(3H)-one, 3-[(1S)-1-(1-{(S)-(4-chlorophenyl)[3-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)phenyl]methyl} azetidin-3-yl)-2-fluoro-2-methylpropyl]-5-fluorobenzonitrile, 3-[(1S)-1-(1-{(S)-(4-cyanophenyl)[3-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)phenyl]methyl} azetidin-3-yl)-2-fluoro-2-methylpropyl]-5-fluorobenzonitrile, 3-[(1S)-1-(1-{(S)-(4-cyanophenyl)[3-(1,3,4-oxadiazol-2-yl)phenyl]methyl}azetidin-3-yl)-2-fluoro-2-methylpropyl]-5-fluorobenzonitrile, 3-[(1S)-1-(1-{(S)-(4-chlorophenyl)[3-(1,3,4-oxadiazol-2-yl)phenyl]methyl}azetidin-3-yl)-2-fluoro-2-methylpropyl]-5-fluorobenzonitrile, 3-((1S)-1-{1-[(S)-[3-(5-amino-1,3,4-oxadiazol-2-yl)phenyl](4-chlorophenyl)methyl]azetidin-3-yl}-2-fluoro-2-methylpropyl)-5-fluorobenzonitrile, 3-((1S)-1-{1-[(S)-[3-(5-amino-1,3,4-oxadiazol-2-yl)phenyl](4-cyanophenyl)methyl]azetidin-3-yl}-2-fluoro-2-methylpropyl)-5-fluorobenzonitrile, 3-[(1S)-1-(1-{(S)-(4-cyanophenyl)[3-(1,2,4-oxadiazol-3-yl)phenyl]methyl}azetidin-3-yl)-2-fluoro-2-methylpropyl]-5-fluorobenzonitrile, 3-[(1S)-1-(1-{(S)-(4-chlorophenyl)[3-(1,2,4-oxadiazol-3-yl)phenyl]methyl}azetidin-3-yl)-2-fluoro-2-methylpropyl]-5-fluorobenzonitrile, 5-[3-((S)-(4-chlorophenyl){3-[(1S)-1-(3,5-difluorophenyl)-2-fluoro-2-methylpropyl] azetidin-1-yl}methyl)phenyl]-1,3,4-oxadiazol-2(3H)-one, 5-[3-((S)-(4-chlorophenyl){3-[(1S)-1-(3,5-difluorophenyl)-2-fluoro-2-methylpropyl]azetidin-1-yl}methyl)phenyl]-1,3,4-oxadiazol-2(3H)-one, 4-{(S)-{3-[(1S)-1-(3,5-difluorophenyl)-2-fluoro-2-methylpropyl]azetidin-1-yl}[3-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)phenyl]methyl}-benzonitrile, and pharmaceutically acceptable salts thereof.

Specific NPY5 antagonists of use in combination with a compound of the present invention include: 3-oxo-N-(5-phenyl-2-pyrazinyl)-spiro[isobenzofuran-1(3H),4'-piperidine]-1'-carboxamide, 3-oxo-N-(7-trifluoromethylpyrido[3,2-b]pyridin-2-yl)spiro-[isobenzofuran-1(3H),4'-piperidine]-1'-carboxamide, N-[5-(3-fluorophenyl)-2-pyrimidinyl]-3-oxospiro-[isobenzofuran-1(3H),4'-piperidine]-1'-carboxamide, trans-3'-oxo-N-(5-phenyl-2-pyrimidinyl)spiro[cyclohexane-1,1'(3'H)-isobenzofuran]-4-carboxamide, trans-3'-oxo-N-[1-(3-quinolyl)-4-imidazolyl]spiro[cyclohexane-1,1'(3'H)-isobenzofuran]-4-carboxamide, trans-3-oxo-N-(5-phenyl-2-pyrazinyl)spiro[4-azaiso-benzofuran- 1(3H),1'-cyclohexane]-4'-carboxamide, trans-N-[5-(3-fluorophenyl)-2-pyrimidinyl]-3-oxospiro[5-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide, trans-N-[5-(2-fluorophenyl)-2-pyrimidinyl]-3-oxospiro[5-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide, trans-N-[1-(3,5-difluorophenyl)-4-imidazolyl]-3-oxospiro[7-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide, trans-3-oxo-N-(1-phenyl-4-pyrazolyl)spiro[4-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide, trans-N-[1-(2-fluorophenyl)-3-pyrazolyl]-3-oxospiro[6-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide, trans-3-oxo-N-(1-phenyl-3-

pyrazolyl)spiro[6-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide, trans-3-oxo-N-(2-phenyl-1,2,3-triazol-4-yl)spiro[6-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide, and pharmaceutically acceptable salts and esters thereof.

Specific ACC-1/2 inhibitors of use in combination with a compound of the present invention include: 1'-[(4,8-dimethoxyquinolin-2-yl)carbonyl]-6-(1H-tetrazol-5-yl)spiro[chroman-2,4'-piperidin]-4-one; (5-{1'-[(4,8-dimethoxyquinolin-2-yl)carbonyl]-4-oxospiro[chroman-2,4'-piperidin]-6-yl}-2H-tetrazol-2-yl)methyl pivalate; 5-{1'-[(8-cyclopropyl-4-methoxyquinolin-2-yl)carbonyl]-4-oxospiro[chroman-2,4'-piperidin]-6-yl}nicotinic acid; 1'-(8-methoxy-4-morpholin-4-yl-2-naphthoyl)-6-(1H-tetrazol-5-yl)spiro[chroman-2,4'-piperidin]-4-one; and 1'-[(4-ethoxy-8-ethylquinolin-2-yl)carbonyl]-6-(1H-tetrazol-5-yl)spiro[chroman-2,4'-piperidin]-4-one; and pharmaceutically acceptable salts and esters thereof. Specific MCH1R antagonist compounds of use in combination with a compound of the persent invention include: 1-{4-[(1-ethylazetidin-3-yl)oxy]phenyl}-4-[(4-fluorobenzyl)oxy]pyridin-2(1H)-one, 4-[(4-fluorobenzyl)oxy]-1-{4-[(1-isopropylazetidin-3-yl)oxy]phenyl}pyridin-2(1H)-one, 1-[4-(azetidin-3-yloxy)phenyl]-4-[(5-chloropyridin-2-yl)methoxy]pyridin-2(1H)-one, 4-[(5-chloropyridin-2-yl)methoxy]-1-{4-[(1-ethylazetidin-3-yl)oxy]phenyl}pyridin-2(1H)-one, 4-[(5-chloropyridin-2-yl)methoxy]-1-{4-[(1-propylazetidin-3-yl)oxy]phenyl}pyridin-2(1H)-one, and 4-[(5-chloropyridin-2-yl)methoxy]-1-(4-{[(2S)-1-ethylazetidin-2-yl]methoxy}phenyl)pyridin-2(1H)-one, or a pharmaceutically acceptable salt thereof.

Specific DP-IV inhibitors of use in combination with a compound of the present invention are selected from Januvia, 7-[(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]-3-(trifluoromethyl)-5,6,7,8-tetrahydro-1,2,4-triazolo[4,3-a]pyrazine. In particular, the compound of formula I is favorably combined with 7-[(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]-3-(trifluoromethyl)-5,6,7,8-tetrahydro-1,2,4-triazolo[4,3-a]pyrazine, and pharmaceutically acceptable salts thereof.

Specific H3 (histamine H3) antagonists/inverse agonists of use in combination with a compound of the present invention include: those described in WO05/077905, including:3-{4-[(1-cyclobutyl-4-piperidinyl)oxy]phenyl}-2-ethylpyrido[2,3-d]-pyrimidin-4(3H)-one, 3-{4-[(1-cyclobutyl-4-piperidinyl)oxy]phenyl}-2-methylpyrido[4,3-d]pyrimidin-4(3H)-one, 2-ethyl-3-(4-{3-[(3S)-3-methylpiperidin-1-yl]propoxy}phenyl)pyrido[2,3-d]pyrimidin-4(3H)-one 2-methyl-3-(4-{3-[(3S)-3-methylpiperidin-1-yl]propoxy}phenyl)pyrido[4,3-d]pyrimidin-4(3H)-one, 3-{4-[(1-cyclobutyl-4-piperidinyl)oxy]phenyl}-2,5-dimethyl-4(3H)-quinazolinone, 3-{4-[(1-cyclobutyl-4-piperidinyl)oxy]phenyl}-2-methyl-5-trifluoromethyl-4(3H)-quinazolinone, 3-{4-[(1-cyclobutyl-4-piperidinyl)oxy]phenyl}-5-methoxy-2-methyl-4(3H)-quinazolinone, 3-{4-[(1-cyclobutylpiperidin-4-yl)oxy]phenyl}-5-fluoro-2-methyl-4(3H)-quinazolinone, 3-{4-[(1-cyclobutylpiperidin-4-yl)oxy]phenyl}-7-fluoro-2-methyl-4(3H)-quinazolinone, 3-{4-[(1-cyclobutylpiperidin-4-yl)oxy]phenyl}-6-methoxy-2-methyl-4(3H)-quinazolinone, 3-{4-[(1-

cyclobutylpiperidin-4-yl)oxy]phenyl}-6-fluoro-2-methyl-4(3H)-quinazolinone, 3-{4-[(1-cyclobutylpiperidin-4-yl)oxy]phenyl}-8-fluoro-2-methyl-4(3H)-quinazolinone, 3-{4-[(1-cyclopentyl-4-piperidinyl)oxy]phenyl}-2-methylpyrido[4,3-d]pyrimidin-4(3H)-one, 3-{4-[(1-cyclobutylpiperidin-4-yl)oxy]phenyl}-6-fluoro-2-methylpyrido[3,4-d]pyrimidin-4(3H)-one, 3-{4-[(1-cyclobutyl-4-piperidinyl)oxy]phenyl}-2-ethylpyrido[4,3-d]pyrimidin-4(3H)-one, 6-methoxy-2-methyl-3-{4-[3-(1-piperidinyl)propoxy]phenyl}pyrido[3,4-d]pyrimidin-4(3H)-one, 6-methoxy-2-methyl-3-{4-[3-(1-pyrrolidinyl)propoxy]phenyl}pyrido[3,4-d]pyrimidin-4(3H)-one, 2,5-dimethyl-3-{4-[3-(1-pyrrolidinyl)propoxy]phenyl}-4(3H)-quinazolinone, 2-methyl-3-{4-[3-(1-pyrrolidinyl)propoxy]phenyl}-5-trifluoromethyl-4(3H)-quinazolinone, 5-fluoro-2-methyl-3-{4-[3-(1-piperidinyl)propoxy]phenyl}-4(3H)-quinazolinone, 6-methoxy-2-methyl-3-{4-[3-(1-piperidinyl)propoxy]phenyl}-4(3H)-quinazolinone, 5-methoxy-2-methyl-3-(4-{3-[(3S)-3-methylpiperidin-1-yl]propoxy}phenyl)-4(3H)-quinazolinone, 7-methoxy-2-methyl-3-(4-{3-[(3S)-3-methylpiperidin-1-yl]propoxy}phenyl)-4(3H)-quinazolinone, 2-methyl-3-(4-{3-[(3S)-3-methylpiperidin-1-yl]propoxy}phenyl)pyrido[2,3-d]pyrimidin-4(3H)-one, 5-fluoro-2-methyl-3-(4-{3-[(2R)-2-methylpyrrolidin-1-yl]propoxy}phenyl)-4(3H)-quinazolinone, 2-methyl-3-(4-{3-[(2R)-2-methylpyrrolidin-1-yl]propoxy}phenyl)pyrido[4,3-d]pyrimidin-4(3H)-one, 6-methoxy-2-methyl-3-(4-{3-[(2R)-2-methylpyrrolidin-1-yl]propoxy}phenyl)-4(3H)-quinazolinone, 6-methoxy-2-methyl-3-(4-{3-[(2S)-2-methylpyrrolidin-1-yl]propoxy}phenyl)-4(3H)-quinazolinone, and pharmaceutically acceptable salts thereof.

Specific CCK1R agonists of use in combination with a compound of the present invention include: 3-(4-{[1-(3-ethoxyphenyl)-2-(4-methylphenyl)-1H -imidazol-4-yl]carbonyl}-1-piperazinyl)-1-naphthoic acid; 3-(4-{[1-(3-ethoxyphenyl)-2-(2-fluoro-4-methylphenyl)-1H -imidazol-4-yl]carbonyl}-1-piperazinyl)-1-naphthoic acid; 3-(4-{[1-(3-ethoxyphenyl)-2-(4-fluorophenyl)-1H -imidazol-4-yl]carbonyl}-1-piperazinyl)-1-naphthoic acid; 3-(4-{[1-(3-ethoxyphenyl)-2-(2,4-difluorophenyl)-1H -imidazol-4-yl]carbonyl}-1-piperazinyl)-1-naphthoic acid; and 3-(4-{[1-(2,3-dihydro-1,4-benzodioxin-6-yl)-2-(4-fluorophenyl)-1H-imidazol-4-yl]carbonyl}-1-piperazinyl)-1-naphthoic acid; and pharmaceutically acceptable salts thereof.

Specific MC4R agonists of use in combination with a compound of the present invention include: 1) (5S)-1'-{[(3R,4R)-1-tert-butyl-3-(2,3,4-trifluorophenyl)piperidin-4-yl]carbonyl}-3-chloro-2-methyl-5-[1-methyl-1-(1-methyl-1H-1,2,4-triazol-5-yl)ethyl]-5H-spiro[furo[3,4-b]pyridine-7,4'-piperidine]; 2) (5R)-1'-{[(3R,4R)-1-tert-butyl-3-(2,3,4-trifluorophenyl)-piperidin-4-yl]carbonyl}-3-chloro-2-methyl-5-[1-methyl-1-(1-methyl-1H-1,2,4-triazol-5-yl)ethyl]-5H-spiro[furo[3,4-b]pyridine-7,4'-piperidine]; 3) 2-(1'-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)pyrrolidin-3-yl]carbonyl}-3-chloro-2-methyl-5H-spiro[furo[3,4-b]pyridine-7,4'-piperidin]-5-yl)-2-methylpropanenitrile; 4) 1'-{[(3S,4R)-1-tert-butyl-4-(2,4-difluorophenyl)pyrrolidin-3-yl]carbonyl}-3-chloro-2-methyl-5-[1-methyl-1-(1-methyl-1H-1,2,4-triazol-5-yl)ethyl]-5H-spiro[furo[3,4-b]pyridine-7,4'-piperidine]; 5) N-[(3R,4R)-3-({3-chloro-2-

methyl-5-[1-methyl-1-(1-methyl-1H-1,2,4-triazol-5-yl)ethyl]-1'H,5H-spiro[furo-[3,4-b]pyridine-7,4'-piperidin]-1'-yl}carbonyl)-4-(2,4-difluorophenyl)-cyclopentyl]-N-methyltetrahydro-2H-pyran-4-amine; 6) 2-[3-chloro-1'-({(1R,2R)-2-(2,4-difluorophenyl)-4-[methyl(tetrahydro-2H-pyran-4-yl)amino]-cyclopentyl}-carbonyl)-2-methyl-5H-spiro[furo[3,4-b]pyridine-7,4'-piperidin]-5-yl]-2-methyl-propane-nitrile; and pharmaceutically acceptable salts thereof.

Suitable neurokinin-1 (NK-1) receptor antagonists may be favorably employed with the AMP-kinase activators of the present invention. NK-1 receptor antagonists of use in the present invention are fully described in the art. Specific neurokinin-1 receptor antagonists of use in the present invention include: (±)-(2R3R,2S3S)-N-{[2-cyclopropoxy-5-(trifluoromethoxy)-phenyl]methyl}-2-phenylpiperidin-3-amine; 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)-phenyl)ethoxy)-3-(S)-(4-fluorophenyl)-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)morpholine; aperpitant; CJ17493; GW597599; GW679769; R673; RO67319; R1124; R1204; SSR146977; SSR240600; T-2328; and T2763.; or a pharmaceutically acceptable salts thereof.

The term "therapeutically effective amount" means the amount the compound of structural formula I that will elicit the biological or medical response of a tissue, system, animal or human that is being sought by the researcher, veterinarian, medical doctor or other clinician, which includes alleviation of the symptoms of the disorder being treated. The novel methods of treatment of this invention are for disorders known to those skilled in the art. The term “mammal” includes humans, and companion animals such as dogs and cats.

The weight ratio of the compound of the Formula I to the second active ingredient may be varied and will depend upon the effective dose of each ingredient. Generally, an effective dose of each will be used. Thus, for example, when a compound of the Formula I is combined with a DPIV inhibitor the weight ratio of the compound of the Formula I to the DPIV inhibitor will generally range from about 1000:1 to about 1:1000, preferably about 200:1 to about 1:200. Combinations of a compound of the Formula I and other active ingredients will generally also be within the aforementioned range, but in each case, an effective dose of each active ingredient should be used.

The compounds of structural formula I of the present invention can be prepared according to the procedures of the following Schemes, Intermediates and Examples, using appropriate materials and are further exemplified by the following specific examples. Moreover, by utilizing the procedures described in the disclosure contained herein, one of ordinary skill in the art can readily prepare additional compounds of the present invention claimed herein. The compounds illustrated in the examples are not, however, to be construed as forming the only genus that is considered as the invention. The Examples further illustrate details for the preparation of the compounds of the present invention. Those skilled in the art will readily understand that known variations of the conditions and processes of the following preparative procedures can be used to prepare these compounds. The instant compounds are generally

isolated in the form of their pharmaceutically acceptable salts, such as those previously described herein. The use of protecting groups for the amine and carboxylic acid functionalities to facilitate the desired reaction and minimize undesired reactions is well documented. Conditions required to remove protecting groups are found in standard textbooks such as Greene, T, and Wuts, P. G. M., Protective Groups in Organic Synthesis, John Wiley & Sons, Inc., New York, NY, 1991. CBZ and BOC are commonly used protecting groups in organic synthesis, and their removal conditions are known to those skilled in the art. All temperatures are degrees Celsius unless otherwise noted. Mass spectra (MS) were measured by electron-spray ion-mass spectroscopy.

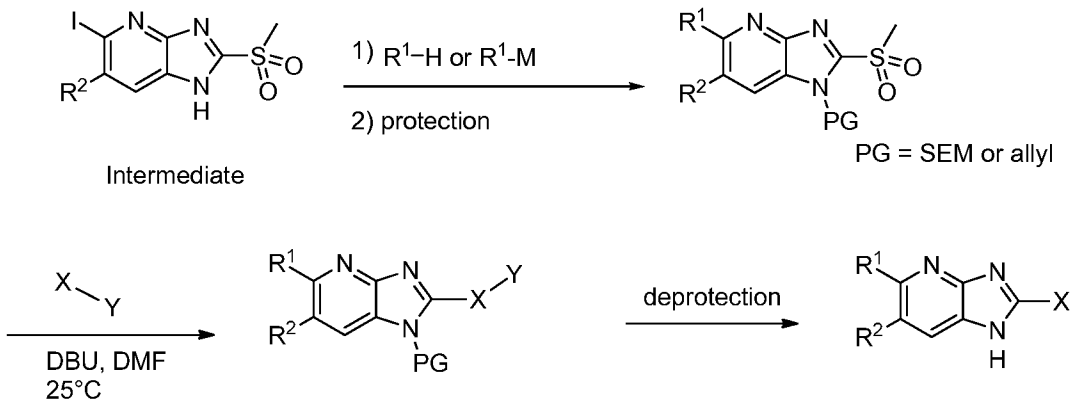
Abbreviations used in the description of the preparation of the compounds of the present invention: ACN is acetonitrile; AcOH is acetic acid; aq or aq. is aqueous; Boc_2O is *t*-butoxycarbonyl anhydride; n-BuLi is *n*-butyllithium; C is carbon; CPME is cyclopentyl methyl ether; CV is column volume(s); DAST is (diethylamino)sulfur trifluoride; DBU is 1,8-diazabicyclo[5.4.0]-undec-7-ene; DIBAL-H is di-isobutyl aluminum hydride; DCE is dichloroethane; DCM is dichloromethane; DEAD is diethyl azodicarboxylate; DIAD is diisopropyl azodicarboxylate; DIEA and DIPEA is diisopropylethyl amine; DMA is dimethyl acetal; DMAP is 4-(Dimethylamino)pyridine; DME is 1,2-dimethoxyethane; DMF is dimethyl formamide; DMSO is dimethyl sulfoxide; dppf DCM complex is 1,1'-bis(diphenyl-phosphino)ferrocene dichloromethane complex; DPPP is diphenyl phosphinopropane; EDC is *N*-(3-Dimethylaminopropyl)-*N'*-ethylcarbodiimide; Et_2O is diethyl ether; EtOAc is ethyl acetate; dppf is 1,1'-Bis(diphenyl-phosphino)ferrocene; EtOH is ethanol; Et_3N is triethyl amine; h is hour(s); HATU is *O*-(7-Azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluoro-phosphate; Hex or hex is hexanes; HOBT is 1-Hydroxybenzotriazole; HPLC is high pressure liquid chromatography; ISCO R_f is the Rf determined via medium pressure liquid chromato-graphy using aTeledyne ISCO RediSep® column; isomannide is 1,4:3,6-Di-anhydro-mannitol; KOAc is potassium acetate; L is liter; LC/MS and LC-MS is liquid chromatography/mass spectroscopy; KOTMS is potassium trimethylsilanolate; LAH is lithium aluminum hydride; M is molar; ml and mL is milliliter; Me is methyl, MeCN is acetonitrile; MeI is methyl iodide; MeMgBr is methyl magnesium bromide; MeOH is methanol; MgBr is magnesium bromide; min is minutes; mmol is millimole(s); m-CPBA is meta chloro per benzoic acid; MPLC is medium pressure liquid chromatography; MS is molecular sieves; MTBE is tert-butyl methyl ether; N is normal; NaOAc is sodium acetate; NBS is N-bromo succinamide; NIS is N-iodo succinamide; $Pd_2(dba)_3$ is tris(dibenzylideneacetone)-dipalladium(0); $[PdCl_2(dppf)]CH_2Cl_2$ or $PdCl_2(dppf)$-DCM is 1,1'-Bis(diphenylphosphino)-ferrocene-palladium(II)dichloride dichloromethane complex; PPh_3 is triphenyl phosphine; PhSiH is phenyl silane; wt % is weight percent; psi is pounds per square inch; RT and rt is room temperature; Rt is retention time; Rochelles' Salt is potassium sodium tartrate; RuPhos is 2-Dicyclohexyl-phosphino-2′,6′-diisopropoxybiphenyl; sat

or sat. is saturated; SEM is 2-(trimethylsilyl)ethoxymethyl; SEM-Cl and SEMCl is 2-(trimethylsilyl)-ethoxymethyl chloride; TBAF is tetrabutyl ammonium fluoride; TBSCl and TBDMSCl is *tert*-butyldimethylsilyl chloride; TEA is triethylamine; TESCl is chlorotriethylsilane; TFA is trifluoro acetic acid; THF is tetrahydrofuran; TMS is trimethylsilyl; Tosyl-Cl is *p*-toluene-sulfonyl chloride; and XPhos is 2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl.

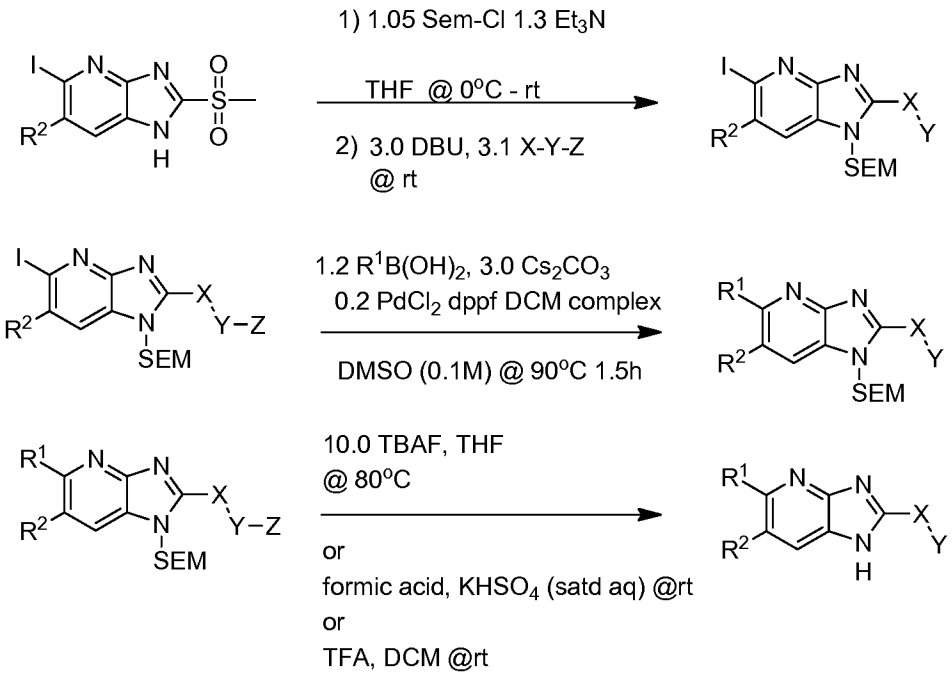
Microwave (MW) reactions were performed with a single mode operating Biotage Emrys Optimizer in sealed reaction vials at the indicated fixed temperature held constant for the designated reaction time. The medium pressure liquid chromatography (MPLC) purifications were performed with Teledyne ISCO RediSep® normal-phase columns pre-packed with 35-60 micron silica gel. The LC-MS system contained an Applied Biosystems API150EX MS operating in a positive ion mode receiving 0.1 mL/min flowrate with a Shimadzu UV detector receiving 0.1 mL/min flowrate. Unless specified, the LC conditions were solvent A = 0.05% TFA in acetonitrile; solvent B = 0.05% TFA in water; flowrate = 10 mL/min; column: Chromolith Performance RP-18e, 100×4.6 mm. Unless specified, the ^{1}H NMRs were obtained in CD_3OD at 500 MHz and spectra were recorded in units δ. C, H, N microanalyses were performed by Robertson Microlit Laboratories, Inc., Madison, NJ.

The following reaction schemes illustrate methods which may be employed for the synthesis of the compounds of structural formula I described in this invention. All substituents are as defined above unless indicated otherwise. Several strategies based upon synthetic transformations known in the literature of organic synthesis may be employed for the preparation of the compounds of general formula I.

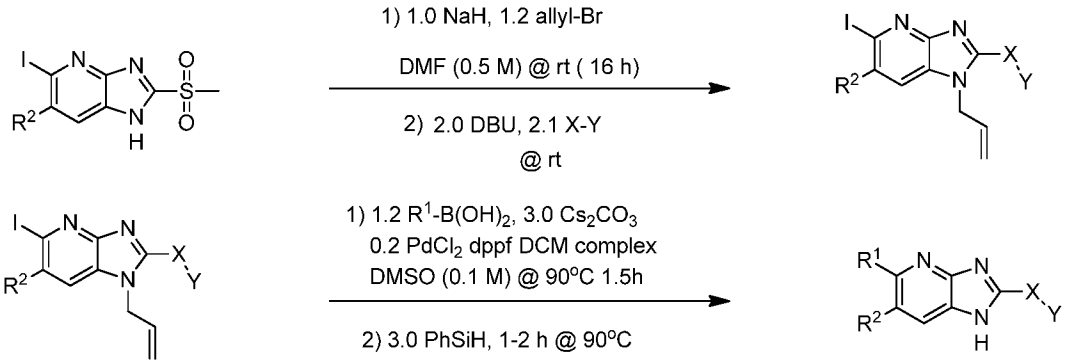
GENERAL SCHEME



SCHEME 1



SCHEME 2



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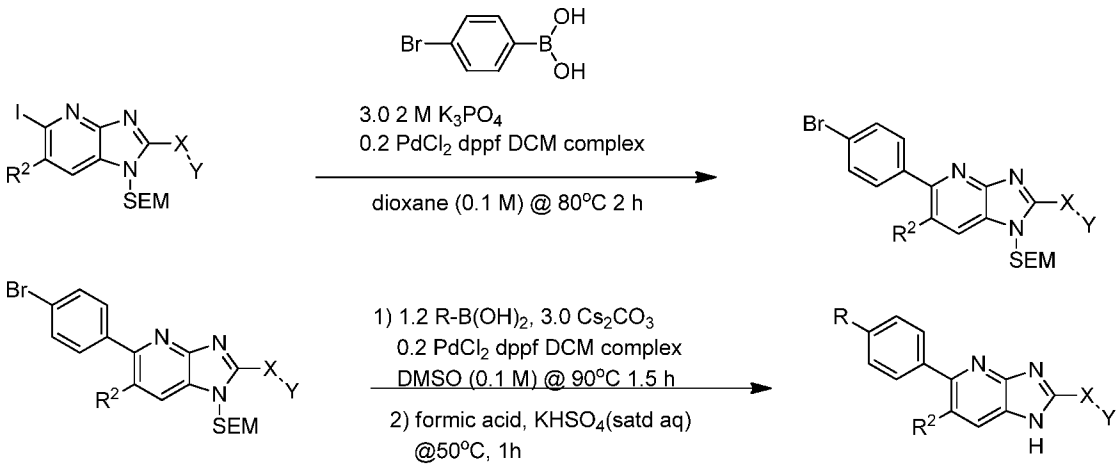
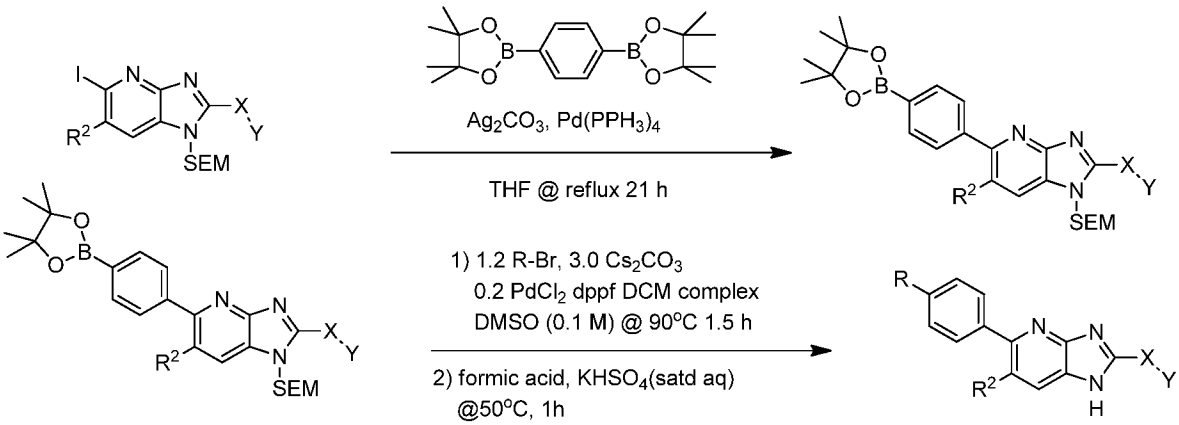
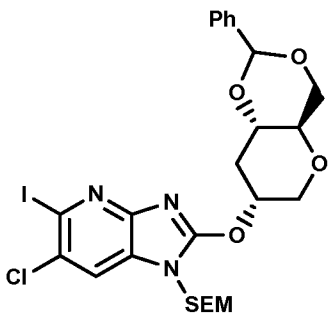


SCHEME 4



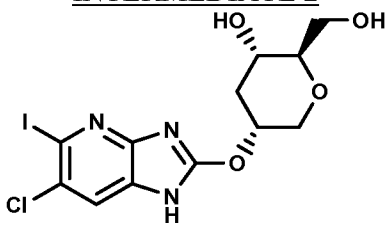
INTERMEDIATE 1



6-chloro-5-iodo-2-(((4aR,7R,8aS)-2-phenylhexahydropyrano[3,2-d][1,3]dioxin-7-yl)oxy)-1-((2-

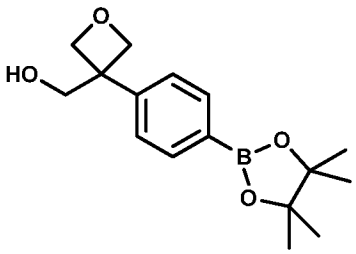
(trimethylsilyl)ethoxy)methyl)-1H-imidazo[4,5-b]pyridine 6-chloro-5-iodo-2-(methylsulfonyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazo[4,5-b]pyridine (100 mg, 0.205 mmol), (4aR,7R,8aS)-2-phenylhexahydro-pyrano[3,2-d][1,3]dioxin-7-ol (58.1 mg, 0.246 mmol), and cesium carbonate (134 mg, 0.410 mmol) were combined in a 10 mL reaction tube. DMF was added and the reaction was stirred overnight at rt. The resulting solution was diluted with water and EtOAc. The layers were separated and the aqueous phase was extracted with EtOAc (x2). The combined extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated. Flash column chromatrography of the resulting residue on Biotage™ 25 g column eluted with 10% to 80% EtOAc in Hexane yielded the desired product. LC-MS: calculated for $C_{25}H_{31}ClIN_3O_5Si$ 643.08 observed m/e: 644.01 $(M+H)^+$ (Rt 1.39 / 2 min).

INTERMEDIATE 2



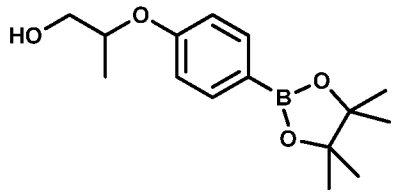
(2R,3S,5R)-5-((6-chloro-5-iodo-1H-imidazo[4,5-b]pyridin-2-yl)oxy)-2-(hydroxymethyl)tetrahydro-2H-pyran-3-ol. 6-chloro-5-iodo-2-(((4aR,7R,8aS)-2-phenylhexahydropyrano[3,2-d][1,3]dioxin-7-yl)oxy)-1-((2-(trimethylsilyl)ethoxy)-methyl)-1H-imidazo[4,5-b]pyridine (185 mg, 0.287 mmol) was dissolved in formic acid (1 ml, 26.1 mmol) and saturated potassium hydrogen sulfate (0.1 ml, 0.287 mmol). The reaction was heated to 50 °C for 4h, and then diluted with EtOAc, followed by the addition of 3 M NaOH until pH 14 was reached. The reaction was stirred for 15 minutes at rt and the layers were separated. The aqueous layer was extracted with EtOAc (x 2) and the combined EtOAc extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The resulting crude product was purified by column chromatography on a Biotage™ 25g column and eluted with 1% to 10% MeOH in DCM to yield the desired product. LC-MS: calculated for $C_{12}H_{13}ClIN_3O_4$ 424.96 observed m/e: 426.00 $(M+H)^+$ (Rt 1.05 / 2 min).

INTERMEDATE 3



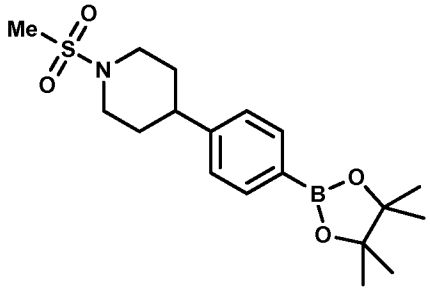
(3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)oxetan-3-yl)methanol A 20 mL microwave vial was charged with (3-(4-bromophenyl)oxetan-3-yl)methanol (167 mg, 0.687 mmol), bis(pinacolato)diboron (349 mg, 1.374 mmol), and potassium acetate (202 mg, 2.061 mmol). The solids were dissolved in DMSO (2748 µl) and sparged with N_2 for 15 min. Then [1,1'-Bis(Diphenyl-phosphino)Ferrocene]Dichloropalladium (II) (101 mg, 0.137 mmol) was added and the reaction was stirred overnight at 80 °C. The resulting mixture was diluted with EtOAc and 1:1 water:brine. The aqueous phase was removed and extracted (x1) with EtOAc. The combined extracts were washed with brine (x2), dried over Na_2SO_4, filtered, and concentrated. The resulting residue was purified by column chromatography on a Biotage™ 25g column by eluting with 10% to 70% EtOAc:Hexane. The resulting solid was triturated with MeOH to yield the desired product. ^{1}H NMR δ (ppm) (CD_3OD): 7.74 (d, 2H), 7.12 (d, 2H), 4.91 (d, 2H), 4.84 (d, 2H), 3.86 (s, 2H), 1.36 (s, 12H).

INTERMEDIATE 4



2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)propan-1-ol 2-(4-bromophenoxy)propan-1-ol (220 mg, 0.952 mmol) and Bispinacolatodiboron (484 mg, 1.904 mmol) were combined in a reaction vessel, followed by the addition of potassium acetate (187 mg, 1.904 mmol). The mixture was then evacuated and backfilled with N_2 (3 times), then dried and degassed. Cyclopentyl-methyl ether (4760 µl) was added to the flask, and the mixture was heated at 110 °C for 12 h. The mixture was then concentrated and purified by column chromatography on a Biotage™ 25 g column by eluting with 10% to 70% EtOAc in Hexane to give the desired product. ^{1}H NMR δ (ppm) (CD_3OD): 7.65 (d, 2H), 6.92 (d, 2H), 4.53(m, 1H), 3.64 (m, 2H), 1.32 (s, 12H), 1.27 (d, 3H).

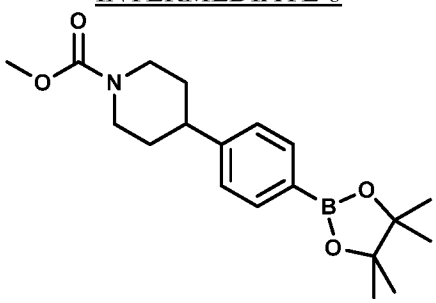
INTERMEDIATE 5



1-(methylsulfonyl)-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperidine

4-(4-bromophenyl)-1-(methylsulfonyl)piperidine (1.325g, 4.16mmol), bispinacolato-diboron (2.115 g, 8.33 mmol), and potassium acetate (1.221 g, 12.44 mmol) were dissolved in DMSO (17 mL). The reaction mixture was sparged with N_2 for 15 minutes and then [1,1'-Bis(Diphenylphosphino)Ferrocene]-Dichloropalladium (II) (0.607 g, 0.829 mmol) was added. The reaction was heated to 80 °C overnight, and then diluted with water and EtOAc. The aqueous phase was removed and extracted with EtOAc. The combined extracts were washed with brine (x 2), then dried over Na_2SO_4, filtered, and concentrated. The resulting residue was purified by column chromatography on a Biotage™ 50g column by eluting with 20% to 80% EtOAc:Hexane to give the desired product. LC-MS: calculated for $C_{18}H_{28}BNO_4S$ 365.18 observed m/e: 365.98 $(M+H)^+$ (Rt 1.21 / 2 min).

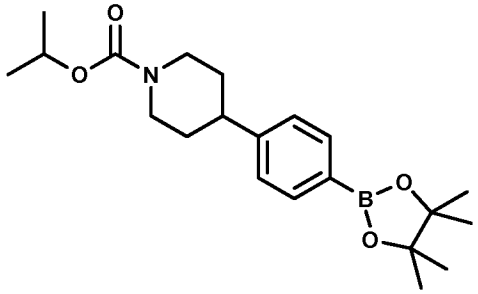
INTERMEDIATE 6



Methyl 4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperidine-1-carboxylate

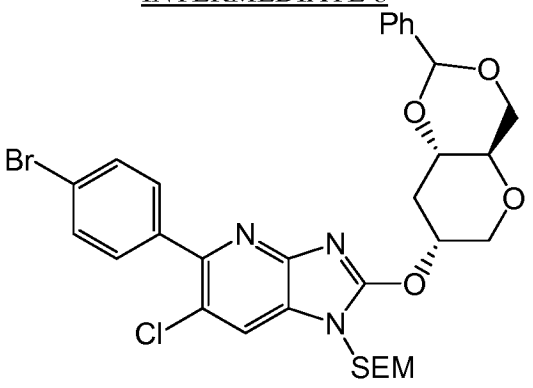
Methyl 4-(4-bromophenyl)piperidine-1-carboxylate (1.24g, 4.16 mmol), bispinacolatodiboron (2.106 g, 8.29 mmol), and potassium acetate (1.221 g, 12.44 mmol) were dissolved in DMSO (17 mL). The reaction mixture was sparged with N_2 for 15 min and then [1,1'- Bis(Diphenyl-phosphino)Ferrocene]-Dichloropalladium (II) (0.607 g, 0.829 mmol) was added. The reaction was heated to 80 °C overnight, then diluted with water and EtOAc. The aqueous phase was removed and extracted (x1) with EtOAc, and the combined extracts were washed with brine (x 2), dried over Na_2SO_4, filtered, and concentrated. The resulting residue was purified by column chromatography on a Biotage™ 50g column by eluting with 20% to 80% EtOAc:Hexane. LC-MS: calculated for $C_{19}H_{28}BNO_4$ 345.21observed m/e: 346.30 $(M+H)^+$ (Rt 2.33 / 4 min).

INTERMEDIATE 7



Isopropyl 4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperidine-1-carboxylate Isopropyl 4-(4-bromophenyl)piperidine-1-carboxylate (1.36g, 4.16 mmol), bispinacolatodiboron (2.106 g, 8.29 mmol), and potassium acetate (1.221 g, 12.44 mmol) were dissolved in DMSO (17 mL). The reaction mixture was sparged with N_2 for 15 min and then [1,1'- Bis(Diphenyl-phosphino)Ferrocene]-Dichloropalladium (II) (0.607 g, 0.829 mmol) was added. The reaction was heated to 80 °C overnight, then diluted with water and EtOAc. The aqueous phase was removed and extracted (x1) with EtOAc and the combined extracts were washed with brine (x 2), dried over Na_2SO_4, filtered, and concentrated. The resulting residue was purified by column chromatography on a Biotage™ 50 g column by eluting with 20% to 80% EtOAc:Hexane. LC-MS: calculated for $C_{21}H_{32}BNO_4$ 373.24 observed m/e: 374.3 $(M+H)^+$ (Rt 2.57 / 4 min).

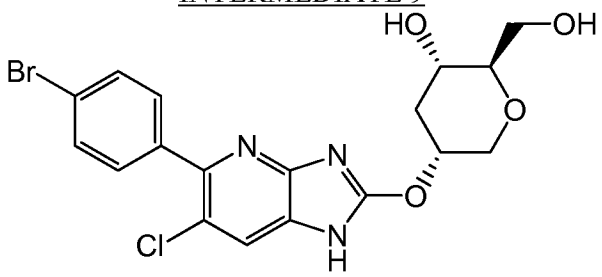
INTERMEDIATE 8



5-(4-bromophenyl)-6-chloro-2-(((4aR,7R,8aS)-2-phenylhexahydropyrano[3,2-d][1,3]dioxin-7-yl)oxy)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazo[4,5-b]pyridine 5-(4-bromophenyl)-6-chloro-2-(methylsulfonyl)-1-((2-(trimethylsilyl)-ethoxy)methyl)-1H-imidazo[4,5-b]pyridine (2.6 g, 5.03 mmol), (4aR,7R,8aS)-2-phenylhexahydropyrano[3,2-d][1,3]dioxin-7-ol (1.307 g, 5.53 mmol), and cesium carbonate (4.92 g, 15.09 mmol) were dissolved in DMF (25.1 mL). The reaction mixture was stirred overnight at rt, then diluted with EtOAc and saturated NH_4Cl/water (50:50). The aqueous phase was extracted with EtOAc (x2) and the combined extracts were washed with sat. $NaHCO_3$ and brine, then dried over Na_2SO_4, filtered, and concentrated. The resulting residue was purified by column chromatography on a Biotage™ 100g column by

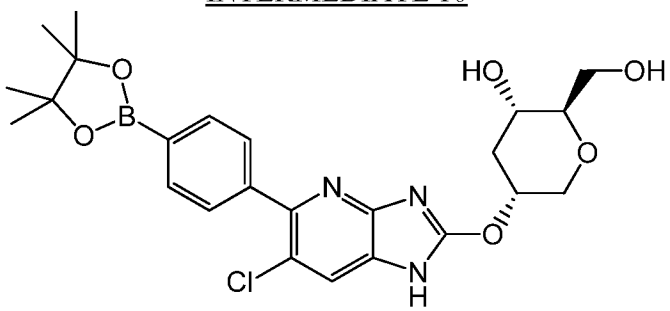
eluting with 10% EtOAc:Hexane to 70% EtOAc:Hexane to yield the desired product. LC-MS: calculated for $C_{31}H_{35}BrClN_3O_5Si$ 671.12 observed m/e: 671.83 $(M+H)^+$ (Rt 1.37 / 2 min).

INTERMEDIATE 9



(2R,3S,5R)-5-((5-(4-bromophenyl)-6-chloro-1H-imidazo[4,5-b]pyridin-2-yl)oxy)-2-(hydroxymethyl)tetrahydro-2H-pyran-3-ol 5-(4-bromophenyl)-6-chloro-2-(((4aR,7R,8aS)-2-phenylhexahydropyrano-[3,2-d][1,3]dioxin-7-yl)oxy)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazo[4,5-b]pyridine (1.5 g, 2.229 mmol) was dissolved in formic acid (30 ml, 782 mmol) and aqueous saturated $KHSO_4$ (2 mL). The reaction was heated to 50 °C overnight, then diluted with EtOAc, followed by the addition of 3M NaOH until a pH of ~13 was reached. After stirring 10 min at rt, saturated NH_4Cl was added until a pH of ~7 was reached. The aqueous phase was separated, and extracted with EtOAc (x2). The combined extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The resulting residue was purified by column chromatography on a Biotage™ 50g column by eluting with 1% to 12% MeOH in $CHCl_3$. LC-MS: calculated for $C_{18}H_{17}BrClN_3O_4$ 453.01 observed m/e: 453.94 $(M+H)^+$ (Rt 1.13 / 2 min).

INTERMEDIATE 10

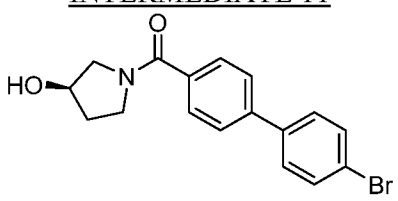


(2R,3S,5R)-5-((6-chloro-5-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1H-imidazo[4,5-b]pyridin-2-yl)oxy)-2-(hydroxymethyl)tetrahydro-2H-pyran-3-ol

A 10 mL reaction tube was charged with bis(pinacolato)diboron (123 mg, 0.484 mmol), Palladium, [2'-(amino-κN)[1,1'-biphenyl]-2-yl-κC][butylbis(tricyclo-[3.3.1.13,7]dec-1-yl)phosphine]chloro (CAS number: 1375477-29-4, 29.4 mg, 0.044 mmol), (2R,3S,5R)-5-((5-(4-bromophenyl)-6-chloro-1H-imidazo[4,5-b]pyridin-2-yl)oxy)-2-(hydroxymethyl)tetrahydro-2H-pyran-3-ol (200 mg, 0.440 mmol), and potassium acetate (86 mg, 0.880 mmol). The reaction tube was evacuated and backfilled with N_2 (x2). Degassed CPME (1759 µl) was added and the

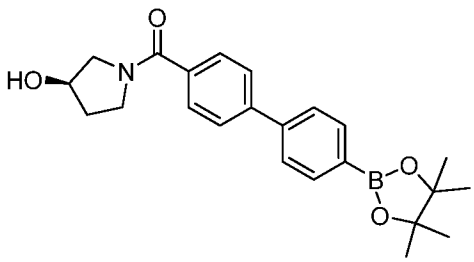
reaction was heated to 85 °C overnight. The reaction mixture was then concentrated and purified by column chormatgraphy on a Biotage™ 25g column by eluting with 1% to 15% MeOH in $CHCl_3$. LC-MS: calculated for $C_{24}H_{29}BClN_3O_6$ 501.18 observed m/e: 502.22 $(M+H)^+$ (Rt 2.01 / 4 min).

INTERMEDIATE 11



(R)-(4'-bromo-[1,1'-biphenyl]-4-yl)(3-hydroxypyrrolidin-1-yl)methanone 4'-bromo-[1,1'-biphenyl]-4-carboxylic acid (2g, 7.22mmol), (R)-pyrrolidin-3-ol (1.3g, 14.92 mmol), and HATU (5.5g, 14.46mmol) were dissolved in DMF (60 mL). To this solution was added TEA (4 ml, 28.7 mmol) and the reaction mixture was stirred under N_2 at room temperature for 24 h. Then the volatiles were removed *in vacuo* and the resulting residue was partitioned between EtOAc and H_2O. The organic layer was separated and washed with 1N HCl, saturated $NaHCO_3$, and brine, and then dried over Na_2SO_4, filtered and concentrated *in vacuo*. Chromatography of the resulting residue over silica eluting with 3% MeOH in DCM afforded the desired product. LC-MS: calculated for $C_{17}H_{16}BrNO_2$ 345.04 observed m/e: 346.09 $(M+H)^+$ (Rt:1.62/4min).

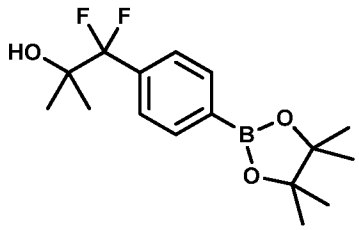
INTERMEDIATE 12



(R)-(3-hydroxypyrrolidin-1-yl)(4'-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,1'-biphenyl]-4-yl)methanone (R)-(4'-bromo-[1,1'-biphenyl]-4-yl)(3-hydroxypyrrolidin-1-yl)methanone (1.61g, 4.65mmol), potassium acetate (1.4g, 14.26mmol), bis(pinacolato)diboran (1.25g, 4.92 mmol) and $PdCl_2$(dppf) were dissolved in DMSO (9 mL). Resulting mixture was evacuated and flushed with N_2 five times, and then heated to 80 °C for 24 hours. The crude reaction was partitioned between water (200 mL) and ether (200 mL). The organic layer was separated and the aqueous layer was further extracted with ether (2 x 100 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Chromatography of the resulting residue over silica eluting with 3% MeOH in DCM afforded the desire product.

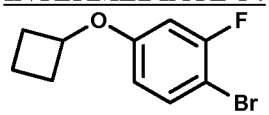
LC-MS: calculated for $C_{23}H_{28}BNO_4$ 393.21 observed m/e: 394.2 $(M+H)^+$ (Rt:2.01/4min).

INTERMEDIATE 13



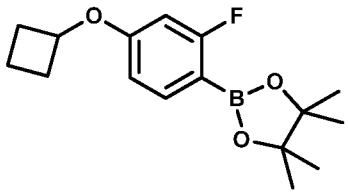
1,1-difluoro-2-methyl-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propan-2-ol Methyl 2-(4-bromophenyl)-2,2-difluoroacetate (264 mg, 0.996 mmol) was dissolved in THF (4.980 mL). The reaction was cooled to 0 °C and methylmagnesium bromide (1.992 mL, 5.98 mmol) was added dropwise. The reaction was warmed to rt and stirred 1h, then cooled to 0 °C and quenched with saturated NH_4Cl. The aqueous phase was extracted with EtOAc (x 2) and the combined EtOAc extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated. The resulting residue was dissolved in DMSO (3999 µl), then bispinacolatodiboron (508 mg, 1.999 mmol) and potassium acetate (294 mg, 3.00 mmol) were added. The reaction was sparged with N_2 for 15 min and then [1,1'-Bis(Diphenylphosphino)-Ferrocene]Dichloropalladium (II) (146 mg, 0.200 mmol) was added. The reaction was heated to 80 °C overnight, then diluted with 1:1 water:brine and EtOAc. The aqueaus phase was extracted with EtOAc (x2) and the combined extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated. The resulting residue was purified by column chromatography on a Biotage™ 25 g column by eluting with 10% to 70% EtOAc:Hexane to provide the desired compound. ^1H NMR δ (ppm) (CD_3OD): 7.78 (d, 2H), 7.51 (d, 2H), 1.34 (s, 6H), 1.23 (12H).

INTERMEDIATE 14



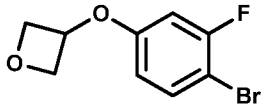
1-bromo-4-cyclobutoxy-2-fluorobenzene 4-bromo-3-fluorophenol (315 mg, 1.648 mmol), cyclobutyl 4-methyl-benzenesulfonate (373 mg, 1.648 mmol), and cesium carbonate (1074 mg, 3.30 mmol) were dissolved in DMSO (1648 µl) and heated to 60 °C overnight. The reaction mixture was diluted with water and EtOAc. The aqueous phase was extracted with EtOAc (x2) and the combined extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated. The resulting residue was purified by column chromatography on a Biotage™ 50g column by eluting with 2% to 50% EtOAc:Hexane. ^1H NMR δ (ppm) 7.4 (t, 1H), 6.10 (dd, 1H), 6.53 (dd, 1H), 4.60 (quintet, 1H), 2.49-2.43 (m, 2H), 2.21-2.13 (m, 2H), 1.93 (m, 1H), 1.73 (sextet, 1H).

INTERMEDIATE 15



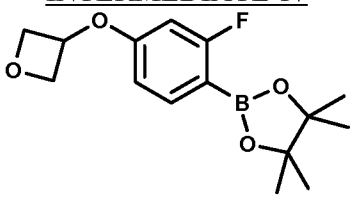
2-(4-cyclobutoxy-2-fluorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane 1-bromo-4-cyclobutoxy-2-fluorobenzene (253 mg, 1.032 mmol), bis(pinacolato)diboron (524 mg, 2.065 mmol), and potassium acetate (304 mg, 3.10 mmol) were dissolved in DMSO (4129 µl). The solution was sparged with N_2 for 15 min and then [1,1'-Bis(Diphenylphosphino)Ferrocene]-Dichloropalladium (II) (151 mg, 0.206 mmol) was added. The reaction heated to 80 °C overnight, then diluted with 1:1 water:brine and EtOAc. The aqueaus phase was extracted with EtOAc (x2) and the combined extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated. The resulting residue was purified by column chromatography on a Biotage™ 25g column by eluting with 10% to 70% EtOAc:Hexane to give the desired product. ^{1}H NMR δ (ppm) 7.56 (t, 1H), 6.62 (dd, 1H), 6.48 (dd, 1H), 4.69 (quinet, 1H), 2.49-2.42 (m, 2H), 2.15-2.07 (m, 2H), 1.88-1.83 (m, 1H), 1.72 (sextet, 1H), 1.31 (s, 12H).

INTERMEDIATE 16



3-(4-bromo-3-fluorophenoxy)oxetane 4-bromo-3-fluorophenol (1.185 g, 6.20 mmol), oxetan-3-yl 4-methyl-benzenesulfonate (1.77 g, 7.75 mmol) and cesium carbonate (5.05 g, 15.51 mmol) were dissolved in DMSO (7.75 mL) and heated to 60 °C overnight. The reaction mixture was diluted with water and EtOAc. The aqueous phase was extracted with EtOAc (x2) and the combined extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated. The resulting residue was purified by column chromatography on a Biotage™ 50g column by eluting with 2% to 50% EtOAc:Hexane to give the desired product. ^{1}H NMR δ (ppm) 7.39 (t, 1H), 6.50 (d, 1H), 6.40 (d, 1H), 5.17-5.12 (m, 1H), 4.97 (t, 2H), 4.73 (t, 2H).

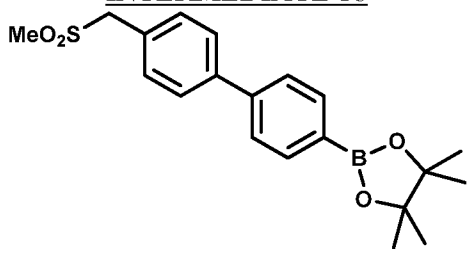
INTERMEDIATE 17



2-(2-fluoro-4-(oxetan-3-yloxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane 3-(4-bromo-3-fluorophenoxy)oxetane (1.3 g, 5.26 mmol), bis(pinacolato)diboron (2.67 g, 10.52 mmol) and

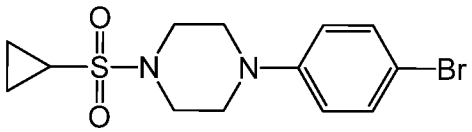
potassium acetate (1.549 g, 15.79 mmol) were dissolved in DMSO (21.05 ml) and the mixture was sparged with N_2 for 15 min. Then [1,1'-Bis(Diphenylphosphino)Ferrocene]Dichloro-palladium (II) (0.770 g, 1.052 mmol) was added and the reaction heated to 80 °C overnight, then diluted with 1:1 water:brine and EtOAc. The aqueous phase was extracted with EtOAc (x2) and the combined extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated. The resulting residue was purified by column chromatography on a Biotage™ 25g column by eluting with 10% to 70% EtOAc:Hexane to provide the desired product. ^{1}H NMR δ (ppm) 7.6 (t, 1H), 6.56 (d, 1H), 6.46 (d, 1H), 5.30-5.25 (m, 1H), 4.99 (t, 2H), 4.65 (t, 2H), 1.33 (s, 12H).

INTERMEDIATE 18



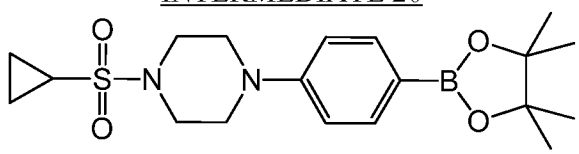
4,4,5,5-tetramethyl-2-(4'-((methylsulfonyl)methyl)-[1,1'-biphenyl]-4-yl)-1,3,2-dioxaborolane 1-bromo-4-((methylsulfonyl)methyl)benzene (1.5 g, 6.02 mmol), 1,4-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzene (4.97 g, 15.05 mmol), and silver carbonate (1.826 g, 6.62 mmol) were dissolved in THF (60.2 ml) and sparged with N_2 for 15 min. Then $Pd(PPh_3)_4$ (0.348 g, 0.301 mmol) was added and the reaction was heated to 80 °C overnight. The reaction was then cooled to rt, filtered through Celite™ and concentrated *in vacuo*. The resulting residue was purified by column chromatography on a Biotage™ 50g column by eluting with 5% to 50% EtOAc:Hex to yield the desired product. ^{1}H NMR δ (ppm) 7.83 (d, 2H), 7.69 (d, 2H), 7.64 (d, 2H), 7.54 (d, 2H), 4.46 (s, 2H), 2.89 (s, 3H), 1.4 (12H).

INTERMEDIATE 19



1-(4-bromophenyl)-4-(cyclopropylsulfonyl)piperazine 1-(4-bromophenyl)piperazine (1 g, 4.15 mmol) was dissolved in DCM (40 ml) and cooled in 0 °C. Then DMAP (0.051 g, 0.415 mmol), triethylamine (0.723 ml, 5.18 mmol), and cyclopropanesulfonyl chloride (0.641 g, 4.56 mmol) were added. The reaction was stirred 1h at rt, then diluted with DCM and saturated NH_4Cl/water (1:1). The aqueous phase was separated, extracted with DCM (x2) and the combined extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated to give the desired product. LC-MS: calculated for $C_{13}H_{17}BrN_2O_2S$ 346.02 observed m/e: 346.88 $(M+H)^+$ (Rt 1.16 / 2 min).

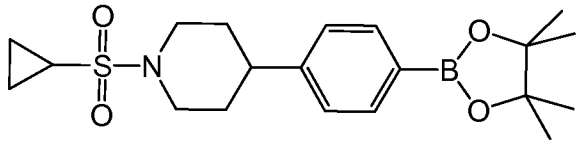
INTERMEDIATE 20



1-(cyclopropylsulfonyl)-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperazine

1-(4-bromophenyl)-4-(cyclopropylsulfonyl)piperazine (1.4g, 4.15 mmol), bis(pinacolato)diboron (2.106 g, 8.29 mmol), and potassium acetate (1.221 g, 12.44 mmol) were dissolved in DMSO (17 ml). The mixture was sparged with N_2 for 15 min, then [1,1'-Bis(Diphenylphosphino)-Ferrocene]Dichloropalladium (II) (0.607 g, 0.829 mmol) was added and the reaction heated to 80 °C overnight. Then the reaction was diluted with water and EtOAc. The aqueous phase was extracted with EtOAc (x2) and the combined extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated. The resulting residue was purified by column chromatography on a Biotage™ 50g column by eluting with 20% to 80% EtOAc:Hexane to provide the desired product. ^{1}H NMR δ (ppm) 7.76 (d, 2H), 6.97 (br s, 2H), 3.51 (br s, 4H), 3.40-3.38 (m, 4H), 2.33-2.29 (m, 1H), 1.35 (s, 12H), 1.24-1.22 (m, 2H), 1.06-1.02 (m, 2H).

INTERMEDIATE 21

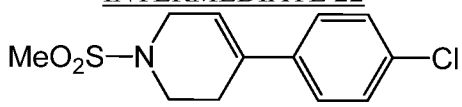


1-(cyclopropylsulfonyl)-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperidine

1-(4-bromophenyl)piperazine (1 g, 4.15 mmol) was dissolved in DCM (40 ml) and cooled to 0 °C. Then DMAP (0.051 g, 0.415 mmol), triethylamine (0.723 ml, 5.18 mmol), and cyclopropanesulfonyl chloride (0.644 g, 4.58 mmol) were added. The reaction was stirred 1h at rt, then diluted with DCM and saturated NH_4Cl/water (1:1). The aqueous phase was extracted with EtOAc (x2) and the combined extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated. The resulting residue was dissolved in DMSO (17 ml), and then bis(pinacolato)diboron (2.106 g, 8.29 mmol) and potassium acetate (1.221 g, 12.44 mmol) were added. The reaction was sparged with N_2 for 15 min, then [1,1'-Bis(Diphenyl-phosphino)Ferrocene]Dichloropalladium (II) (0.607 g, 0.829 mmol) was added and the reaction heated to 80 °C overnight. The reaction was diluted with water and EtOAc. The aqueaus phase was separated, extracted with EtOAc (x2) and the combined extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated. The resulting residue was purified by column chromatography on a Biotage™ 50g column eluted with 20% to 80% EtOAc:Hexane to provide the desired product. ^{1}H NMR δ (ppm) 7.79 (d, 2H), 7.24 (d, 2H), 3.96 (d, 2H), 2.94 (t, 2H), 2.69-2.63 (m, 1H), 2.35-2.30 (m, 1H), 1.95 (br d, 2H), 1.86 (ddd, 2H), 1.36 (s, 12H), 1.28-1.20

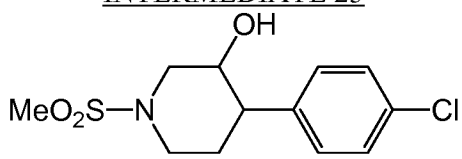
(m, 2H), 1.04-1.00 (m, 2H).

INTERMEDIATE 22



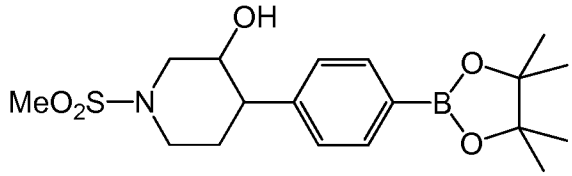
4-(4-chlorophenyl)-1-(methylsulfonyl)-1,2,3,6-tetrahydropyridine 4-(4-chlorophenyl)-1,2,3,6-tetrahydropyridine (645 mg, 3.33 mmol) was dissolved in DCM (20 ml) and then DMAP (40.7 mg, 0.333 mmol), triethylamine (1.858 ml, 13.33 mmol), and methane sulfonylchloride (0.286 ml, 3.67 mmol) were added. The reaction was stirred 1h at rt, then diluted with DCM and saturated NH_4Cl/water (1:1). The aqueous phase was extracted with DCM (x 2) and the combined extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated. The resulting residue was purified by column chromatography on a Biotage™ 50 g column by eluting with 10% to 100% EtOAc:Hexane to provide the desired product. LC-MS: calculated for $C_{12}H_{14}ClNO_2S$ 271.04 observed m/e: 271.91 $(M+H)^+$ (Rt 1.15/2 min).

INTERMEDIATE 23



4-(4-chlorophenyl)-1-(methylsulfonyl)piperidin-3-ol 4-(4-chlorophenyl)-1-(methylsulfonyl)-1,2,3,6-tetrahydropyridine (654 mg, 2.407 mmol) was dissolved in THF (4.81 mL). Borane-THF complex (2.407 mL, 2.407 mmol) was added dropwise via syringe and the reaction was stirred 72 h at rt. Then sodium hydroxide (1.5 mL, 4.50 mmol) and hydrogen peroxide (1.2 mL, 11.75 mmol, 30% solution) were added. The reaction was stirred 2h at rt, then diluted with saturated $Na_2S_2O_3$ and EtOAc. The aqueous phase was extracted with EtOAc (x2) and the combined extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated. The resulting residue was purified by column chromatography on a Biotage™ 25 g column by eluting with 20% to 100% EtOAc:Hexane to provide the desired product. LC-MS: calculated for $C_{12}H_{16}ClNO_3S$ 289.05 observed m/e: 289.92 $(M+H)^+$ (Rt 1.35/4 min).

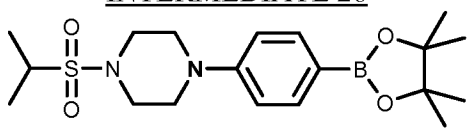
INTERMEDIATE 24



1-(methylsulfonyl)-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperidin-3-ol

A 10 mL reaction vial was charged with: 4-(4-chlorophenyl)-1-(methylsulfonyl)-piperidin-3-ol (150 mg, 0.518 mmol), $Pd_2(dba)_3$ (23.70 mg, 0.026 mmol), bis(pina-colato)diboron (394 mg, 1.553 mmol), XPhos (24.68 mg, 0.052 mmol), and potassium acetate (152 mg, 1.553 mmol). The vial was evacuated and backfilled with N_2 (x2), then dioxane (1035 µl) was added and the reaction heated to 100 °C overnight. The reaction mixture was diluted with water and EtOAc. The aqueous phase was extracted with EtOAc (x2) and the combined extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated. The resulting residue was purified by column chromatography on a Biotage™ 25g column by eluting with 40% to 100% EtOAc:Hexane to provide the desired product. LC-MS: calculated for $C_{18}H_{28}BNO_5S$ 381.18 observed m/e: 381.97 $(M+H)^+$ (Rt 1.11/2 min).

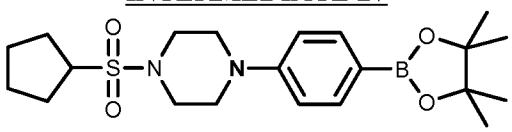
INTERMEDIATE 26



1-(isopropylsulfonyl)-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperazine

1-(4-bromophenyl)piperazine (1 g, 4.15 mmol) was dissolved in DCM (40 ml) and cooled to 0 °C. Then DMAP (0.051 g, 0.415 mmol), triethylamine (0.723 ml, 5.18 mmol), and isopropyl-sulfonyl chloride (0.445 ml, 3.96 mmol) were added. The reaction was stirred for 1h at rt, then diluted with DCM and saturated NH_4Cl/water (1:1). The aqueous phase was separated, extracted with DCM (x2), and the combined extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated. The resulting residue was dissolved in DMSO (17 ml), and bis(pinacolato)-diboron (2.106 g, 8.29 mmol), and potassium acetate (1.221 g, 12.44 mmol) were added. The solution was sparged with N_2 for 15 min and [1,1'-Bis(Diphenylphosphino)Ferrocene]-Dichloropalladium(II)) (0.607 g, 0.829 mmol) was added. The reaction was heated to 80 °C overnight, then diluted with water and EtOAc. The aqueous phase was extracted with EtOAc (x2) and the combined extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated. The resulting residue was purified by column chromatography on a Biotage™ 50g column by eluting with 20% to 80% EtOAc:Hexane to provide the desired product. LC-MS: calculated for $C_{19}H_{31}BN_2O_4S$ 394.21 observed m/e: 394.98 $(M+H)^+$ (Rt 1.21/2 min).

INTERMEDIATE 27

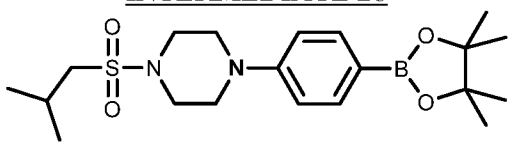


1-(cyclopentylsulfonyl)-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperazine

1-(4-bromophenyl)piperazine (1 g, 4.15 mmol) was dissolved in DCM (40 ml) and cooled in 0

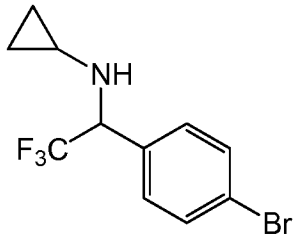
°C. Then DMAP (0.051 g, 0.415 mmol), triethylamine (0.723 ml, 5.18 mmol), and cyclopentyl sulfonyl chloride (0.699 g, 4.15 mmol) were added. The reaction was stirred for 1h at rt, then diluted with DCM and saturated NH_4Cl/water (1:1). The aqueous phase was extracted with DCM (x2), and the combined extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated. The resulting residue was dissolved in DMSO (17 ml), and bis(pinacolato)diboron (2.106 g, 8.29 mmol), and potassium acetate (1.221 g, 12.44 mmol) were added. The solution was sparged with N_2 for 15 min and [1,1'-Bis(Diphenylphosphino)Ferrocene]Dichloropalladium (II)) (0.607 g, 0.829 mmol) was added. The reaction was heated to 80 °C overnight, then diluted with water and EtOAc. The aqueous phase was extracted with EtOAc (x2), and the combined extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated. The resulting residue was purified by column chromatography on a Biotage™ 50g column by eluting with 20% to 80% EtOAc:Hexane to provide the desired product. LC-MS: calculated for $C_{21}H_{33}BN_2O_4S$ 420.23 observed m/e: 420.98 $(M+H)^+$ (Rt 1.23/2 min).

INTERMEDIATE 28



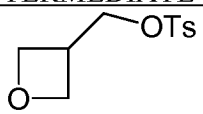
1-(isobutylsulfonyl)-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperazine. 1-(4-bromophenyl)piperazine (1 g, 4.15 mmol) was dissolved in DCM (40 ml) and cooled to 0 °C. Then DMAP (0.051 g, 0.415 mmol), triethylamine (0.723 ml, 5.18 mmol), and 2-methylpropane-1-sulfonyl chloride (466 mg, 2.97 mmol) were added. The reaction was stirred for 1h at rt, then diluted with DCM and saturated NH_4Cl/water (1:1). The aqueous phase was extracted with DCM (x2), and the combined extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated. The resulting residue was dissolved in DMSO (17 ml) and then bis(pinacolato)-diboron (2.106 g, 8.29 mmol), and potassium acetate (1.221 g, 12.44 mmol) were added. The solution was sparged with N_2 for 15 min and [1,1'-Bis(Diphenylphosphino)Ferrocene]-Dichloropalladium (II)) (0.607 g, 0.829 mmol) was added. The reaction was heated to 80 °C overnight, then diluted with water and EtOAc. The aqueous phase was extracted with EtOAc (x2); and the combined extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated. The resulting residue was purified by column chromatography on a Biotage™ 50g column by eluting with 20% to 80% EtOAc:Hexane to provide the desired product. ^1H NMR δ (ppm) 7.76 (d, 2H), 6.96 (br s, 2H), 3.45 (br s, 4H), 3.39 (br s, 4H), 2.80 (d, 2H), 2.34 (septet, 1H), 1.34 (s, 12H), 1.14 (d, 6H).

INTERMEDIATE 29



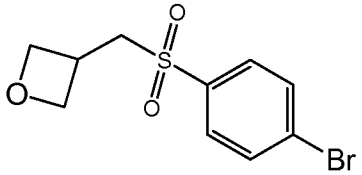
N-(1-(4-bromophenyl)-2,2,2-trifluoroethyl)cyclopropanamine Potassium hydrogen fluoride (0.697 g, 8.92 mmol) and *N*-(4-bromobenzylidene)-cyclopropanamine (2 g, 8.92 mmol) were dissolved in acetonitrile (17.85 ml) and cooled to 0 °C. TFA (1.031 ml, 13.39 mmol) was added and the reaction was stirred for 5 min. Then (trifluoromethyl)trimethylsilane (2.64 ml, 17.85 mmol) was added and the reaction was allowed to stir at rt overnight. Saturated Na_2CO_3 was added to the reaction mixture and the reaction stirred 5 min, then diluted with water and EtOAc/Hexane (1:1). The aqueous phase was extracted with EtOAc (x2), and the combined extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated. The resulting residue was purified by column chromatography on a Biotage™ 50g column by eluting with 2% to 25% EtOAc:Hexane to give product. A second purification was performed on this product on a Biotage™ 100g column by eluting with 2% to 25% EtOAc to provide the desired product. LC-MS: calculated for $C_{11}H_{11}BrF_3N$ 293.00 observed m/e: 294.15 $(M+H)^+$ (Rt 1.23/2 min).

INTERMEDIATE 30



Oxetan-3-ylmethyl 4-methylbenzenesulfonate Oxetan-3-ylmethanol (0.5 g, 5.68 mmol) was dissolved in DCM (11.35 ml), then triethylamine (1.186 ml, 8.51 mmol), DMAP (0.069 g, 0.568 mmol), and Tosyl-Cl (1.298 g, 6.81 mmol) were added. The reaction was stirred overnight at rt, then diluted with EtOAc and saturated NH_4Cl/water (1:1). The aqueous phase was extracted with EtOAc (x2); and the combined extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated. The resulting residue was purifed by column chormatogaphy on a Biotage™ 50 g column by eluting with 5% to 70% EtOAc in Hexane to provide the desired product. ^1H NMR δ (ppm) 7.82 (d, 2H), 7.39 (d, 2H), 4.76 (t, 2H), 4.34 (t, 2H), 4.28 (d, 2H), 3.31 (septet, 1H), 2.48 (s, 3H).

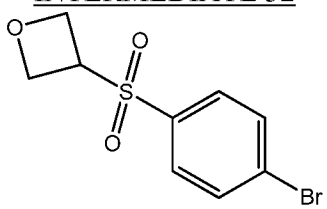
INTERMEDIATE 31



4-bromothiophenol (1g, 5.29 mmol), oxetan-3-ylmethyl 4-methylbenzenesulfonate (1.281 g,

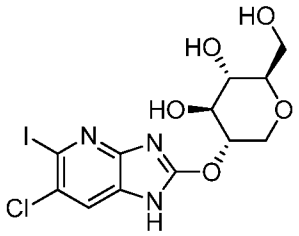
5.29 mmol), and cesium carbonate (3.45 g, 10.58 mmol) were suspended in DMSO (5.29 ml). The reaction was stirred 2 days at rt, and then diluted with water and EtOAc. The aqueous phase was extracted with EtOAc (x2); and the combined extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated. The resulting residue was purified by column chormatography on a Biotage™ 50 g column by eluting with 10% to 90% EtOAc:Hexane. The major peak was isolated, concentrated and dissolved in MeOH (8 mL), THF (8 mL) and water (4 mL). Oxone (5.9g, 9.6 mmol) was added and the reaction was stirred overnight at rt. The reaction was then diluted with water and EtOAc. The organic phase was washed with water, $Na_2S_2O_3$, and brine, and then dried over Na_2SO_4, filtered and concentrated. The resulting residue was purified by column chromatography on a Biotage™ 50 g column by eluting with 10% to 90% EtOAc:Hexane to provide the desired product. ^{1}H NMR δ 7.78-7.74 (m, 4H), 4.79 (t, 2H), 4.45 (t, 2H), 3.51-3.48 (m, 3H).

INTERMEDIATE 32



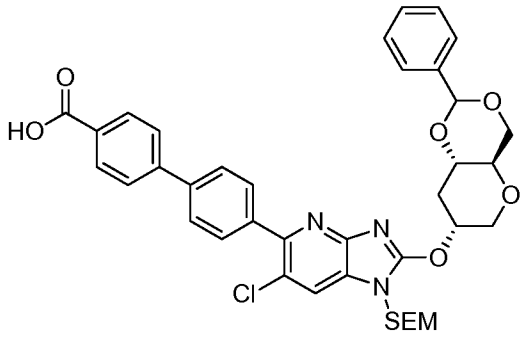
3-((4-bromophenyl)sulfonyl)oxetane 4-bromothiophenol (1.15g, 6.08 mmol), oxetan-3-yl 4-methylbenzenesulfonate (1.66 g, 7.3 mmol), and cesium carbonate (3.96 g, 12.16 mmol) were suspended in DMSO (6 ml). The reaction mixture was stirred for 2 days at rt, then diluted with water and EtOAc. The aqueous phase was extracted with EtOAc (x2); and the combined extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated. The resulting residue was purified by column chormatogaphy on a Biotage™ 50g column by eluting with 5% to 75% EtOAc:Hexane. The major peak was isolated, concentrated and dissolved in MeOH (10mL), THF (10 mL) and water (5 mL). Oxone (4.05g, 6.59 mmol) was added and the reaction was stirred overnight at rt, and then diluted with water and EtOAc. The EtOAc phase was washed with water, $Na_2S_2O_3$, and brine, and then dried over Na_2SO_4, filtered and concentrated to provide the desired product. ^{1}H NMR δ 7.80-7.75 (m, 4H), 4.96 (t, 2H), 4.82 (t, 2H), 4.46 (pentet, 1H).

INTERMEDIATE 33



(2R,3S,4S,5S)-5-((6-chloro-5-iodo-1H-imidazo[4,5-b]pyridin-2-yl)oxy)-2-(hydroxymethyl)-tetrahydro-2H-pyran-3,4-diol To a stirred solution of 6-chloro-5-iodo-2-(methylsulfonyl)-1-((2-(trimethylsilyl)-ethoxy)methyl)-1H-imidazo[4,5-b]pyridine (2.814 g, 5.77 mmol) in anhydrous DMF (33.0 mL) under nitrogen was added (4aR,7S,8R,8aS)-2-phenylhexahydropyrano[3,2-d][1,3]dioxine-7,8-diol (7.28 g, 28.8 mmol) and cesium carbonate (11.28 g, 34.6 mmol). After stirring for 2 hours at room temperature, the mixture was poured into water (150 mL), and then extracted with ethyl acetate (2 x 200 mL). The combined organic layers were washed with brine (100 mL), dried over sodium sulfate, and concentrated under reduced pressure. The resultant solid was passed through silica gel with eluted with EtOAc in Hexane/DCM to remove excess (4aR,7S,8R,8aS)-2-phenylhexahydropyrano-[3,2-d][1,3]dioxine-7,8-diol. Following concentration of the filtrate, the resultant white solid was chromatographed using a Biotage™ 100g silica gel cartridge by eluting with 0-20% EtOAc in 1:1 Hexane/DCM over 10 column volumes with a 5 column volume hold at 20% EtOAc. The fractions containing the first eluted isomeric product (desired) were concentrated under reduced pressure. The resultant residue was dissolved in formic acid (11 mL). Then saturated aqueous potassium hydrogen sulfate (1 mL) was added and the mixture was stirred at 50°C for 3 hours, then allowed to cool to room temperature. The mixture was slowly added to a saturated aqueous solution of sodium bicarbonate (300 mL), extracted with ethyl acetate (2 x 250 mL), and concentrated under reduced pressure. The resultant white solid was dissolved in methanol (10 mL). Then 5N aqueous NaOH (3 mL) was added and the mixture was stirred at room temperature. After 30 minutes, the mixture was neutralized with aqueous 1N HCl. The mixture was poured into water (50 mL) and extracted with ethyl acetate (2 x 150 mL). The combined organic layers were washed with brine (100 mL), dried over sodium sulfate, and concentrated under reduced pressure. The resultant white solid was chromatographed using a Biotage™ 25 g silica gel cartridge by eluting with 0-10% methanol in DCM over 15 column volumes. The combined product fractions were concentrated under reduced pressure, dissolved in MeCN/water, frozen at -78°C, and lyophilized to dryness to give the title compound as a white solid. LC-MS: calculated for $C_{12}H_{13}ClIN_3O_5$ 440.96, observed m/e: 441.81 $(M+H)^+$ (Rt 1.26/4 min).

INTERMEDIATE 34

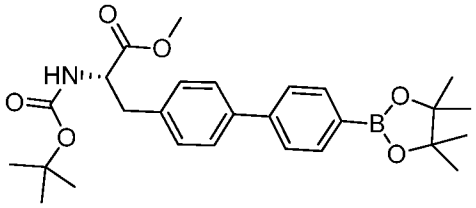


4'-(6-chloro-2-(((4aR,7R,8aS)-2-phenylhexahydropyrano[3,2-d][1,3]dioxin-7-yl)oxy)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazo[4,5-b]pyridin-5-yl)-[1,1'-biphenyl]-4-carboxylic acid

Step A. Methyl 4'-(6-chloro-2-(((4aR,7R,8aS)-2-phenylhexahydropyrano[3,2-d][1,3]dioxin-7-yl)oxy)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazo[4,5-b]pyridin-5-yl)-[1,1'-biphenyl]-4-carboxylate. To a stirred solution of 5-(4-bromophenyl)-6-chloro-2-(((4aR,7R,8aS)-2-phenylhexahydropyrano[3,2-d][1,3]dioxin-7-yl)oxy)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazo[4,5-b]pyridine (586 mg, 0.871 mmol), dicyclohexyl(2',6'-dimethoxy-[1,1'-biphenyl]-2-yl)phosphine (36 mg, 0.088 mmol), methyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (297 mg, 1.132 mmol), and tribasic potassium phosphate (554 mg, 2.61 mmol) in tolune (2 mL) and water (0.1 mL) under nitrogen was added palladium acetate (10 mg, 0.045 mmol). The mixture was stirred at 100°C for 16 hours, then allowed to cool to room temperature. The mixture was filtered, concentrated under reduced pressure, and chromatographed using a Biotage™ 50g silica gel cartridge eluted with 0-30% EtOAc in 1:1 Hexane/DCM over 30 column volumes. The product fractions were concentrated under reduced pressure to provide the desired product as a foamy off-white solid. LC-MS: calculated for $C_{39}H_{42}ClN_3O_7Si$ 727.25, observed m/e: 728.33 $(M+H)^+$ (Rt 3.11/4 min).

Step B. 4'-(6-chloro-2-(((4aR,7R,8aS)-2-phenylhexahydropyrano[3,2-d][1,3]dioxin-7-yl)oxy)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazo[4,5-b]pyridin-5-yl)-[1,1'-biphenyl]-4-carboxylic acid. To a stirred solution of methyl 4'-(6-chloro-2-(((4aR,7R,8aS)-2-phenylhexahydropyrano-[3,2-d][1,3]dioxin-7-yl)oxy)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazo[4,5-b]pyridin-5-yl)-[1,1'-biphenyl]-4-carboxylate (474 mg, 0.651 mmol) in THF (5.2 mL) under nitrogen was added a 2.5N aqueous solution of NaOH (5.2 mL, 10.4 mmol). The mixture was allowed to stir at 40°C for 24 hours. The mixture was then cooled to room temperature and diluted with water (40 mL). The mixture was acidified with 1N aqueous HCl and extracted with EtOAc (2 x 70 mL). The combined organic layers were washed with brine (50 mL), dried over sodium sulfate, and concentrated under reduced pressure to provide the title compound as a yellow solid. LC-MS: calculated for $C_{38}H_{40}ClN_3O_7Si$ 713.23, observed m/e: 714.21 $(M+H)^+$ (Rt 2.85/4 min).

INTERMEDIATE 35

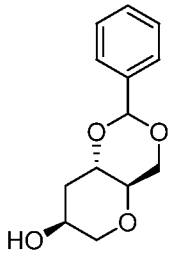


(S)-Methyl 2-((tert-butoxycarbonyl)amino)-3-(4'-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,1'-biphenyl]-4-yl)propanoate

Step A. (S)-methyl 2-((tert-butoxycarbonyl)amino)-3-(4-(((perfluorobutyl)sulfonyl)oxy)-phenyl)propanoate. A stirred solution of (S)-methyl 2-((tert-butoxycarbonyl)amino)-3-(4-hydroxyphenyl)propanoate (1.257 g, 4.26 mmol), DMAP (26 mg, 0.213 mmol), and triethylamine (0.71 mL, 0.51 g, 5.11 mmol) in anhydrous DCM (15 mL) was cooled to 0°C. Then nonafluorobutanesulfonyl fluoride (0.82 mL, 1.41 g, 4.68 mmol) was added in one portion. The mixture was allowed to warm and stirred at room temperature. After 18 hours, the mixture was poured into water (80 mL) and extracted with DCM (2 x 100 mL). The combined organic layers were washed with brine (50 mL), dried over sodium sulfate, and concentrated under reduced pressure. The resultant residue was chromatographed using a Biotage™ 50g silica gel cartridge by eluting with 0-10% EtOAc in 1:1 Hexane/DCM over 10 column volumes. The product fractions were combined and concentrated under reduced pressure to give the desired product as a clear, colorless oil. LC-MS: calculated for $C_{19}H_{20}F_9NO_7S$ 577.08, observed m/e: 478.14 (M+H with loss of BOC)$^+$ (Rt 2.67/4 min).

Step B. (S)-methyl 2-((tert-butoxycarbonyl)amino)-3-(4'-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,1'-biphenyl]-4-yl)propanoate. Placed (S)-methyl 2-((tert-butoxycarbonyl)amino)-3-(4-(((perfluorobutyl)sulfonyl)oxy)phenyl)propanoate (800 mg, 1.385 mmol), 1,4-benzenediboronic acid bis(pinacol) ester (1372 mg, 4.16 mmol), palladium acetate (16 mg, 0.071 mmol), 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (57 mg, 0.139 mmol), and tribasic potassium phosphate (882 mg, 4.16 mmol) under nitrogen in nitrogen flushed toluene (2.0 mL) and water (0.1 mL). The mixture was stirred at 100°C for 1 hour, then cooled to room temperature and poured into saturated aqueous sodium bicarbonate (30 mL). The mixture was extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with brine, dried over sodium sulfate, and concentrated under reduced pressure. The resultant residue was chromatographed using a Biotage™ 50 g silica gel cartridge eluted with 0-10% methanol in DCM over 20 column volumes. The product fractions were collected and concentrated under reduced pressure. Further purification of the resultant white solid was performed by chromatography using a Biotage™ 25g silica gel cartridge eluted with 0-20% EtOAc in 1:1 Hexane/DCM over 20 column volumes. The product fractions were combined, concentrated under reduced pressure, redissolved in MeCN and water, frozen at -78°C, and lyophilized to dryness to provide the title compound as a white solid. LC-MS: calculated for $C_{27}H_{36}BNO_6$ 481.26, observed m/e: 482.33 (M+H)$^+$ (Rt 2.65/4 min).

INTERMEDIATE 36

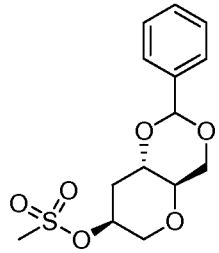


(4aR,7S,8aS)-2-phenylhexahydropyrano[3,2-d][1,3]dioxin-7-ol

Step A. (4aR,7S,8aS)-2-phenylhexahydropyrano[3,2-d][1,3]dioxin-7-yl benzoate. To a stirred solution of triphenylphosphine (560 mg, 2.134 mmol) and benzoic acid (261 mg, 2.134 mmol) under nitrogen in anhydrous THF (8.0 mL) was added (4aR,7R,8aS)-2-phenylhexahydropyrano[3,2-d][1,3]dioxin-7-ol (500 mg, 2.134 mmol), then DIAD (0.41 mL, 428 mg, 2.116 mmol) dropwise over 10 minutes. After stirring at room temperature for 1 hour, the mixture was concentrated under reduced pressure. The resultant oil was dissolved in DCM, then loaded directly onto a Biotage™ 50 g (2 x 25g in series) silica gel cartridge and eluted with 0-100% EtOAc in 1:1 Hexane/DCM over 25 column volumes. The product fractions were combined and concentrated under reduced pressure to provide the desired product as a white solid. LC-MS: calculated for $C_{20}H_{20}O_5$ 340.13, observed m/e: 341.13 $(M+H)^+$ (Rt 2.21/4 min).

Step B. (4aR,7S,8aS)-2-phenylhexahydropyrano[3,2-d][1,3]dioxin-7-ol. To a stirred solution of (4aR,7S,8aS)-2-phenylhexahydropyrano[3,2-d][1,3]dioxin-7-yl benzoate (650 mg, 1.910 mmol) in methanol (10 mL) and THF (5 mL) was added 5N aqueous NaOH (4.0 mL, 20.0 mmol). After 18 hours the mixture was poured into saturated aqueous sodium bicarbonate (100 mL) and extracted with EtOAc (2 x 120 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. The resultant white solid was chromatographed using a Biotage™ 25g silica gel cartridge eluted with 0-100% EtOAc in 1:1 Hexane/DCM over 20 column volumes. The product fractions were combined and concentrated under reduced pressure to provide the title compound as a white solid. LC-MS: calculated for $C_{13}H_{16}O_4$ 236.10, observed m/e: 237.15 $(M+H)^+$ (Rt 1.13/4 min).

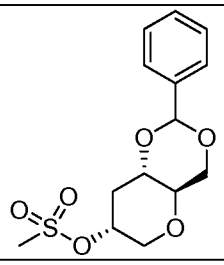
INTERMEDIATE 37



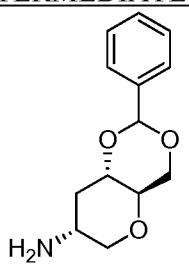
(4aR,7S,8aS)-2-phenylhexahydropyrano[3,2-d][1,3]dioxin-7-yl methanesulfonate

To a stirred solution of (4aR,7S,8aS)-2-phenylhexahydropyrano[3,2-d][1,3]dioxin-7-ol (850 mg, 3.60 mmol) and DMAP (22 mg, 0.180 mmol) under nitrogen in anhydrous pyridine (10.0 mL) at 0°C was added methanesulfonyl chloride (0.51 mL, 742 mg, 6.48 mmol) dropwise over 2 minutes. After stirring at 0°C for 1.5 hours, the mixture was diluted with toluene (10 mL) and concentrated under reduced pressure. The resultant white solid was dissolved in DCM and filtered to remove solids. The filtrate was then chromatographed using a Biotage™ 50 g silica gel cartridge eluted with 0-50% EtOAc in 1:1 Hexane/DCM over 20 column volumes. The product fractions were combined and concentated under reduced pressure to provide the title compound as a white solid. LC-MS: calculated for $C_{14}H_{18}O_6S$ 314.08, observed m/e: 315.06 $(M+H)^+$ (Rt 1.56/4 min).

Table 1. Intermediates prepared according to the methods described in Intermediate 37.

Intermediate Number	Structure	HPLC-mass spectrum m/e
38		315.06

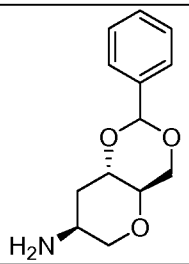
INTERMEDIATE 39



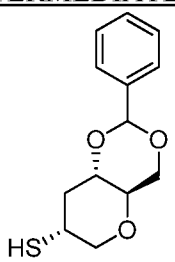
(4aR,7R,8aS)-2-phenylhexahydropyrano[3,2-d][1,3]dioxin-7-amine To a stirred solution of (4aR,7S,8aS)-2-phenylhexahydropyrano[3,2-d][1,3]dioxin-7-yl methanesulfonate (109 mg, 0.347 mmol) under nitrogen in anhydrous DMF (2.0 mL) was added sodium azide (90 mg, 1.387 mmol). The mixture was heated to 80°C. After 24 hours, the mixture was concentrated under reduced pressure. The resultant oil was chromatographed using a Biotage™ 10g silica gel cartridge eluted with 0-50% EtOAc in 1:1 Hexane/DCM over 20 column volumes. The product fractions were combined and concentrated under reduced pressure. The resultant white solid (67

mg, 0.256 mmol) was dissolved in anhydrous THF (2.0 mL) under nitrogen and a 1M solution of trimethylphosphine (0.51 mL, 0.51 mmol) was added. The mixture was allowed to stir at room temperature for 40 minutes until the azide was consumed, then saturated aqueous ammonium hydroxide (0.5 mL) was added. After stirring for 30 minutes, the mixture was concentrated under reduced pressure and dried under high vacuum. The resultant residue was dissolved in acetonitrile (2 mL), frozen at -78°C, and lyophilized to dryness to provide the title compound as a white solid. LC-MS: calculated for $C_{13}H_{17}NO_3$ 235.12, observed m/e: 236.19 $(M+H)^+$ (Rt 0.45/4 min).

Table 2. Intermediates prepared according to the methods described in Intermediate 39.

Intermediate Number	Structure	HPLC-mass spectrum m/e
40		236.18

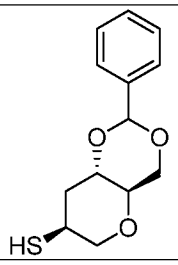
INTERMEDIATE 41



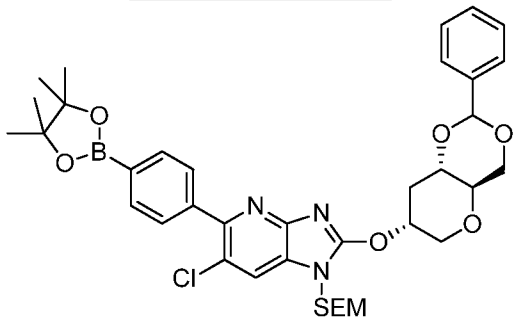
(4aR,7R,8aS)-2-phenylhexahydropyrano[3,2-d][1,3]dioxine-7-thiol To a stirred solution of (4aR,7S,8aS)-2-phenylhexahydropyrano[3,2-d][1,3]dioxin-7-yl methanesulfonate (110 mg, 0.350 mmol) under nitrogen in anhydrous DMF (2.0 mL) was added potassium thioacetate (180 mg, 1.575 mmol). The mixture was degassed by pulling a vacuum and introducing nitrogen (3x). The mixture was heated at 80°C for 5.5 hours. Upon cooling to room temperature, the mixture was diluted with diethyl ether (30 mL), and then washed with brine (20 mL). The aqueous layer was extracted again with diethyl ether (30 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. The resultant residue was chromatographed using a Biotage™ 20 g (2 x 10g in series) silica gel cartridge by eluting with

0-30% EtOAc in 1:1 Hexane/DCM over 20 column volumes. The product fractions were combined and concentrated under reduced pressure. The resultant white solid (58 mg, 0.197 mmol) was dissolved in anhydrous methanol (2.0 mL) under nitrogen. In a seperate vessel, metallic sodium (9 mg, 0.39 mmol) was dissolved in anhydrous methanol (1.0 mL), then added to the reaction mixture containing the thioester. After stirring for 30 minutes at room temperature, the mixture was poured into saturated aqueous ammonium chloride (30 mL). The mixture was extracted with DCM (50 mL). The organic layer was dried over sodium sulfate and concentrated under reduced pressure to provide the title compound as an off-white solid. LC-MS: calculated for $C_{13}H_{16}O_3S$ 252.08, observed m/e: 253.11 $(M+H)^+$ (Rt 1.82/4 min).

Table 3. Intermediates prepared according to the methods described in Intermediate 41.

Intermediate Number	Structure	HPLC-mass spectrum m/e
42		253.12

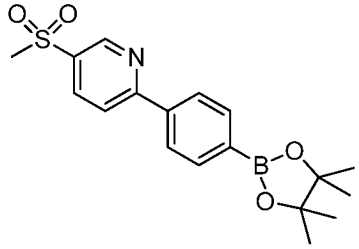
INTERMEDIATE 43



6-chloro-2-(((4aR,7R,8aS)-2-phenylhexahydropyrano[3,2-d][1,3]dioxin-7-yl)oxy)-5-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazo[4,5-b]pyridine To a stirred solution of 6-chloro-5-iodo-2-(((4aR,7R,8aS)-2-phenylhexahydropyrano[3,2-d][1,3]dioxin-7-yl)oxy)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazo[4,5-b]pyridine (4.29 g, 9.31 mmol) under nitrogen in anhydrous THF (30 mL) was added silver carbonate (3.08 g, 11.18 mmol), $Pd(PPh_3)_4$ (538 mg, 0.466 mmol), and 1,4-

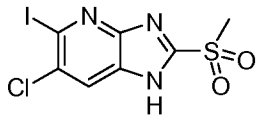
benzenediboronic acid bis(pinacol) ester (9.22 g, 27.9 mmol). The mixture was cooled to -78°C, a hard vacuum was pulled, and nitrogen was introduced (3x). The mixture was allowed to warm to room temperature, then heated to reflux. After 21 hours, the mixture was cooled to room temperature and diluted with EtOAc (80 mL). The mixture was filtered through celite with EtOAc rinse until filtrate was colorless. The filtrate was concentrated under reduced pressure. The resultant residue was chromatographed using a Biotage™ 150g (100g + 50g in series) silica gel cartridge eluted with 0-30% EtOAc in 1:1 Hexane/DCM over 15 column volumes. The product fractions were combined and concentrated under reduced pressure, then the resultant oil was dissolved in MeCN and water, frozen at -78°C, and lyophilized to dryness to provide the title compound as a yellow solid. LC-MS: calculated for $C_{37}H_{47}BClN_3O_7Si$ 719.30, observed m/e: 720.43 $(M+H)^+$ (Rt 3.25/4 min).

INTERMEDIATE 44



5-(methylsulfonyl)-2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)pyridine The title compound was synthesized according to the procedure described for Intermediate 3.

INTERMEDIATE 45



6-chloro-5-iodo-2-(methylsulfonyl)-1*H*-imidazo [4,5-b] pyridine

Step A 5, 6-dichloro-3-nitropyridin-2-amine. To a solution of 5-chloro-3-nitropyridin-2-amine (16 g, 92 mmol) in AcOH (70 mL) was added N-chlorosuccinimide (14.8 g 111 mmol). The mixture was stirred overnight at 80 °C for 3 h, cooled to rt, diluted with MeOH (30 mL) and filtered. The solid residue was washed with AcOH, water, and then dried to afford the desired product as a white solid, which was used in the next step without further purification. LC-MS: calculated for $C_5H_3Cl_2N_3O_2$ 208.0, observed m/e: 208.07 $(M+H)^+$ (Rt 1.48/5 min).

Step B 5-chloro-6-iodo-3-nitropyridin-2-amine. To a solution of 5,6-dichloro-3-nitropyridin-2-amine (15 g, 72.1 mmol) in AcOH (70 mL) was added sodium iodide (43.2 g 149.9 mmol). The mixture was stirred at 90 °C for 2 h, cooled to rt, diluted with water (70 mL) and filtered. The

solid residue was washed with water, and then dried under vacuum to afford the desired product as a pale yellow solid, which was used in the next step without further purification. LC-MS: calculated for $C_5H_3ClIN_3O_2$ 299.45, observed m/e: 299.94 $(M+H)^+$ (Rt 2.18/5 min).

Step C 5-chloro-6-iodopyridine-2,3-diamine. To a suspension of 5-chloro-6-iodo-3-nitropyridin-2-amine (18.9 g, 63.1 mmol) in EtOH (100 mL) was added tin (II) chloride dihydrate (57 g, 252 mmol). The mixture was heated at 70 °C for 0.5 h. The rxn was warmed to rt and treated with a slurry of 150 mL water and 60 g KF and stirred for 0.5 h. The mixture was then partitioned between ethyl acetate (300 mL) and water (300 mL). The ethyl acetate layer was washed with brine, dried over magnesium sulfate and filtered through a 100 g pad of silica gel. The filtrate was concentrated and dried under vacuum to give an off-white solid, which was used in next step without further purification. LC-MS: calculated for $C_5H_5ClIN_3$ 269.47, observed m/e: 269.99 $(M+H)^+$ (Rt 1.35/5 min).

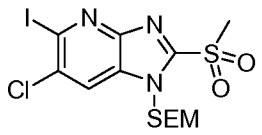
Step D 6-chloro-5-iodo-1,3-dihydro-2*H*-imidazo [4,5-b] pyridine-2-thione. DMAP (15.4 g, 126 mmol) was added to a THF (200 mL) solution of 5-chloro-6-iodopyridine-2,3-diamine (17 g, 63.1 mmol). Thiophosgene (4.9 mL, 63.1 mmol) was then added drop-wise via addition funnel under nitrogen and allowed to stir at rt for 1 h. The mixture was then partitioned between ethyl acetate (500 mL) and 2N HCl (100 mL). The ethyl acetate layer was washed with brine, dried over magnesium sulfate and concentrated to give the desired product as a white powder, which was used in the next step without further purification. LC-MS: calculated for $C_6H_3ClIN_3S$ 311.5, observed m/e: 311.91 $(M+H)^+$ (Rt 1.69/5 min).

Step E 6-chloro-5-iodo-2-(methysulfanyl)-1*H*-imidazo[4,5-b] pyridine. A suspension of 6-chloro-5-iodo-1,3-dihydro-2*H*-imidazo [4,5-b] pyridine-2-thione (11.0 g, 35.3 mmol) and KOH (2.38 g, 42.4 mmol) in ethanol (200 mL) was stirred at rt for 0.5 h. Iodomethane (2.2 mL, 35.3 mmol) was then added and the reaction was allowed to stir for 1 h at rt. The ethanol was removed *in vacuo* and the resulting residue was partitioned between ethyl acetate (250 mL) and 2N HCl (50 mL). The ethyl acetate layer was washed with brine, dried over magnesium sulfate, filtered through a 100 g pad of silica gel and concentrated to give the desired product as a white solid. LC-MS: calculated for $C_7H_5ClIN_3S$ 325.56, observed m/e: 325.88 $(M+H)^+$ (Rt 2.05/5 min).

Step F 6-chloro-5-iodo-2-(methysulfonyl)-1H-imidazo[4,5-b] pyridine. Oxone (20.8 g, 33.8 mmol) was added to an acetonitrile (100 mL)/water (100 mL) suspension of 6-chloro-5-iodo-2-(methysulfanyl)-1*H*-imidazo[4,5-b] pyridine (5.0 g, 15.4 mmol) and the reaction was allowed to stir for 18 h at rt. The suspension was filtered through a sintered glass funnel and the filtrate was partitioned between ethyl acetate and saturated sodium bisulfate. The ethyl acetate layer was washed with brine, dried over magnesium sulfate and concentrated to afford the title compound as a white solid that was used in subsequent steps without further purification. LC-MS: calculated for $C_7H_5ClN_3O_2S$ 357.56, observed m/e: 357.07 $(M+H)^+$ (Rt 1.36/4 min) ^1H NMR δ

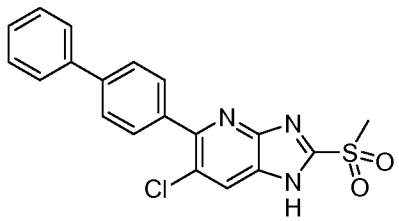
(ppm)(DMSO-d_6): 8.44 (1 H, s), 3.53 (3 H, s).

INTERMEDIATE 46



6-chloro-5-iodo-2-(methylsulfonyl)- 1-{[2-(trimethylsilyl)ethoxy]methyl}-imidazo [4,5-b] pyridine SEM-Cl (2.48 mL, 14 mmol) was added to a THF (100 mL) solution of Intermediate 45 (5.0 g, 14 mmol) and triethylamine (2.92 mL, 21 mmol) at 0°C under nitrogen atmosphere. The reaction was warmed to rt over 30 min. The reaction was partitioned between ethyl acetate and saturated aqueous ammonium chloride. The organic layer was washed with water, brine, dried over magnesium sulfate and concentrated. Flash chromatography of the resulting residue utilizing a Biotage™ 100G SNAP cartridge and employing a linear gradient: 0-20% EtOAc/hexane and then 20-100% EtOAc/hexane; afforded the title compound as a clear oil. LC-MS: calculated for $C_{13}H_{19}ClN_3O_3SSi$ 487.8, observed m/e: 428.9 $(M+H)^+$ (Rt 2.54/4 min).

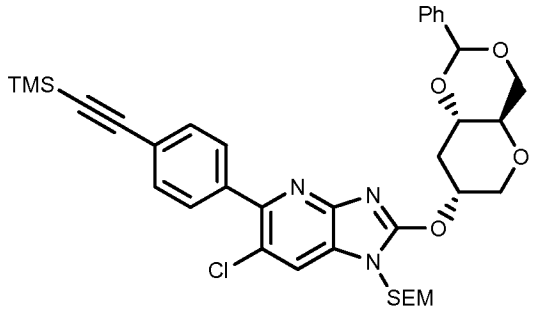
INTERMEDIATE 47



5-(biphenyl-4-yl)-6-chloro-2-(methylsulfonyl)-1H-imidazo[4,5-b]pyridine
Intermediate 45 (50 g, 140 mmol), 4 - Biphenylboronic acid (33.2 g, 168 mmol) and tripotassium phosphate (89 g, 212.3 mmol) were dissolved in THF (500 mL) and water (50 mL), then sparged with N_2 for 20 min. A solution of palladium acetate (3.14g, 14.0 mmol) and n-butyldiadamantylphosphine (Catacxium A, 10g, 28 mmol) in THF (30 mL) was sparged with N_2 for 20 minutes, and then added to the mixture of Intermediate 45, biphenylboronic acid and base. The reaction was heated to 45 °C for 18 h. An additional aliquot of palladium acetate (3.14g, 14.0 mmol) and n-butyldiadamantylphosphine (Catacxium A, 10g, 28 mmol) in THF (30 mL) was sparged with N_2 for 20 minutes and added to the reaction mixture. After 24 h at 45 °C, the reaction was cooled to rt and diluted with EtOAc and brine. The organic layer was concentrated and triturated with THF/MTBE to provide the title compound as a tan solid. LC-MS: calculated

for $C_{19}H_{14}ClN_3O_2S$ 383.05; observed m/e: 383.9 $(M+H)^+$ (Rt 2.01/4 min).

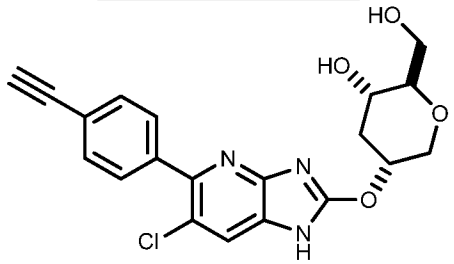
INTERMEDIATE 48



6-chloro-2-(((4aR,7R,8aS)-2-phenylhexahydropyrano[3,2-d][1,3]dioxin-7-yl)oxy)-1-((2-(trimethylsilyl)ethoxy)methyl)-5-(4-((trimethylsilyl)ethynyl)phenyl)-1H-imidazo[4,5-b]pyridine

A mixture of 5-(4-bromophenyl)-6-chloro-2-(((4aR,7R,8aS)-2-phenylhexahydropyrano[3,2-d][1,3]dioxin-7-yl)oxy)-1-((2-(trimethylsilylethoxy)methyl)-1H-imidazo[4,5-b]pyridine (270 mg, 0.401 mmol), ethynyltrimethylsilane (118 mg, 1.203 mmol), $Pd(Ph_3P)_4$ (46.4 mg, 0.040 mmol), copper(I) iodide (7.63 mg, 0.040 mmol) and diisopropylethylamine (0.210 ml, 1.203 mmol) in dioxane (5 ml) was charged in a microwave tube. The tube was sealed and N_2 was bubbled through for 5 min. The reaction was heated at 80 C for 3 hr, and then concentrated. The resulting residue was purified on reverse phase HPLC eluting with 10-70% CH_3CN/H_2O with TFA as an additive to give the title compound. LC-MS: m/e: 690.53 $(M+H)^+$ (Rt 3.35/ 4 min).

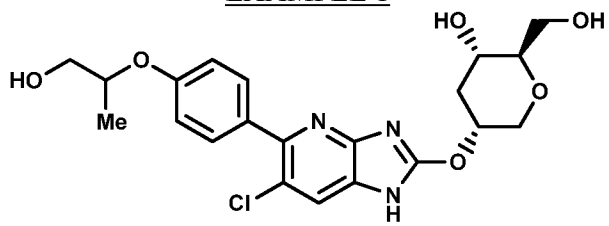
INTERMEDIATE 49



(2R,3S,5R)-5-((6-chloro-5-(4-ethynylphenyl)-1H-imidazo[4,5-b]pyridin-2-yl)oxy)-2-(hydroxymethyl)tetrahydro-2H-pyran-3-ol 6-chloro-2-(((4aR,7R,8aS)-2-phenylhexahydropyrano[3,2-d][1,3]dioxin-7-yl)oxy)-1-((2-(trimethylsilyl)ethoxy)methyl)-5-(4-((trimethylsilyl)ethynyl)phenyl)-1H-imidazo[4,5-b]pyridine (220 mg, 0.319 mmol) was dissolved in formic Acid (4.5 ml, 117 mmol) and sat. potassium hydrogen sulfate (0.5 ml, 0.319 mmol). The mixture was stirred at rt for 1h, and then diluted with EtOAc. Then 3 M NaOH was added until a pH of pH 14 was reached. The mixture was stirred for 15 minutes at rt and then the

layers were separated. The aqueous phase was extracted with EtOAc (x2). The combined organic extracts were washed with brine and dried over Na_2SO_4, filtered and concentrated. The resulting crude product was purified by column chromatorgaphy on Biotage™ 25g column by eluting with 50% EtOAc in DCM to yield the title compound. LC-MS: m/e = 400.32 $(M+H)^+$ (Rt 1.71 / 4 min).

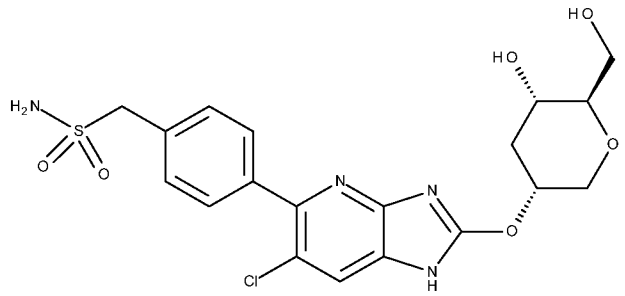
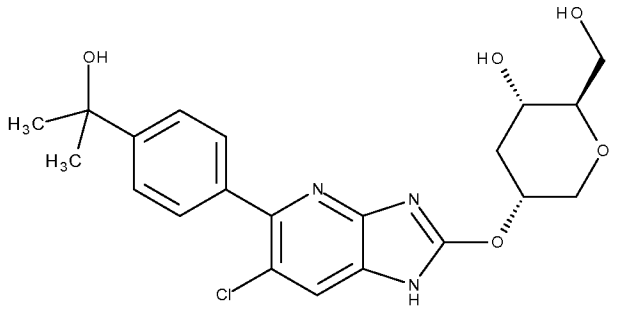
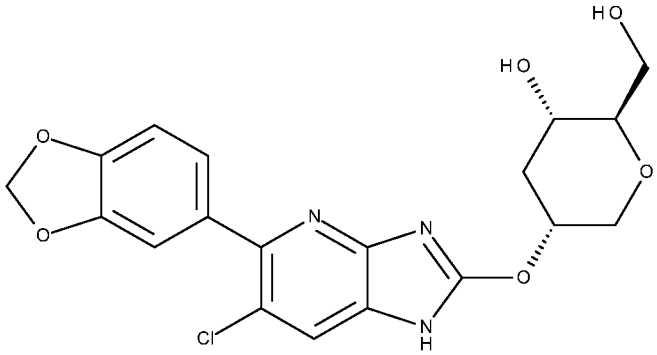
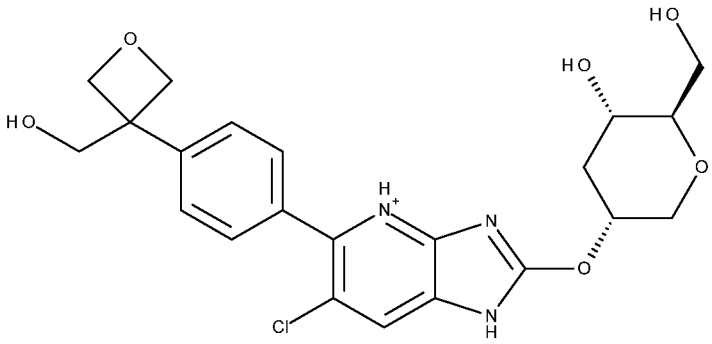
EXAMPLE 1

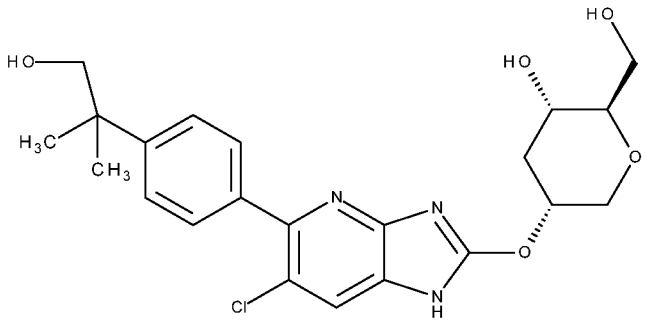
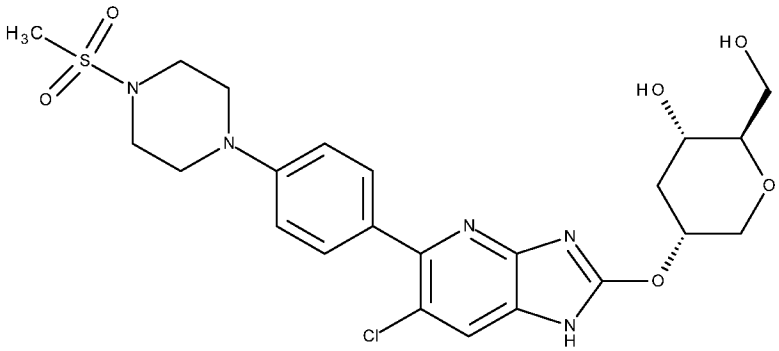
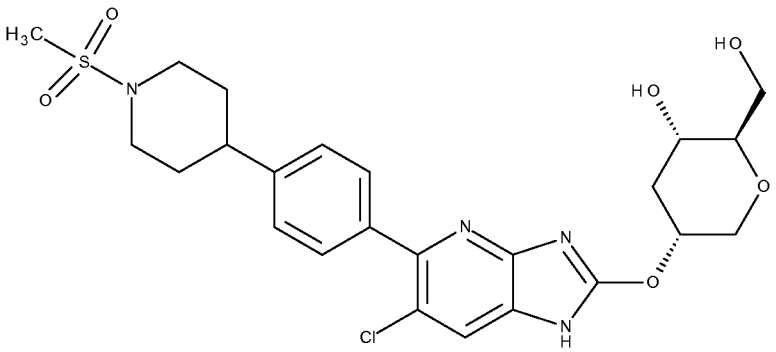
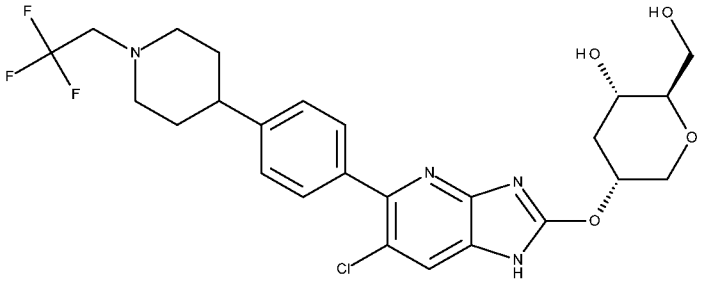


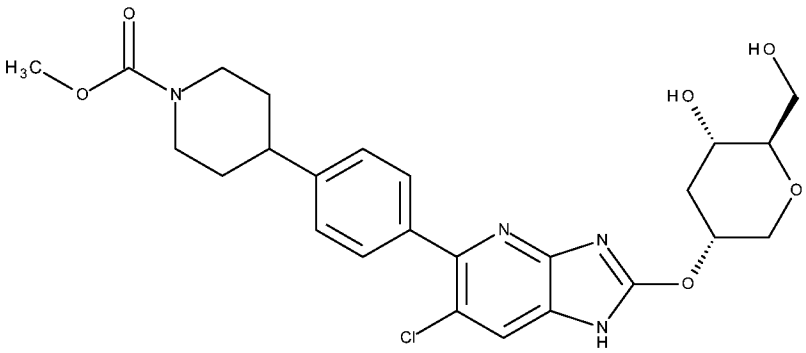
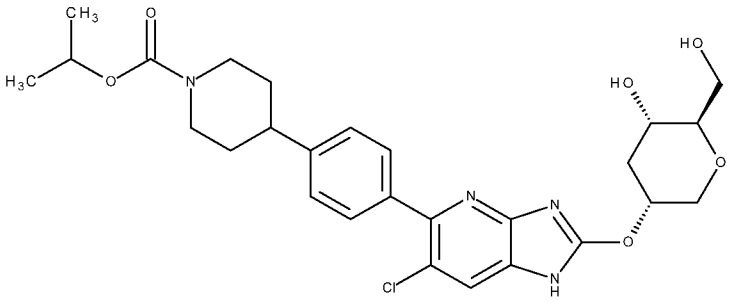
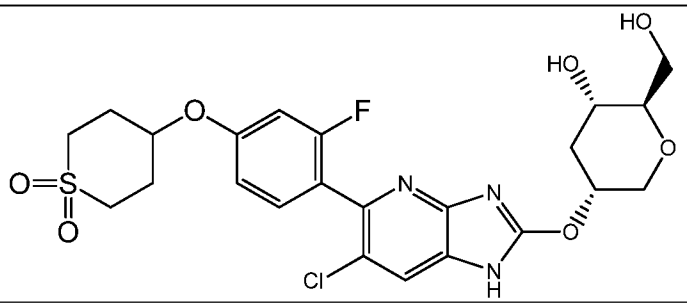
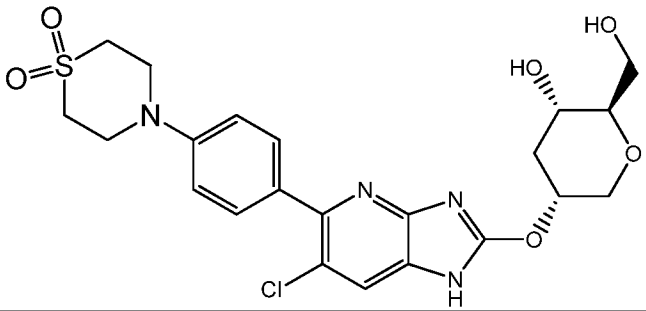
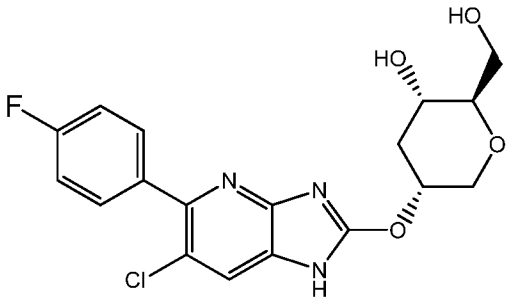
(2R,3S,5R)-5-((6-chloro-5-(4-((1-hydroxypropan-2-yl)oxy)phenyl)-1H-imidazo[4,5-b]pyridin-2-yl)oxy)-2-(hydroxymethyl)tetrahydro-2H-pyran-3-ol 2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)propan-1-ol (61.3 mg, 0.220 mmol), (2R,3S,5R)-5-((6-chloro-5-iodo-1H-imidazo[4,5-b]pyridin-2-yl)oxy)-2-(hydroxymethyl)tetrahydro-2H-pyran-3-ol (75 mg, 0.176 mmol) and potassium phosphate tribasic (150mg, 0.70 mmol) were dissolved in dioxane (600 µl) and water (600 µl). The mixture was sparged with N_2 with for 15 min and [1,1'-Bis(Diphenyl-phosphino)Ferrocene]Dichloropalladium(II) (25.8 mg, 0.035 mmol) was added. The reaction was stirred 3h at 80 °C, then diluted with water and EtOAc. The aqueous phase was extracted with EtOAc (x2), and the combined extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated. The resulting residue was purified by mass directed reverse phase HPLC eluted with acetonitrile in water containing 0.1% formic acid. The desired fractions were combined and lyophilized to give the title compound as a white solid. LC-MS: calculated for $C_{21}H_{24}ClN_3O_6$ 449.14 observed m/e: 449.92 $(M+H)^+$ (Rt 1.03 / 2 min); ^1H NMR δ (ppm) (CD_3OD): 7.77 (s, 1H), 7.58 (d, 2H), 7.02 (d, 2H), 5.10 (septet, 1H), 4.57-4.54 (m, 2H), 4.32 (dd, 1H), 3.88 (d, 1H), 3.73-3.59 (m, 3H), 3.36 (t, 1H), 3.17-3.14 (m, 1H), 2.75-2.73 (m, 1H), 1.67 (dd, 1H), 1.31 (d, 3H).

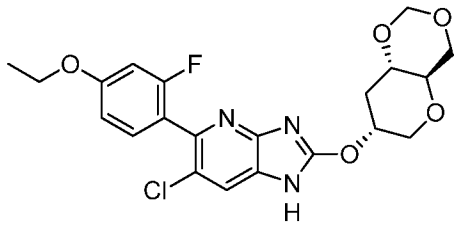
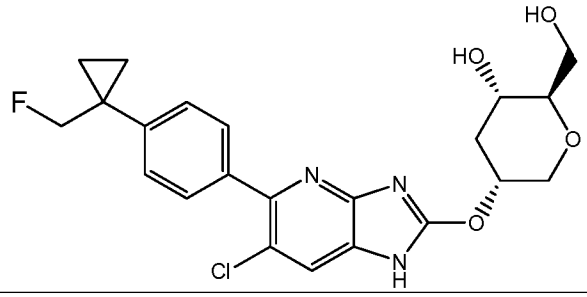
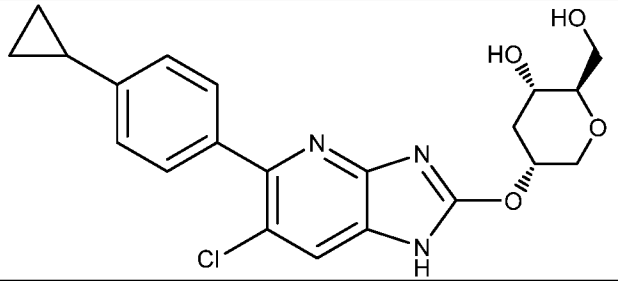
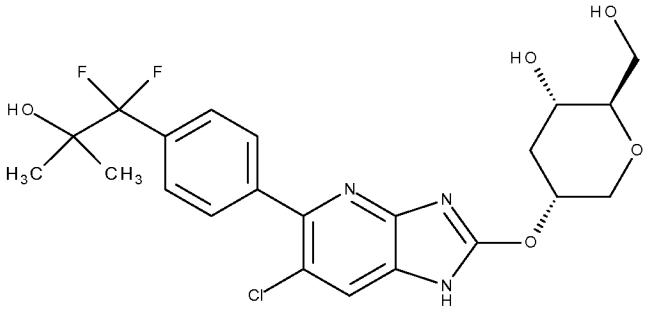
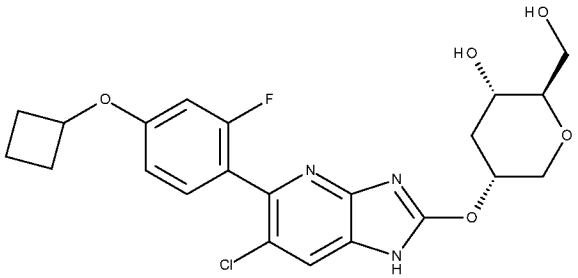
Table 4. Compounds prepared according to the methods in Example 1.

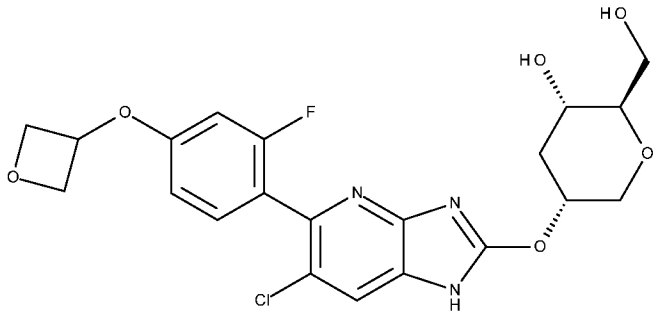
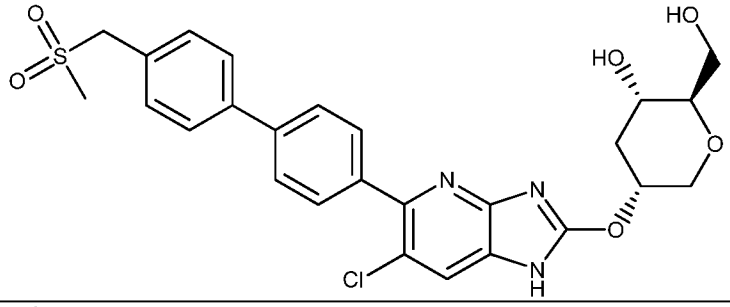
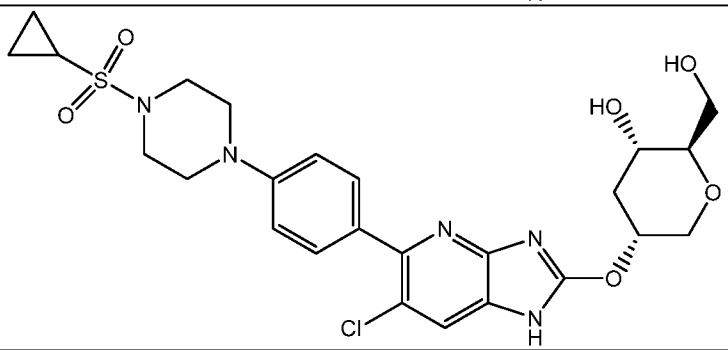
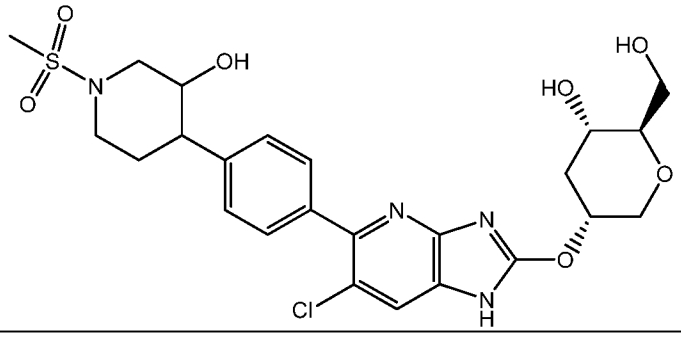
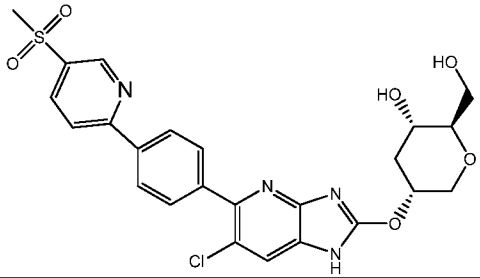
Example Number	Structure	HPLC-mass spectum m/e

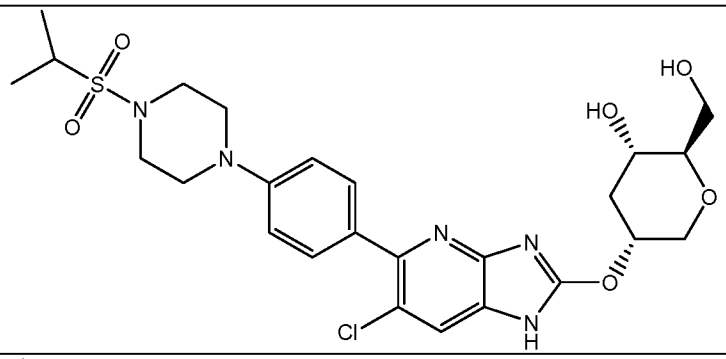
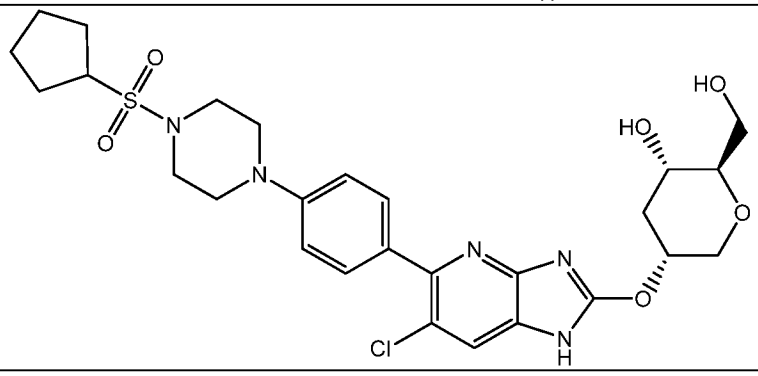
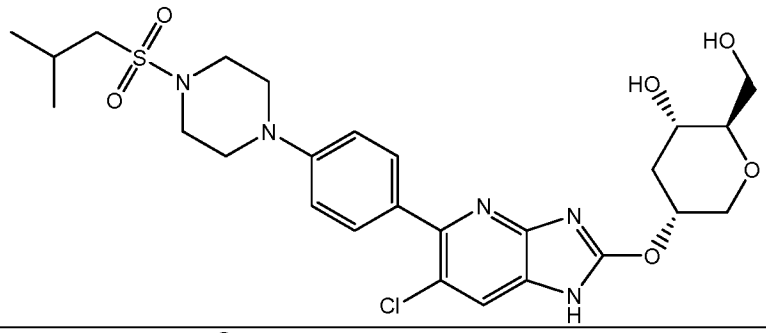
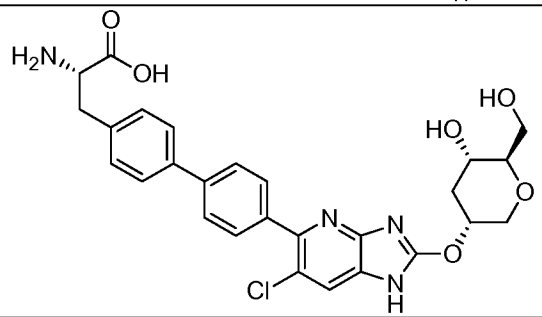
2		468.97
3		433.97
4		419.93
5		461.95

6		447.91
7		537.83
8		537.07
9		541.11

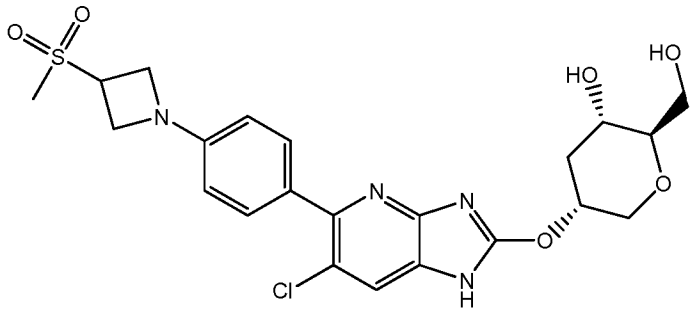
10		517.14
11		545.20
12		542.00
13		509.01
14		393.89

15		542.01
16		447.98
17		416.30
18		483.9
19		463.88

20		465.85
21		543.90
22		563.84
23		552.82
24		531.4

25		565.87
26		591.86
27		580.14
28		539.28

EXAMPLE 29



(2R,3S,5R)-5-((6-chloro-5-(4-(3-(methylsulfonyl)azetidin-1-yl)phenyl)-1H-imidazo[4,5-b]pyridin-2-yl)oxy)-2-(hydroxymethyl)tetrahydro-2H-pyran-3-ol

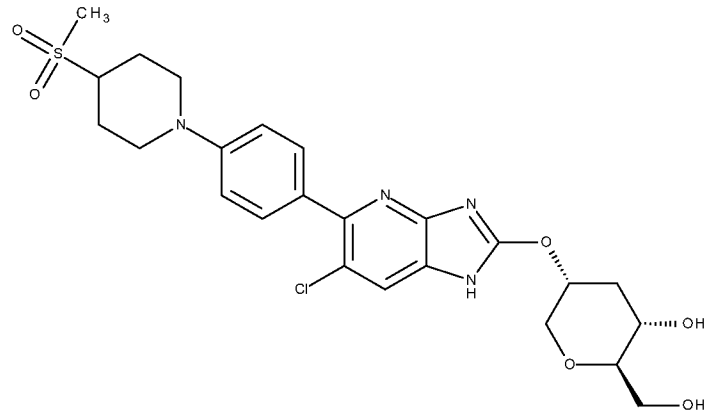
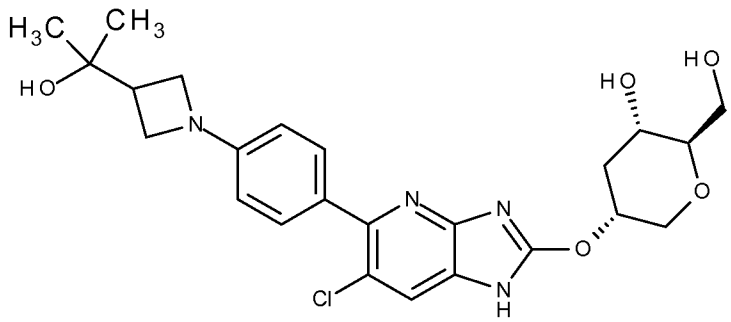
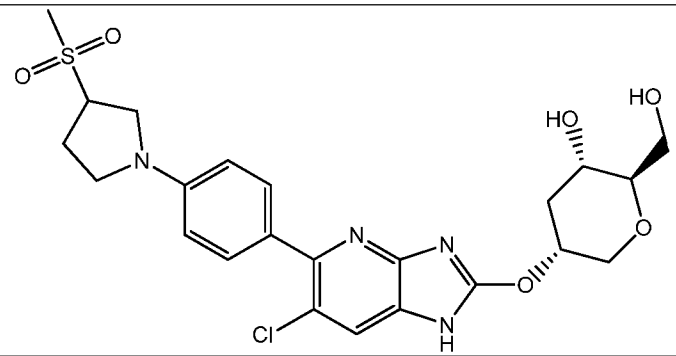
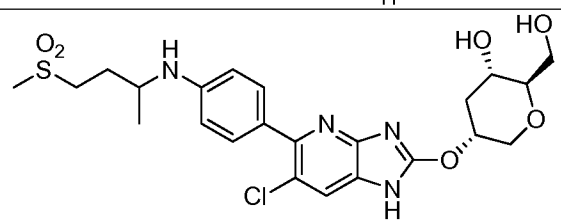
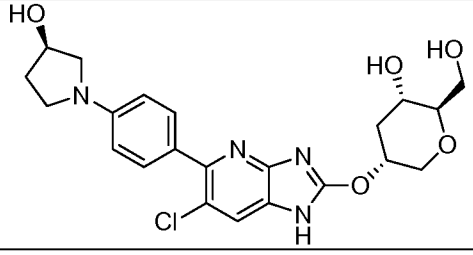
Step A: 3-(methylsulfonyl)azetidine (57.4 mg, 0.334 mmol), 5-(4-bromophenyl)-6-chloro-2-(((4aR,7R,8aS)-2-phenylhexahydropyrano[3,2-d][1,3]dioxin-7-yl)oxy)-1-((2-(trimethylsilyl)-ethoxy)methyl)-1H-imidazo[4,5-b]pyridine (150 mg, 0.223 mmol), $Pd_2(dba)_3$ (10.20 mg, 0.011 mmol), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (12.90 mg, 0.022 mmol), and cesium carbonate (290 mg, 0.891 mmol) were charged in a 10 mL reaction tube. The reaction tube was evacuated and backfilled with N_2 (x3), then dioxane (2229 µl) was added and the reaction was heat to 100 °C overnight. The reaction mixture was dilute with EtOAc and water. The aqueous phase was extracted with EtOAc (x2); and the combined extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The resulting residue was purified by column chromatography on a Biotage™ 10g column eluted with 10% to 100% EtOAc:Hexane. The desired fractions were collected and concentrated.

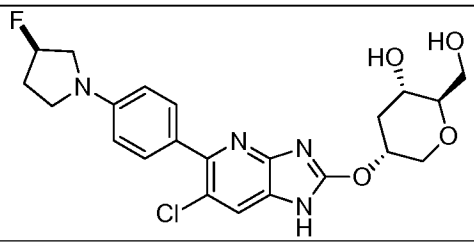
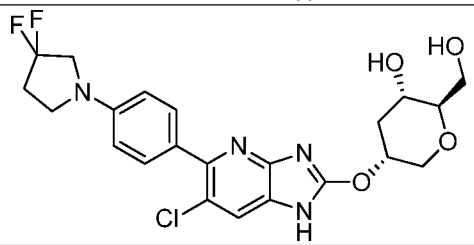
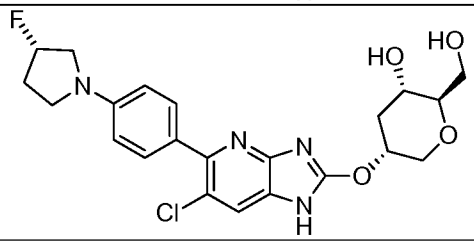
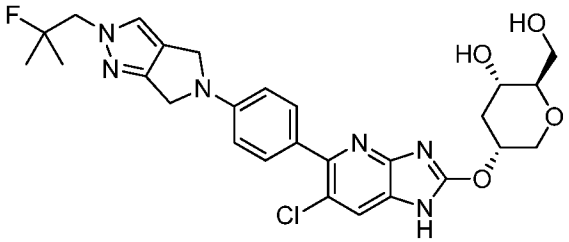
Step B: The resulting residue was dissolved in formic acid (2.7 mL, 70.4 mmol) and aqueous potassium hydrogen sulfate saturated solution (0.3 ml, 0.119 mmol) and stirred 1h at 50 °C.

Step C: The reaction mixture was diluted with EtOAc, and 3 M NaOH was added until pH ~ 14 was reached. After stirring 10 min at rt, saturated NH_4Cl was added until pH 7 was reached. The aqueous phase was then extracted with EtOAc (x2); and the combined extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The resulting residue was purified by mass directed reverse phase HPLC eluted with acetonitrile in water containing 0.1% formic acid. The desired fractions were combined and lyophilized to give the title compound as a white solid. LC-MS: calculated for $C_{22}H_{25}ClN_4O_6S$ 508.12 observed m/e: 509.18 $(M+H)^+$ (Rt 1.39 / 4 min); ^1H NMR δ (ppm) (CD_3OD): 7.75 (s, 1H), 7.54 (d, 2H), 6.61 (d, 2H), 5.10 (septet, 1H), 4.40-4.32 (m, 2H), 4.26-4.20 (m, 4H), 3.87 (dd, 1H), 3.65-3.58 (m, 2H), 3.44 (app t, 1H), 3.30-3.04 (m, 1H), 3.04 (s, 3H), 2.75-2.72 (m, 1H), 1.67 (q, 1H).

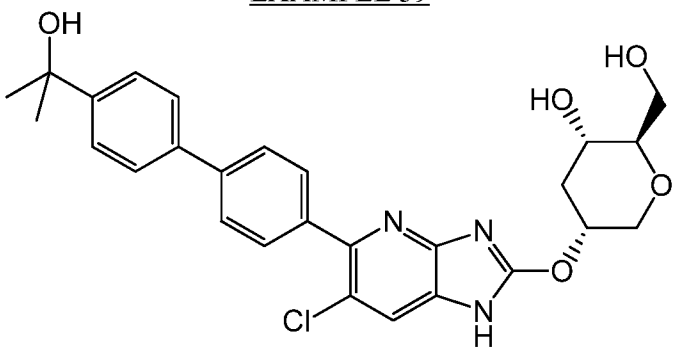
Table 5. Compounds prepared according to the methods in Example 29.

Example Number	Structure	HPLC -mass spectu

		m m/e
30		536.85
31		490.16
32		523.12
33		674.99
34		461.18

35		463.17
36		481.15
37		463.17
38		556.96

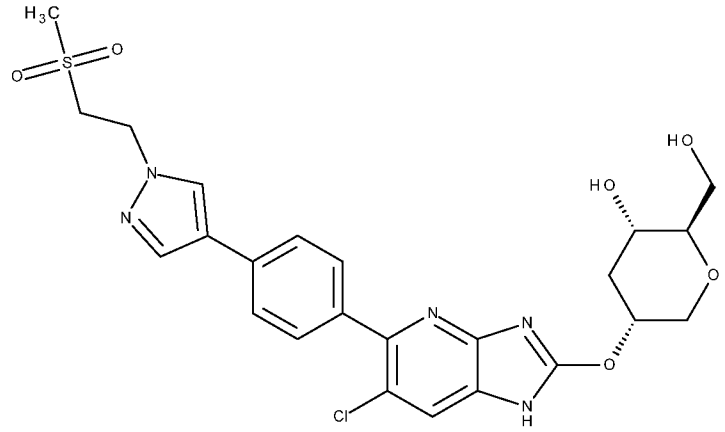
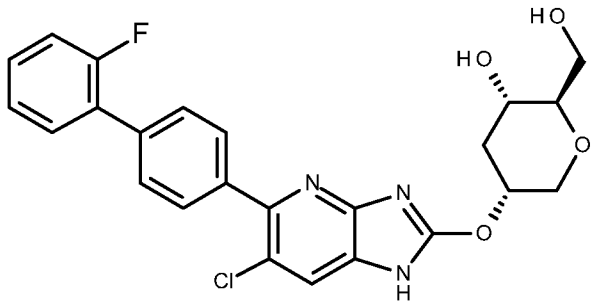
EXAMPLE 39

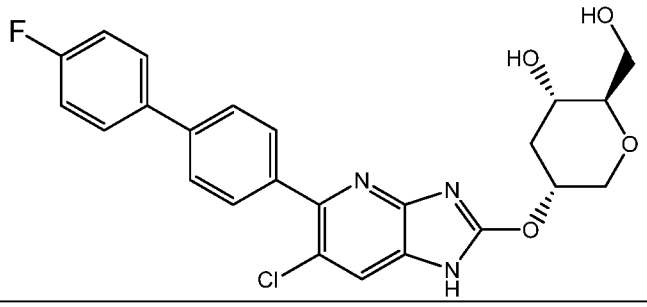
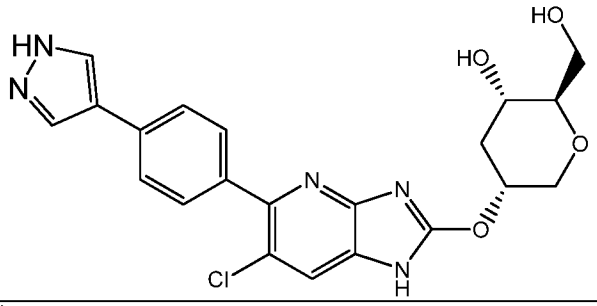
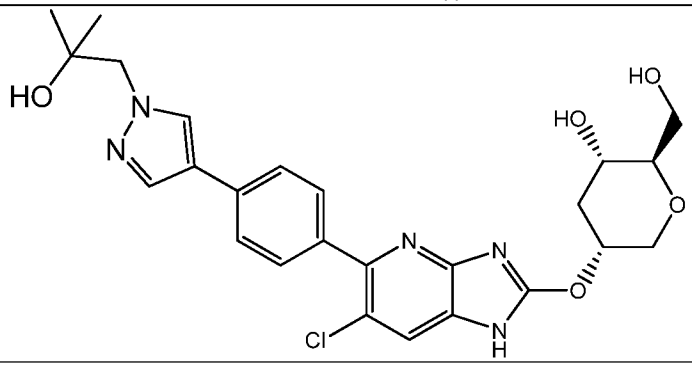
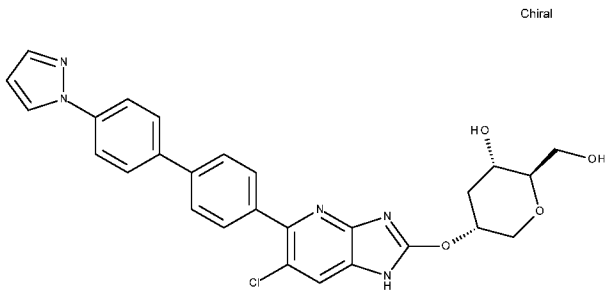
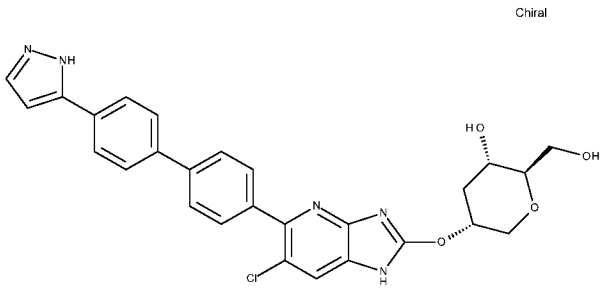


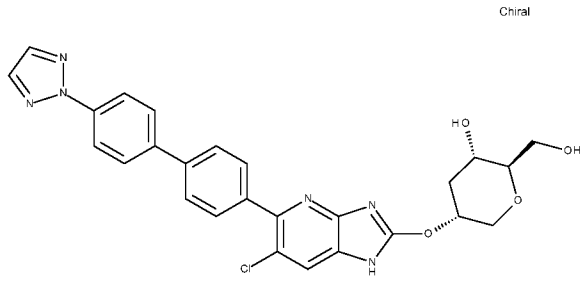
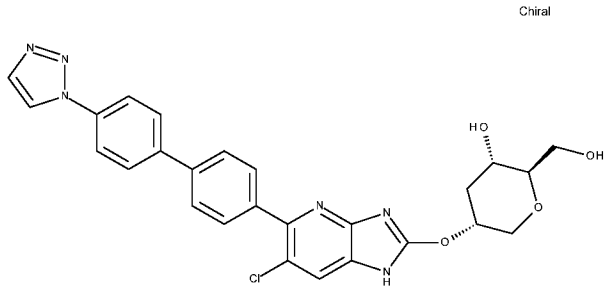
(2R,3S,5R)-5-((6-chloro-5-(4'-(2-hydroxypropan-2-yl)-[1,1'-biphenyl]-4-yl)-1H-imidazo[4,5-b]pyridin-2-yl)oxy)-2-(hydroxymethyl)tetrahydro-2H-pyran-3-ol 2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propan-2-ol (50.4 mg, 0.192 mmol) and (2R,3S,5R)-5-((5-(4-bromophenyl)-6-chloro-1H-imidazo[4,5-b]pyridin-2-yl)oxy)-2-(hydroxymethyl)-tetrahydro-2H-

pyran-3-ol (70 mg, 0.154 mmol) were dissolved in dioxane (600 µl) and water (600 µl). The reaction mixture was sparged with N_2 with 15 min and then [1,1'-Bis(Diphenylphosphino)-Ferrocene]Dichloropalladium (II) (22.53 mg, 0.031 mmol) was added. After stirring 3h at 80 °C, the reaction mixture was diluted with water and EtOAc. The aqueous phase was extracted with EtOAc (x2); and the combined extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The resulting residue was purified by mass directed reverse phase HPLC eluted with acetonitrile in water containing 0.1% formic acid. The desired fractions were combined and lyophilized to give the title compound as a white solid. LC-MS: calculated for $C_{27}H_{28}ClN_3O_5$ 509.17 observed m/e: 509.87 $(M+H)^+$ (Rt 1.12 / 2 min); ^1H NMR δ (ppm) (CD_3OD): 7.82 (s, 1H), 7.72 (s, 4H), 7.66 (d, 2H), 7.59 (d, 2H), 5.11 (septet, 1H), 4.34 (dd, 1H), 3.88 (dd, 1H), 3.66-3.59 (m, 2H), 3.37 (t, 1H), 3.18-3.15 (m, 1H), 2.76-2.74 (m, 1H), 1.68 (q, 1H), 1.58 (s, 6H).

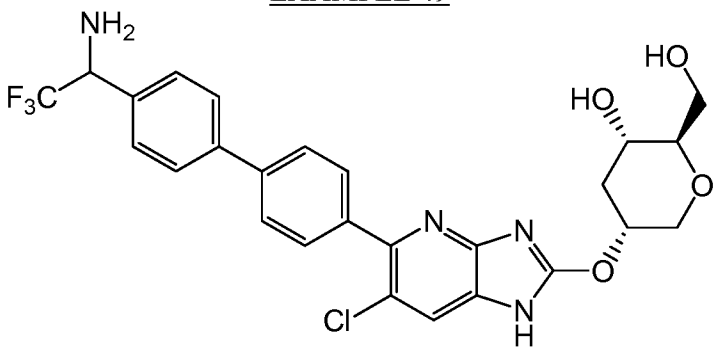
Table 6. Compounds prepared according to the methods in Example 39.

Example Number	Structure	HPLC-mass spectum m/e
40		548.15
41		470.01

42		470.01
43		441.84
44		513.96
45	Chiral 	518.19
46	Chiral 	518.18

47		519.16
48		519.16

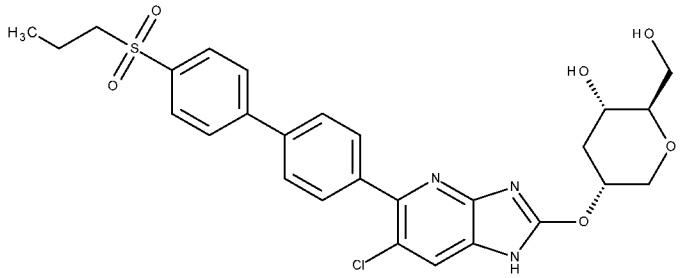
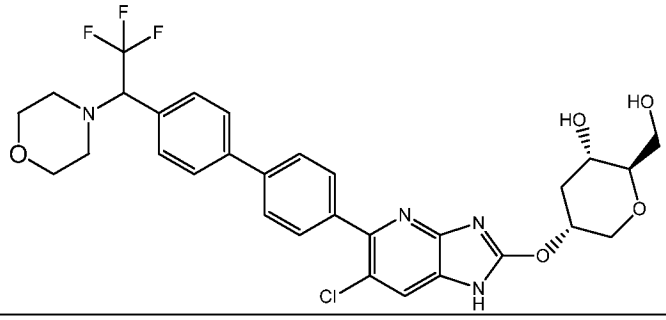
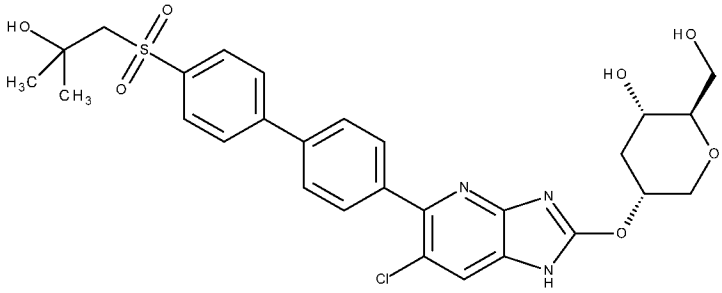
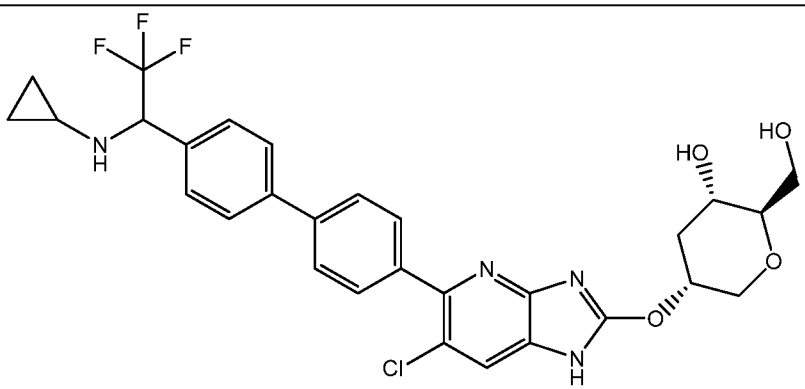
EXAMPLE 49

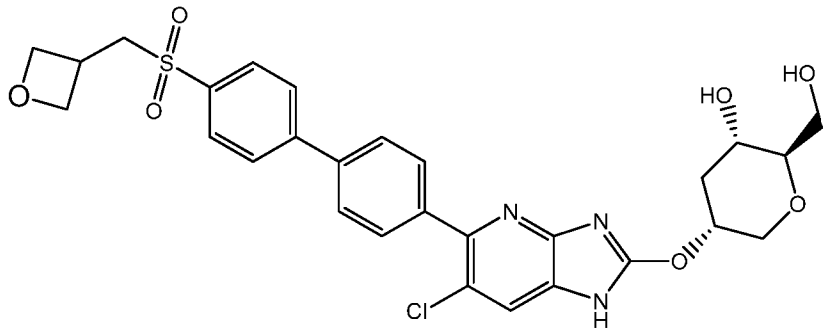
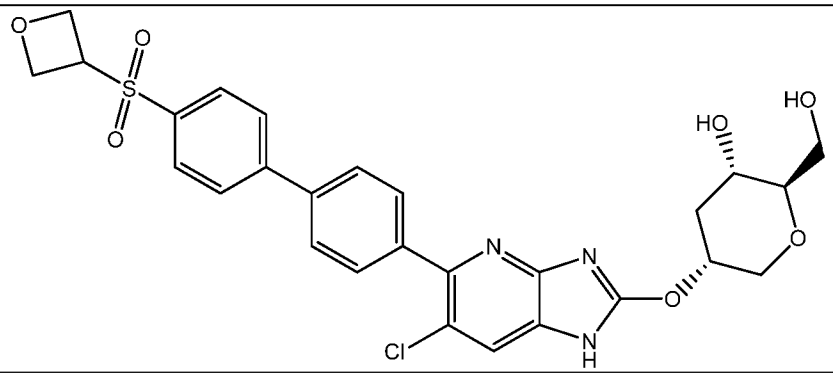
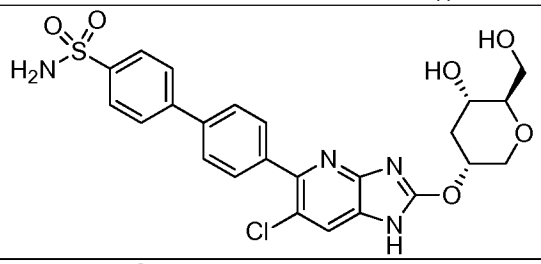
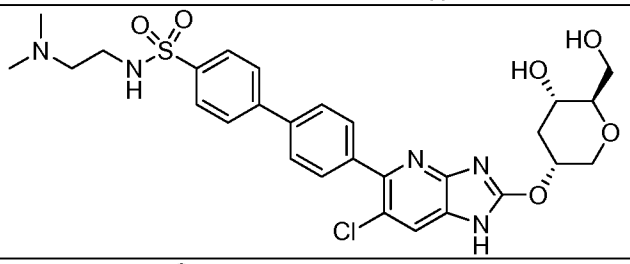
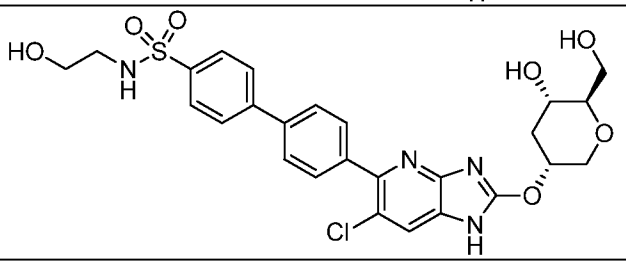


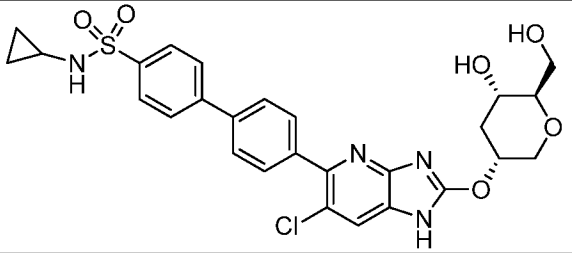
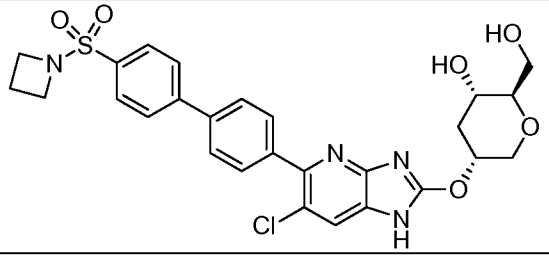
(2R,3S,5R)-5-((5-(4'-(1-amino-2,2,2-trifluoroethyl)-[1,1'-biphenyl]-4-yl)-6-chloro-1H-imidazo[4,5-b]pyridin-2-yl)oxy)-2-(hydroxymethyl)tetrahydro-2H-pyran-3-ol A 10 mL reaction vial was charged with (2R,3S,5R)-5-((6-chloro-5-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1H-imidazo[4,5-b]pyridin-2-yl)oxy)-2-(hydroxymethyl)-tetrahydro-2H-pyran-3-ol (61.2 mg, 0.122 mmol), 1-(4-bromophenyl)-2,2,2-trifluoroethanamine (35 mg, 0.102 mmol), potassium phosphate tribasic (108 mg, 0.509 mmol), and [1,1'-[1,1'-Bis(Diphenyl-phosphino)-Ferrocene]Dichloropalladium (II) (14.89 mg, 0.020 mmol). The reaction vessel was evacuated and backfilled with N_2 (x3), and degassed dioxane (339 µl) and water (339 µl) were added. The reaction was heated to 80 °C for 4h, then diluted with water and EtOAc. The aqueous phase was extracted with EtOAc (x2); and the combined extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The resulting residue was purified by mass directed reverse phase HPLC eluted with acetonitrile in water containing 0.1% formic acid. The desired fractions were combined and lyophilized to give the title compound as a white solid. LC-MS: calculated for $C_{26}H_{24}ClF_3N_4O_4$ 548.14 observed m/e: 549.14 $(M+H)^+$ (Rt 1.55 / 4 min);

^{1}H NMR δ (ppm) (CD_3OD): 7.90 (d, 1H), 7.84 (s, 1H), 7.78 (s, 4H), 7.67 (d, 2H), 5.42 (q, 1H), 5.12 (septet, 1H), 4.35 (dd, 1H), 3.88 (d, 1H), 3.66-3.59 (m, 2H), 3.37 (t, 1H), 3.18-3.15 (m, 1H), 2.76-2.74 (m, 1H), 1.69 (q, 1H).

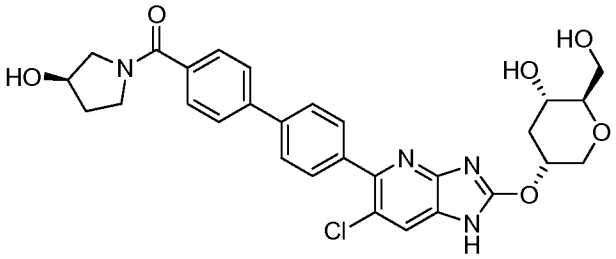
Table 7. Compounds prepared according to the methods in Example 49.

Example Number	Structure	HPLC-mass spectum m/e
50		560.21
51		619.28
52		588.16
53		589.22

54		586.27
55		572.12
56		531.14
57		602.21
58		575.16

59		571.16
60		571.15

EXAMPLE 61



(4'-(6-chloro-2-(((3R,5S,6R)-5-hydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-3-yl)oxy)-1H-imidazo[4,5-b]pyridin-5-yl)-[1,1'-biphenyl]-4-yl)((R)-3-hydroxypyrrolidin-1-yl)methanone

Step A: (R)-(3-hydroxypyrrolidin-1-yl)(4'-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,1'-biphenyl]-4-yl)methanone (1.1 g, 2.80 mmol) and 6-chloro-5-iodo-2-(methylsulfonyl)-1H-imidazo[4,5-b]pyridine (1 g, 2.80 mmol) were dissolved in dioxane (14 ml). To this solution, was added 3M lithium hydroxide (2.80 ml, 8.39 mmol), then water (3.73 ml) and 1,1'-bis(diphenylphosphino)ferrocenedichloro palladium (II) dichloromethane complex (0.205 g, 0.280 mmol). The resulting reaction mixture was purged with N_2 and heated to 80 °C for 2h. The crude reaction was partitioned between EtOAc/NH_4Cl (saturated). The aqueous layer was extracted with EtOAc twice, and the combined organics were washed with brine, dried over Na_2SO_4, and filtered. The organic layer was concentrated to afford the desired product, which was used in the next step without further purification. LC-MS: calculated for $C_{24}H_{21}ClN_4O_4S$ 496.10 observed m/e: 497.2 $(M+H)^+$ (Rt:1.66/4min).

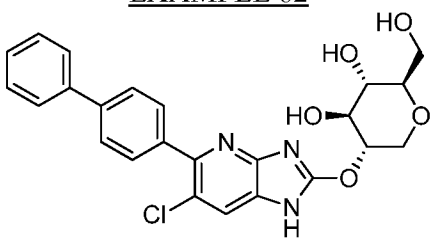
Step B: To a solution of (R)-(4'-(6-chloro-2-(methylsulfonyl)-1H-imidazo[4,5-b]pyridin-5-yl)-[1,1'-biphenyl]-4-yl)(3-hydroxypyrrolidin-1-yl)methanone (930mg, 1.483 mmol) in DMF (10 ml), was added first tetrabutylammonium iodide (602 mg, 1.631 mmol),DIPEA (0.5 ml, 2.86

mmol) and then SEMCl (0.56 ml, 3.16 mmol). The reaction mixture was stirred at 45 °C overnight. The crude reaction was partitioned between water (200 ml) and EtOAc (200 ml), and the layers were separated. The aqueous layer was further extracted with EtOAc (2 x 100ml), and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Chromatography of the resulting residue over silica eluting with 3% MeOH in DCM afforded the desired product. LC-MS: calculated for $C_{36}H_{49}ClN_4O_6SSi_2$ 756.26 observed m/e: 757.32 $(M+H)^+$ (Rt:2.90/4min).

Step C: To a solution of (R)-(4'-(6-chloro-2-(methylsulfonyl)-1-((2 (trimethylsilyl)ethoxy)-methyl)-1H-imidazo[4,5-b]pyridin-5-yl)-[1,1'-biphenyl]-4-yl)(3-((2-(trimethylsilyl)-ethoxy)methoxy)pyrrolidin-1-yl)methanone (150 mg, 0.198 mmol) and (4aR,7R,8aS)-2-phenylhexahydropyrano[3,2-d][1,3]dioxin-7-ol (100 mg, 0.423 mmol) in DMF (2 mL), was added cesium carbonate (150 mg, 0.460 mmol). The reaction mixture was stirred at room temperature for 2 h, then partitioned between water and EtOAc. The organic layer was separated and washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The chromatography of the resulting residue over silica (preparative TLC) eluting with 25% EtOAc in Hexanes afforded the title compound (Rf:0.7) LC-MS: calculated for $C_{48}H_{61}ClN_4O_8Si_2$ 912.37, observed m/e: 913.6 $(M+H)^+$ (Rt:3.30/4min)

Step D: To a solution of (4'-(6-chloro-2-(((4aR,7R,8aS)-2-phenylhexahydropyrano[3,2-d][1,3]dioxin-7-yl)oxy)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazo[4,5-b]pyridin-5-yl)-[1,1'-biphenyl]-4-yl)((R)-3-((2-(trimethylsilyl)ethoxy)methoxy)pyrrolidin-1-yl)methanone (181mg, 0.198mmol) in formic acid (1ml, 26.1mmol) at 0°C, was added saturated potassium hydrogen sulfate (0.2ml, 0.198mmol). The resulting mixture was stirred at room temperature for 48 h. The reaction mixture was then cooled down to 0°C and basified to pH 11 with 2.5N NaOH. The mixture was stirred at room temperature for 30 minutes, then the layers were separated. The aqueous layer was extracted with EtOAc; and the combined organic layers was washed with brine, dried over Na_2SO_4, filtered and concentarted *in vacuo*. The purification of the resulting residue by HPLC eluting with 10-100% MeCN:H_2O 0.1% formic acid afforded the title compound LC-MS: calculated for $C_{29}H_{29}ClN_4O_6$ 564.18 observed m/e: 565.09 $(M+H)^+$ (Rt:1.72/4min).

EXAMPLE 62

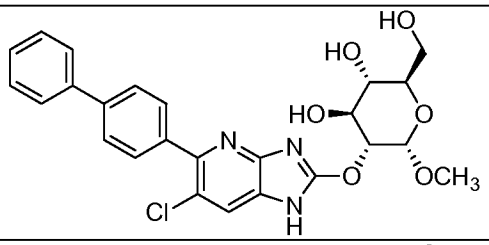
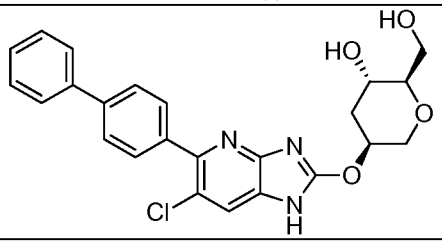


(2R,3S,4S,5S)-5-((5-([1,1'-biphenyl]-4-yl)-6-chloro-1H-imidazo[4,5-b]pyridin-2-yl)oxy)-2-

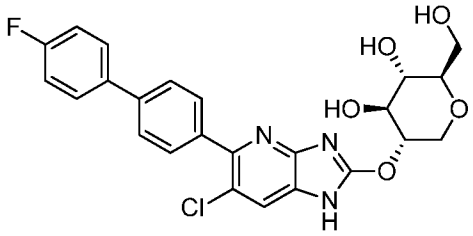
(hydroxymethyl)tetrahydro-2H-pyran-3,4-diol To a solution of 5-([1,1'-biphenyl]-4-yl)-6-chloro-2-(methylsulfonyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazo[4,5-b]pyridine (333 mg, 0.648 mmol) in anhydrous DMF (4.0 mL) under nitrogen at room temperature was added (4aR,7S,8R,8aS)-2-phenylhexahydropyrano[3,2-d][1,3]dioxine-7,8-diol (196 mg, 0.777 mmol) and cesium carbonate (633 mg, 1.943 mmol). After stirring at room temperature for 1.5 h, the mixture was poured into water (50 mL) and extracted with ethyl acetate (2 x 70 mL). The combined organic layers were washed with brine, dried over sodium sulfate, and concentrated under reduced pressure. The resultant orange film was dissolved in formic acid (3.6 mL) and saturated aqueous potassium hydrogen sulfate (0.8 mL) was added. After stirring at room temperature for 72 hours, the mixture was warmed to 50°C for 3.5 h, and then allowed to cool to room temperature. The mixture was slowly poured into saturated aqueous sodium bicarbonate (80 mL) and extracted with ethyl acetate (2 x 100 mL). The combined organic layers were washed with brine (60 mL), dried over sodium sulfate, and concentrated under reduced pressure. The resultant brown oil was dissolved in methanol (10 mL) and THF (3 mL). 1N aqueous lithium hydroxide (5 mL) was added and the mixture was stirred at room temperature. After 30 minutes, the mixture was poured into saturated aqueous sodium bicarbonate (80 mL) and extracted with ethyl acetate (2 x 100 mL). The combined organic layers were washed with brine (60 mL), dried over sodium sulfate, and concentrated under reduced pressure. The resultant beige solid film was chromatographed using a Gilson™ reverse phase preparatory HPLC eluted with MeCN/water/TFA. The slower eluting isomeric product fractions were poured into saturated sodium bicarbonate and extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate, and concentrated under reduced pressure. The resultant clear oil was dissolved in MeCN and water, frozen at -78°C, then lyophilized to dryness to provide the title compound as a white solid. LC-MS: calculated for $C_{24}H_{22}ClN_3O_5$ 467.12, observed m/e: 468.17 $(M+H)^+$ (Rt 1.92/4 min). ^1H NMR δ (ppm)(DMSO-d_6): 7.91 (s, 1H), 7.77-7.73 (m, 6H), 7.49 (t, *J* = 8.0Hz, 2H), 7.39 (t, *J* = 7.5Hz, 1H), 5.44 (br s, 1H), 5.26 (d, *J* = 5.5Hz, 1H), 4.91 (m, 1H), 4.59 (t, *J* = 5.5Hz, 1H), 4.18 (q, *J* = 5.5Hz, 1H), 3.69 (dd, *J* = 11.0Hz, 6.0Hz, 1H), 3.55 (t, *J* = 9.0Hz, 1H), 3.45 (m, 1H), 3.29 (t, *J* = 10.5Hz, 1H), 3.21 (m, 1H), 3.15 (m, 1H).

Table 8. Compounds prepared according to the methods described in Example 62.

Example Number	Structure	HPLC-mass spectrum m/e

63		498.04
64		451.83

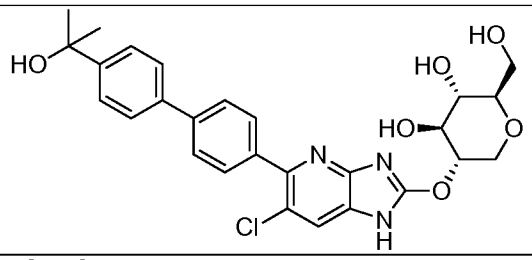
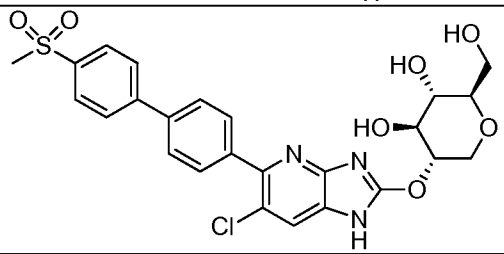
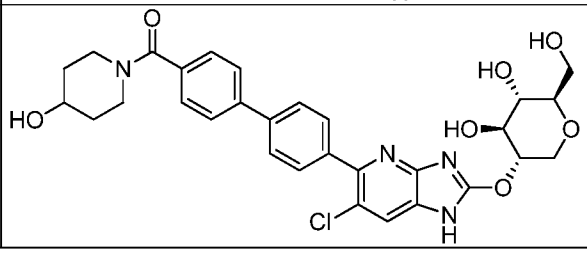
EXAMPLE 65



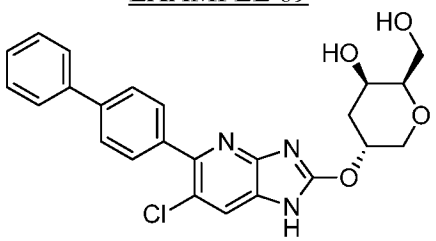
(2R,3S,4S,5S)-5-((6-chloro-5-(4'-fluoro-[1,1'-biphenyl]-4-yl)-1H-imidazo[4,5-b]pyridin-2-yl)oxy)-2-(hydroxymethyl)tetrahydro-2H-pyran-3,4-diol To a stirred solution of (2R,3S,4S,5S)-5-((6-chloro-5-iodo-1H-imidazo[4,5-b]pyridin-2-yl)oxy)-2-(hydroxymethyl)-tetrahydro-2H-pyran-3,4-diol (85 mg, 0.192 mmol) in anhydrous dioxane (1.5 mL) under nitrogen was added 2-(4'-fluoro-[1,1'-biphenyl]-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (69 mg, 0.231 mmol), $PdCl_2$dppf-DCM (31 mg, 0.038 mmol), and 1M aqueous LiOH (0.58 mL, 0.58 mmol). The mixture was cooled, placed under vacuum, and then nitrogen was reintroduced (2x). Then the mixture was heated to 80°C. After stirring for 1 hour, the mixture was allowed to cool. The mixture was diluted with methanol, a few drops of TFA were added to neutralize the solution, and the mixture was filtered using a syringe filter. The filtrate was purified using a Gilson™ reverse phase preparatory HPLC eluted with MeCN/water/TFA. The product fractions were free-based using saturated aqueous sodium bicarbonate solution and ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate, and concentrated under reduced pressure. The resultant white solid was dissolved in MeCN and water, frozen at -78°C, and lyophilized to dryness. The resultant white solid was additionally purified by silica gel chromatography using a Biotage™ 10 g silic gel cartridge eluted with 0-10% methanol in DCM over 10 column volumes with a 5 column volume hold at 10% methanol. The desired fractions were collected, concentrated under reduced pressure, dissolved in MeCN and water, frozen at -78°C, and lyophilized to dryness to give the title compound as a white solid. LC-MS: calculated

for $C_{24}H_{21}ClFN_3O_5$ 485.12, observed m/e: 485.95 $(M+H)^+$ (Rt 1.92/4 min). ^1H NMR δ (ppm)(DMSO-d_6): 7.85 (s, 1H), 7.79-7.76 (m, 2H), 7.75-7.71 (m, 4H), 7.31 (t, *J* = 9Hz, 2H), 5.30 (d, *J* = 6.0Hz, 1H), 4.89 (m, 1H), 4.62 (t, *J* = 6.0Hz, 1H), 4.17 (dd, *J* = 11.0, 5.5Hz, 1H), 3.68 (dd, *J* = 11.0, 5.5Hz, 1H), 3.55 (t, *J* = 9.0Hz, 1H), 3.45 (m, 1H), 3.28 (t, *J* = 11.0Hz, 1H), 3.21 (m, 1H), 3.14 (m, 1H).

Table 9. Compounds prepared according to the methods described in Example 65.

Example Number	Structure	HPLC-mass spectrum m/e
66		526.03
67		546.01
68		595.33

EXAMPLE 69



(2R,3R,5R)-5-((5-([1,1'-biphenyl]-4-yl)-6-chloro-1H-imidazo[4,5-b]pyridin-2-yl)oxy)-2-(hydroxymethyl)tetrahydro-2H-pyran-3-ol

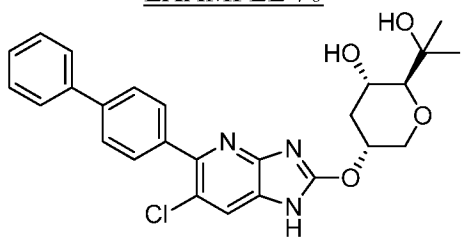
Step A. (2R,3S,5R)-5-((5-([1,1'-biphenyl]-4-yl)-6-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazo[4,5-b]pyridin-2-yl)oxy)-2-(hydroxymethyl)tetrahydro-2H-pyran-3-ol. To a stirred solution of 5-([1,1'-biphenyl]-4-yl)-6-chloro-2-(((4aR,7R,8aS)-2-phenylhexahydropyrano[3,2-d][1,3]dioxin-7-yl)oxy)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazo[4,5-b]pyridine (476 mg, 0.710 mmol) under nitrogen in anhydrous DCM (6.0 mL) was added 4A molecular sieves (1.6 g). The mixture was cooled to 0°C, then triethylsilane (0.85 mL, 619 mg, 5.33 mmol) and TFA (0.41 mL, 607 mg, 5.33 mmol) were added. The mixture was stirred at 0°C for 1.5 hours, and then allowed to stir 1 hour at room temperature. The mixture was then cooled to 0°C and a saturated aqueous solution of potassium carbonate (30 mL) was added dropwise over 3 minutes. After stirring at room temperature for an additional 5 minutes, the mixture was filtered, diluted with saturated aqueous sodium bicarbonate (30 mL), and extracted with ethyl acetate (2 x 150 mL). The combined organic layers were washed with brine (60 mL), dried over sodium sulfate, and concentrated under reduced pressure. The resultant residue was chromatographed using a Biotage™ 25g silica gel cartridge eluted with 0-100% EtOAc in 1:1 Hexane/DCM over 25 column volumes with a 15 column volume hold at 100% EtOAc. The product fractions were combined and concentrated under reduced pressure to give the desired product as a white solid. LC-MS: calculated for $C_{30}H_{36}ClN_3O_5Si$ 581.21, observed m/e: 582.31 $(M+H)^+$ (Rt 2.66/4 min).

Step B. (2R,3S,5R)-5-((5-([1,1'-biphenyl]-4-yl)-6-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazo[4,5-b]pyridin-2-yl)oxy)-2-(((tert-butyldimethylsilyl)oxy)methyl)tetrahydro-2H-pyran-3-ol. To a stirred solution of (2R,3S,5R)-5-((5-([1,1'-biphenyl]-4-yl)-6-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazo[4,5-b]pyridin-2-yl)oxy)-2-(hydroxymethyl)tetrahydro-2H-pyran-3-ol (242 mg, 0.416 mmol) in anhydrous DMF (2.0 mL) under nitrogen was added DMAP (10 mg, 0.083 mmol) and triethylamine (0.13 mL, 93 mg, 0.915 mmol). The mixture was cooled to 0°C, then TBSCl (132 mg, 0.873 mmol) was added as a solution in anhydrous DCM (0.5 mL). After stirring at 0°C for 0.5 hours, methanol (5 mL) was added and the mixture was poured into saturated aqueous sodium bicarbonate (75 mL). The mixture was extracted with ethyl acetate (2 x 100 mL), and the combined organic layers were washed with brine (50 mL), dried over sodium sulfate, and concentrated under reduced pressure. The resultant oil was chromatographed using a Biotage™ 10g silica gel cartridge eluted with 0-20% EtOAc in 1:1 Hexane/DCM over 20 column volumes. The combined product fractions were concentrated under reduced pressure and dried under high vacuum overnight to provide the desired product as a white solid film. LC-MS: calculated for $C_{36}H_{50}ClN_3O_5Si_2$ 695.30, observed m/e: 696.39 $(M+H)^+$ (Rt 3.33/4 min).

Step C. (2R,3R,5R)-5-((5-([1,1'-biphenyl]-4-yl)-6-chloro-1H-imidazo[4,5-b]pyridin-2-yl)oxy)-2-(hydroxymethyl)tetrahydro-2H-pyran-3-ol. To a stirred solution of (2R,3S,5R)-5-((5-([1,1'-biphenyl]-4-yl)-6-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazo[4,5-b]pyridin-2-yl)oxy)-2-(((tert-butyldimethylsilyl)oxy)methyl)tetrahydro-2H-pyran-3-ol (46 mg, 0.066 mmol)

in anhydrous DCM (1.0 mL) under nitrogen was added pyridine (0.11 mL, 11 mg, 0.132 mmol) and Dess-Martin Periodinane (42 mg, 0.099 mmol). The mixture was stirred at room temperature for 30 minutes, then loaded directly onto a Biotage™ 10g silica gel cartridge which was eluted with 0-30% EtOAc in 1:1 Hexane/DCM over 20 column volumes. The product fractions were combined and concentrated under reduced pressure to provide the desired product as a clear, oily film (18 mg). The oily film was dissolved in anhydrous THF (1.0 mL) and cooled to 0°C, than a 1M solution of L-selectride (0.03 mL, 0.03 mmol) in THF was added. After 1.5 hours, the mixture was poured into water (20 mL) and extracted with EtOAc (2 x 40 mL). The combined organic layers were washed with brine (20 mL), dried over sodium sulfate, and concentrated under reduced pressure. The resultant oily film was dissolved in formic acid (1.7 mL). Saturated aqueous potassium hydrogen sulfate (0.3 mL) was added and the mixture was stirred at room temperature for 1 hour, then at 50°C for 20 minutes. The mixture was allowed to cool to room temperature, poured into saturated aqueous sodium bicarbonate (50 mL), and extracted with EtOAC (2 x 50 mL). The combined organic layers were dried over sodium sulfate, concentrated under reduced pressure, and dried under high vacuum for 20 minutes. The resultant yellow oil was dissolved in methanol (1.0 mL), then 1N aqueous LiOH (0.1 mL) was added. The mixture was stirred at room temperature for 10 minutes, then acidified with TFA to pH 5, and purified using a Gilson™ preparatory reverse phase HPLC eluted with MeCN/water/TFA. The product fractions were lyophilized to dryness to provide the title compound as a white solid. LC-MS: calculated for $C_{24}H_{22}ClN_3O_4$ 451.13, observed m/e: 452.02 $(M+H)^+$ (Rt 1.96/4 min). ^1H NMR δ (ppm)(CD_3OD): 7.83 (s, 1H), 7.72 (m, 4H), 7.68 (d, J = 8.0Hz, 2H), 7.46 (t, J = 7.5Hz, 2H), 7.35 (t, J = 7.5Hz, 1H), 5.46 (heptet, J = 5.0Hz, 1H), 4.39 (ddd, J = 10.5, 4.9, 1.8Hz, 1H), 4.07 (br. m, 1H), 3.71 (m, 2H), 3.50 (m, 1H), 3.46 (t, J = 10.5Hz, 1H), 2.57 (m, 1H), 1.91 (m, 1H).

EXAMPLE 70



(2S,3S,5R)-5-((5-([1,1'-biphenyl]-4-yl)-6-chloro-1H-imidazo[4,5-b]pyridin-2-yl)oxy)-2-(2-hydroxypropan-2-yl)tetrahydro-2H-pyran-3-ol

Step A. 5-([1,1'-biphenyl]-4-yl)-6-chloro-2-(((3R,5S,6R)-5-((triethylsilyl)oxy)-6-(((triethylsilyl)oxy)methyl)tetrahydro-2H-pyran-3-yl)oxy)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazo[4,5-b]pyridine. To a stirred solution of (2R,3S,5R)-5-((5-([1,1'-biphenyl]-4-yl)-6-chloro-1H-imidazo[4,5-b]pyridin-2-yl)oxy)-2-(hydroxymethyl)tetrahydro-2H-pyran-3-ol (256

mg, 0.566 mmol) and triethylamine (0.40 mL, 287 mg, 2.83 mmol) in anhydrous DMF (3.0 mL) under nitrogen at 0°C was added TESCl (0.38 mL, 342 mg, 2.266 mmol), dropwise over 1 minute. The mixture was allowed to stir at room temperature for 2.5 hours, then poured into saturated aqueous sodium bicarbonate (40 mL) and extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with brine (40 mL), dried over sodium sulfate, and concentrated under reduced pressure. After drying under high vacuum for 1 hour, the resultant clear oil was dissolved in anhydrous DMF (3.0 mL). To this solution was added triethylamine (0.16 mL, 115 mg, 1.133 mmol) and SEMCl (0.12 mL, 113 mg, 0.680 mmol). After stirring at room temperature for 30 minutes, the mixture was poured into saturated aqueous sodium bicarbonate (40 mL) and extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with brine (40 mL), dried over sodium sulfate, and concentrated under reduced pressure to provide the desired product as a yellow oil. LC-MS: calculated for $C_{42}H_{64}ClN_3O_5Si_3$ 809.38, observed m/e: 810.46 $(M+H)^+$ (Rt 3.80/4 min).

Step B. ((2R,3S,5R)-5-((5-([1,1'-biphenyl]-4-yl)-6-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazo[4,5-b]pyridin-2-yl)oxy)-3-((triethylsilyl)oxy)tetrahydro-2H-pyran-2-yl)methanol. To a stirred solution of 5-([1,1'-biphenyl]-4-yl)-6-chloro-2-(((3R,5S,6R)-5-((triethylsilyl)oxy)-6-(((triethylsilyl)oxy)-methyl)tetrahydro-2H-pyran-3-yl)oxy)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazo[4,5-b]pyridine (99 mg, 0.122 mmol) under nitrogen in DCM (2.0 mL) and methanol (2.0 mL) at -20°C was added pyridinium-paratoluenesulfonic acid (6 mg, 0.024 mmol). After stirring for 2.5 hours at -20°C, the mixture was poured into saturated aqueous sodium bicarbonate (40 mL) and extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with brine (40 mL), dried over sodium sulfate, and concentrated under reduced pressure. The resultant oil was chromatographed using a Biotage™ 20g (2 x 10g in series) silica gel cartridge eluted with 0-20% EtOAc in 1:1 Hexane/DCM over 15 column volumes, then 20-100% EtOAc over 10 column volumes. The desired SEM regiosiomeric products were combined and concentrated under reduced pressure to provide the title compound as a clear oil. LC-MS: calculated for $C_{36}H_{50}ClN_3O_5Si_2$ 695.30, observed m/e: 696.23 $(M+H)^+$ (Rt 3.26/4 min, minor isomer), 696.23 $(M+H)^+$ (Rt 3.39/4 min, major isomer).

Step C. (2S,3S,5R)-5-((5-([1,1'-biphenyl]-4-yl)-6-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazo[4,5-b]pyridin-2-yl)oxy)-3-((triethylsilyl)oxy)tetrahydro-2H-pyran-2-carbaldehyde. To a stirred solution of ((2R,3S,5R)-5-((5-([1,1'-biphenyl]-4-yl)-6-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazo[4,5-b]pyridin-2-yl)oxy)-3-((triethylsilyl)oxy)tetrahydro-2H-pyran-2-yl)methanol (56 mg, 0.080 mmol) in anhydrous DCM under nitrogen was added pyridine (13 µL, 12.7 mg, 0.161 mmol) and Dess-Martin periodinane (51 mg, 0.121 mmol). After stirring at room temperature for 2 hours, the mixture was directly loaded onto a Biotage™ 10 g silica gel cartridge and eluted with 0-20% EtOAc in 1:1 Hexane/DCM over 20 column volumes. The desired SEM regioisomeric product fractions were

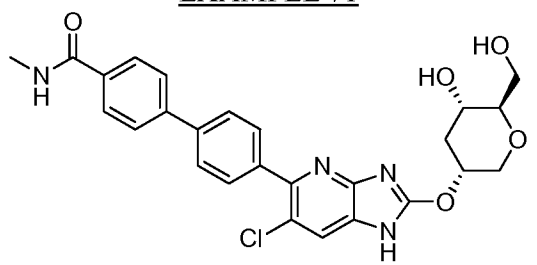
combined and concentrated under reduced pressure to provide the title compound as a clear oil. LC-MS: calculated for $C_{36}H_{48}ClN_3O_5Si_2$ 693.28, observed m/e: 694.25 $(M+H)^+$ (Rt 3.23/4 min, minor isomer), 694.23 $(M+H)^+$ (Rt 3.31/4 min, major isomer).

Step D. (R)-1-((2R,3S,5R)-5-((5-([1,1'-biphenyl]-4-yl)-6-chloro-1-((2-(trimethylsilyl)ethoxy)-methyl)-1H-imidazo[4,5-b]pyridin-2-yl)oxy)-3-((triethylsilyl)oxy)tetrahydro-2H-pyran-2-yl)ethanol. To a stirred solution of (2S,3S,5R)-5-((5-([1,1'-biphenyl]-4-yl)-6-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazo[4,5-b]pyridin-2-yl)oxy)-3-((triethylsilyl)oxy)-tetrahydro-2H-pyran-2-carbaldehyde (32 mg, 0.046 mmol) in anhydrous THF(2.0 mL) under nitrogen at 0°C was added a 3M solution of methylmagnesium bromide (30 µL, 0.090 mmol). The solution was allowed to stir at room temperature overnight and additional methylmagnesium bromide solution was added portionwise until starting material was consumed. The mixture was poured into saturated aqueous sodium bicarbonate (30 mL) and extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with brine (40 mL), dried over sodium sulfate, and concentrated under reduced pressure. The resultant clear oil was chromatographed using a Biotage™ 10g silica gel cartridge eluted with 0-20% EtOAc in 1:1 Hexane/DCM over 20 column volumes. The desired SEM regioisomeric products were combined and concentrated under reduced pressure to provide a clear, colorless oily film. LC-MS: calculated for $C_{37}H_{52}ClN_3O_5Si_2$ 709.31, observed m/e: 710.35 $(M+H)^+$ (Rt 3.34/4 min, minor isomer), 710.35 $(M+H)^+$ (Rt 3.48/4 min, major isomer).

Step E. (2S,3S,5R)-5-((5-([1,1'-biphenyl]-4-yl)-6-chloro-1H-imidazo[4,5-b]pyridin-2-yl)oxy)-2-(2-hydroxypropan-2-yl)tetrahydro-2H-pyran-3-ol. To a stirred solution of (R)-1-((2R,3S,5R)-5-((5-([1,1'-biphenyl]-4-yl)-6-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazo[4,5-b]pyridin-2-yl)oxy)-3-((triethylsilyl)oxy)tetrahydro-2H-pyran-2-yl)ethanol (21 mg, 0.030 mmol) in anhydrous DCM (1.75 mL) under nitrogen was added pyridine (5 µL, 5 mg, 0.060 mmol) and Dess-Martin periodinane (19 mg, 0.045 mmol). After 1.5 hours, the mixture was filtered and concentrated under reduced pressure. The resultant oily film was dissolved in anhydrous THF (2.0 mL) and cooled to 0°C. Then 3M methylmagnesium bromide (~0.10 mL, 0.30 mmol) in THF was added portionwise until all of the ketone intermediate was consumed. The reaction mixture was poured into water (30 mL) and extracted with EtOAc (2 x 30 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure to provide a yellow oily film. The oily film was dissolved in formic acid (1.8 mL) and saturated aqueous potassium hydrogen sulfate (0.2 mL). The reaction mixture was stirred at 50°C for 1 hour, then allowed to cool to room temperature. The mixture was then poured into saturated aqueous sodium bicarbonate (30 mL), and extracted with EtOAc (2 x 30 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. The resultant white solid was dissolved in methanol (10 mL) and treated with 5N NaOH (0.5 mL). After stirring at room temperature for 15 minutes, the mixture was poured into water and

neutralized with 1N aquoues HCl to pH 6. The mixture was extracted with EtOAc (2 x 40 mL). The combined organic layers were washed with brine (30 mL), dried over sodium sulfate, and concentrated under reduced pressure. The resultant residue was chromatographed using a Biotage™ 20g (2 x 10g in series) silica gel cartridge eluted with 0-10% methanol in DCM over 20 column volumes. The combined product fractions were concentrated under reduced pressure, dissolved in MeCN and water, frozen at -78°C, and lyophilized to dryness to provide the title compound as a white solid. LC-MS: calculated for $C_{26}H_{26}ClN_3O_4$ 479.16, observed m/e: 480.10 $(M+H)^+$ (Rt 2.22/4 min). ^1H NMR δ (ppm)(DMSO-d_6): 7.92 (s, 1H), 7.74 (m, 6H), 7.49 (t, *J* = 8.0Hz, 2H), 7.39 (dd, *J* = 7.5, 7.5Hz, 1H), 5.30 (s, 1H), 5.02 (heptet, *J* = 5.5Hz, 1H), 4.25 (m,1H), 3.74 (m, 1H), 3.29 (t, *J* = 10.0Hz, 1H), 2.92 (d, *J* = 10Hz, 1H), 2.60 (m, 1H), 1.64 (q, *J* = 11.5Hz, 1H), 1.18 (s, 3H), 1.15 (s, 3H).

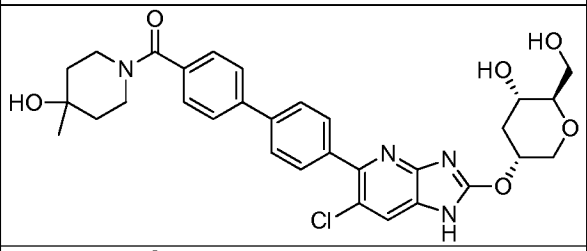
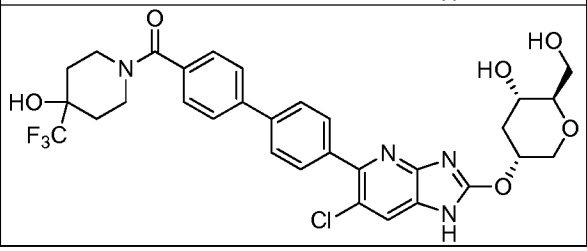
EXAMPLE 71



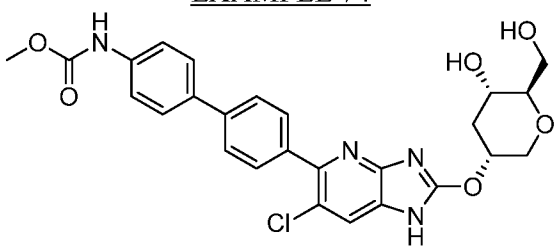
4'-(6-chloro-2-(((3R,5S,6R)-5-hydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-3-yl)oxy)-1H-imidazo[4,5-b]pyridin-5-yl)-N-methyl-[1,1'-biphenyl]-4-carboxamide To a stirred solution of 4'-(6-chloro-2-(((4aR,7R,8aS)-2-phenylhexahydropyrano[3,2-d][1,3]dioxin-7-yl)oxy)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazo[4,5-b]pyridin-5-yl)-[1,1'-biphenyl]-4-carboxylic acid (30 mg, 0.042 mmol) under nitrogen in anhydrous DMF (1.0 mL) at room temperature was added EDC (124 mg, 0.690 mmol), HOBT (93 mg, 0.690 mmol), and triethylamine (0.20 mL, 15 mg, 1430 mmol). The mixture was allowed to stir at room temperature while a stream of methylamine gas was bubbled through. After 20 minutes, the mixture was stored overnight in the freezer. Upon warming to room temperature, the mixture was poured into saturated aqueous sodium bicarbonate (30 mL) and extracted with EtOAc (2 x 40 mL). The combined organic layers were washed with brine (20 mL), dried over sodium sulfate, and concentrated under reduced pressure. The resultant yellow oil was chromatographed using a Biotage™ 20g (2 x 10 g in series) silica gel cartridge eluted with 0-10% methanol in DCM over 20 column volumes. The product fractions were combined and concentrated under reduced pressure. The resultant yellow oily film was dissolved in formic acid (1.8 mL) and saturated aqueous potassium hydrogen sulfate (0.2 mL). The mixture was stirred at 50°C for 1 hour, then allowed to cool to room temperature. The mixture was poured into saturated aqueous sodium bicarbonate (30 mL) and extracted with EtOAc (2 x 30 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. The resultant white solid was dissolved in methanol (5

mL) and treated with 5N aqueous NaOH (0.2 mL). After stirring at room temperature for 15 minutes, the mixture was poured into water and neutralized with 1N aqueous HCl to pH 7. The mixture was extracted with EtOAc (2 x 40 mL); and the combined organic layers were washed with brine (30 mL), dried over sodium sulfate, and concentrated under reduced pressure. The resultant white solid was chromatographed using a Biotage™ 10g silica gel cartridge eluted with 0-10% methanol in DCM over 10 column volumes with a 15 column volume hold at 10% methanol. The combined product fractions were concentrated under reduced pressure, and the resultant oil was dissolved in MeCN and water, frozen at -78°C, then lyophilized to dryness to provide the title compound as a white solid. LC-MS: calculated for $C_{26}H_{25}ClN_4O_5$ 508.15, observed m/e: 509.18 $(M+H)^+$ (Rt 1.63/4 min).

Table 10. Compounds prepared according to the methods described in Example 71.

Example Number	Structure	HPLC-mass spectrum m/e
72		593.36
73		647.32

EXAMPLE 74

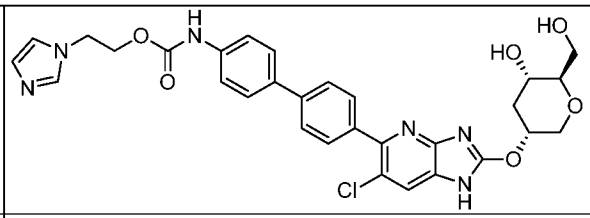
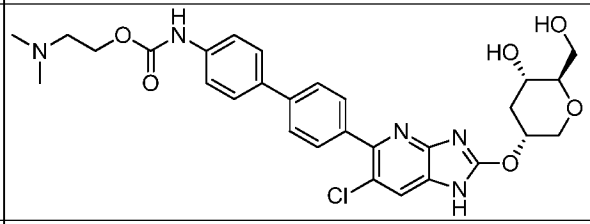
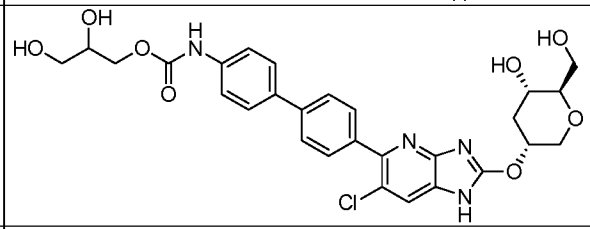
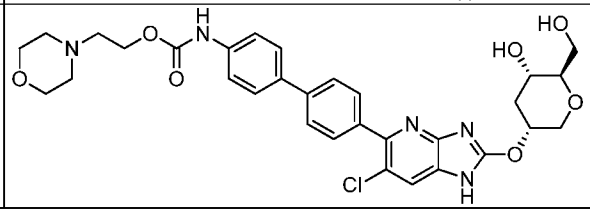


Methyl (4'-(6-chloro-2-(((3R,5S,6R)-5-hydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-3-yl)oxy)-1H-imidazo[4,5-b]pyridin-5-yl)-[1,1'-biphenyl]-4-yl)carbamate

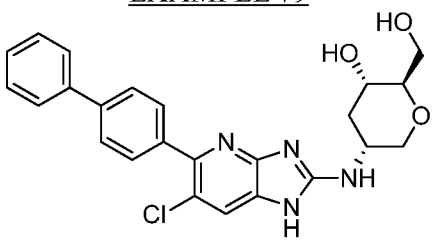
To a stirred solution of 4'-(6-chloro-2-(((4aR,7R,8aS)-2-phenylhexahydropyrano[3,2-d][1,3]dioxin-7-yl)oxy)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazo[4,5-b]pyridin-5-yl)-[1,1'-biphenyl]-4-carboxylic acid (50 mg, 0.070 mmol) under nitrogen in anhydrous THF (1.5 mL) at room temperature was added triethylamine (17 µL, 12 mg, 0.119 mmol) and DPPA ((23 µL, 29 mg, 0.105 mmol). After stirring for 2 hours, anhydrous methanol (26 µL, 22 mg, 0.700 mmol) was added and the mixture was heated to 80°C. After 3 hours, the mixture was allowed to cool and was poured into saturated aqueous sodium bicarbonate (30 mL) and extracted with EtOAc (2 x 50 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. The resultant oil was chromatographed using a Biotage™ 20g (2 x 10g in series) silica gel cartridge eluted with 0-10% methanol in DCM over 15 column volumes with a 10 column volume hold at 10% methanol. The combined fractions containing the desired product were concentrated under reduced pressure. The resultant oil was dissolved in formic acid (1.8 mL) and saturated aqueous potassium hydrogen sulfate (0.3 mL). The mixture was stirred at 50°C for 2 hours, then allowed to cool to room temperature. The mixture was poured into saturated aqueous sodium bicarbonate (30 mL) and extracted with EtOAc (2 x 50 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. The resultant white solid was dissolved in methanol (5 mL) and treated with 5N aqueous NaOH (0.2 mL). After stirring at room temperature for 15 minutes, the mixture was poured into water and neutralized with 1N aqueous HCl to pH 7. The mixture was extracted with EtOAc (2 x 40 mL); and the combined organic layers were washed with brine (30 mL), dried over sodium sulfate, and concentrated under reduced pressure. The resultant oil was chromatographed using a Biotage™ 20g (2 x 10g in series) silica gel cartridge eluted with 0-10% methanol in DCM over 15 column volumes with a 10 column volume hold at 10% methanol. The desired product fractions were combined and concentrated under reduced pressure, dissolved in MeCN and water, frozen at -78°C, then lyophilized to dryness to give the title compound as a white solid. LC-MS: calculated for $C_{26}H_{25}ClN_4O_6$ 524.15, observed m/e: 525.08 $(M+H)^+$ (Rt 1.80/4 min). ^1H NMR δ (ppm)(DMSO-d_6): 12.85 (br. s, 1H), 9.77 (s, 1H), 7.73-7.67 (m, 6H), 7.57 (d, J = 8.5Hz, 2H), 5.09 (d, J = 5.5Hz, 1H), 5.01 (heptet, J = 5.5Hz, 1H), 4.56 (t, J = 6.0Hz, 1H), 4.22 (m, 1H), 3.71 (m, 1H), 3.68 (s, 3H), 3.46-3.40 (m, 2H), 3.25 (t, J = 10.5Hz, 1H), 3.04 (m, 1H), 2.60 (m, 1H), 1.57 (q, J = 11.5Hz, 1H).

Table 11. Compounds prepared according to the methods described in Example 74.

Example Number	Structure	HPLC-mass spectrum m/e

75		605.25
76		582.15
77		585.23
78		624.30

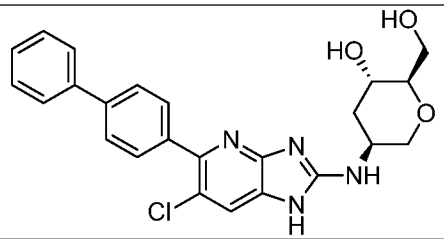
EXAMPLE 79



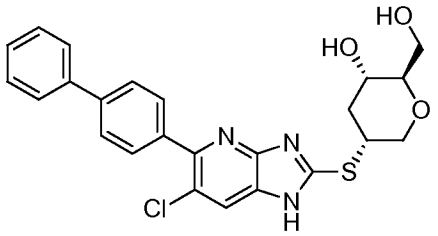
(2R,3S,5R)-5-((5-([1,1'-biphenyl]-4-yl)-6-chloro-1H-imidazo[4,5-b]pyridin-2-yl)amino)-2-(hydroxymethyl)tetrahydro-2H-pyran-3-ol To a stirred solution of (4aR,7R,8aS)-2-phenylhexahydropyrano[3,2-d][1,3]dioxin-7-amine (17 mg, 0.073 mmol) under nitrogen in anhydrous THF (0.5 mL) at 0°C was added 2.5M n-BuLi (30 µL, 0.075 mmol). The mixture was allowed to warm to room temperature. After stirring for 1 hour, a solution of 5-([1,1'-biphenyl]-4-yl)-6-chloro-2-(methylsulfonyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazo[4,5-b]pyridine (25 mg, 0.049 mmol) in anhydrous THF (0.5 mL) was added. After 1.5 hours, the mixture was poured into saturated aqueous sodium bicarbonate (30 mL) and extracted with EtOAc (2 x 40 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. The resultant yellow was chromatographed using a

Biotage™ 20 g (2 x 10g in series) silica gel cartridge eluted with 0-40% EtOAc in 1:1 Hexane/DCM over 20 column volumes. The product fractions were combined and concentrated under reduced pressure. The resultant orange oil was dissolved in formic acid (1.0 mL). Saturated aqueous potassium hydrogen sulfate (0.2 mL) was added and the mixture was stirred at 50°C. After 45 minutes, the mixture was poured into saturated aqueous sodium bicarbonate (50 mL) and extracted with EtOAc (75 mL). The organic layer was concentrated under reduced pressure, and then dissolved in methanol (3 mL), and 5N aqueous NaOH was added and the mixture was stirred at room temperature. After 20 minutes the mixture was neutralized with aqueous 1N HCl (2.5 mL). The mixture was then poured into saturated aqueous sodium bicarbonate (30 mL) and extracted with EtOAc (80 mL). The organic layer was washed with brine, dried over sodium sulfate, and concentrated under reduced pressure. The resultant white film was chromatographed using a Biotage™ 20g (2 x 10g in series) silica gel cartridge eluted with 0-10% MeOH in DCM (with 1% triethylamine) over 20 column volumes with a 10 column volume hold at 10% methanol (with 1% triethylamine). The product fractions were combined and concentrated under reduced pressure. The resultant white film was dissolved in MeCN and water, frozen at -78°C, and lyophilized to dryness to provide the title compound as a white solid. LC-MS: calculated for $C_{24}H_{23}ClN_4O_3$ 450.15, observed m/e: 451.14 $(M+H)^+$ (Rt 1.75/4 min). ^1H NMR δ (ppm)(CD_3OD): 7.73-7.67 (m, 6H), 7.56 (s, 1H), 7.45 (t, J = 8.0Hz, 2H), 7.35 (t, J = 7.5Hz, 1H), 4.16 (ddd, J = 11.0, 4.9, 1.8Hz, 1H), 3.97 (m, 1H), 3.87 (dd, J = 11.5, 2.3Hz, 1H), 3.64 (dd, J = 11.5, 2.3Hz, 1H), 3.57 (m, 1H), 3.17 (t, J = 10.5Hz, 1H), 3.12 (m, 1H), 2.47 (m, 1H), 1.53 (q, J = 11.5Hz, 1H).

Table 12. Compounds prepared according to the methods described in Example 79.

Example Number	Structure	HPLC-mass spectrum m/e
80		451.16

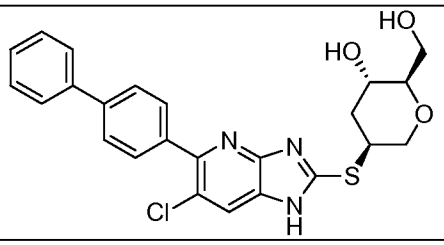
EXAMPLE 81



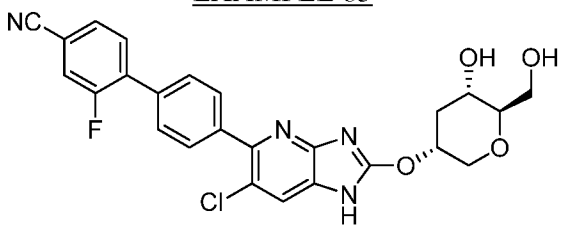
(2R,3S,5R)-5-((5-([1,1'-biphenyl]-4-yl)-6-chloro-1H-imidazo[4,5-b]pyridin-2-yl)thio)-2-(hydroxymethyl)tetrahydro-2H-pyran-3-ol To a stirred solution of 5-([1,1'-biphenyl]-4-yl)-6-chloro-2-(methylsulfonyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazo[4,5-b]pyridine (35 mg, 0.066 mmol) and (4aR,7R,8aS)-2-phenylhexahydropyrano[3,2-d][1,3]dioxine-7-thiol (21 mg, 0.082 mmol) under nitrogen in anhydrous DMF (0.7 mL) at room temperature was added NaH (4 mg, 0.102 mmol) in one portion. After stirring at room temperature for 1 hour, the mixture was poured into saturated aqueous sodium bicarbonate (30 mL) and extracted with EtOAc (60 mL). The organic layer was dried over sodium sulfate and concentrated under reduced pressure. The resultant orange oil was dissolved in formic acid (1.0 mL). Then saturated aqueous potassium hydrogen sulfate (0.2 mL) was added and the mixture was stirred at 50°C. After 1.5 hours, the mixture was poured into saturated aqueous sodium bicarbonate (60 mL) and extracted with EtOAc (2 x 60 mL). The combined organic layers were concentrated under reduced pressure. The resultant white film was dissolved in methanol (3 mL). Then 5N aqueous NaOH (0.5 mL, 2.5 mmol) was added and the mixture was allowed to stir at room temperature. After 15 minutes, the mixture was neutralized with 1N aqueous HCl (2.5 mL, 2.5 mmol), poured into saturated aqueous sodium bicarbonate (30 mL) and extracted with EtOAc (60 mL). The organic layer was separated, dried over sodium sulfate and concentrated under reduced pressure. The resultant white film was chromatographed using a Biotage™ 20g (2 x 10g in series) silica gel cartridge eluted with 0-10% methanol in DCM over 20 column volumes. The combined product fractions were concentrated under reduced pressure, dissolved in MeCN and water, frozen at -78°C, and lyophilized to dryness to provide the title compound as a white solid. LC-MS: calculated for $C_{24}H_{22}ClN_3O_3S$ 467.11, observed m/e: 468.10 $(M+H)^+$ (Rt 2.03/4 min). ^1H NMR δ (ppm)(CD_3OD): 7.97 (s, 1H), 7.75-7.68 (m, 5H), 7.46 (t, *J* = 7.5Hz, 2H), 7.36 (t, *J* = 7.5Hz, 1H), 4.28 (dd, *J* = 11.0, 4.5Hz, 1H), 4.03 (m, 1H), 3.87 (dd, *J* = 11.5, 0.8Hz, 1H), 3.66-3.57 (m, 2H), 3.37 (t, *J* = 11.0Hz, 1H), 3.15 (m, 1H), 2.54 (m, 1H), 1.60 (q, *J* = 12.0Hz, 1H)

Table 13. Compounds prepared according to the methods described in Example 81.

Example Number	Structure	HPLC-mass spectrum m/e

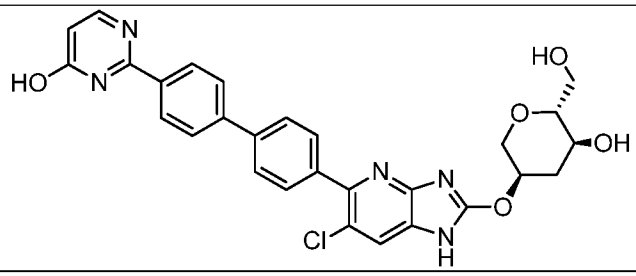
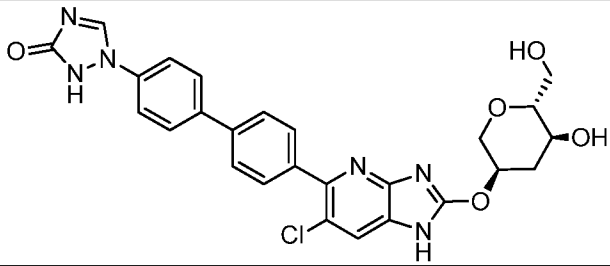
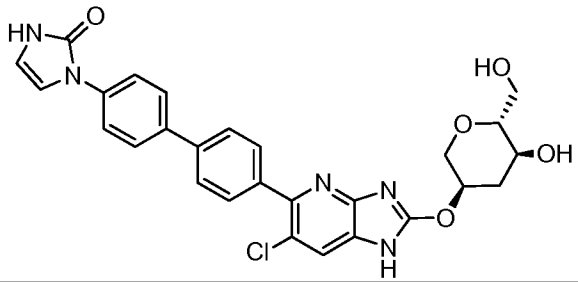
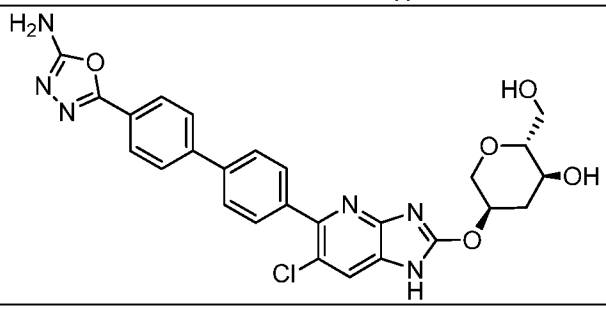
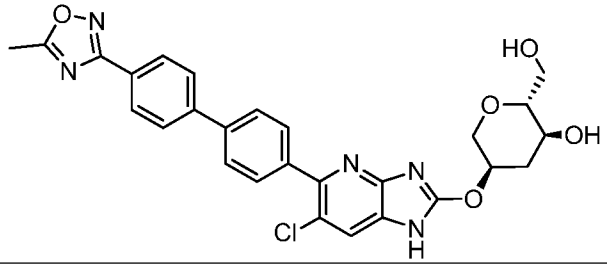
82		451.16

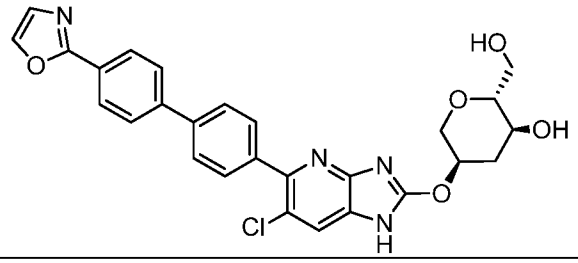
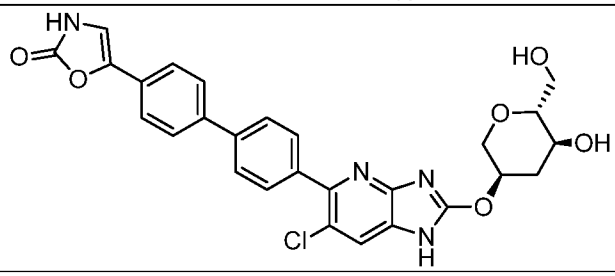
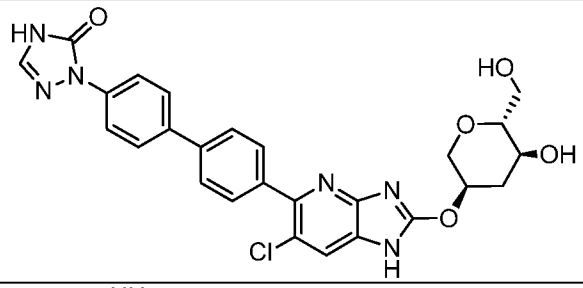
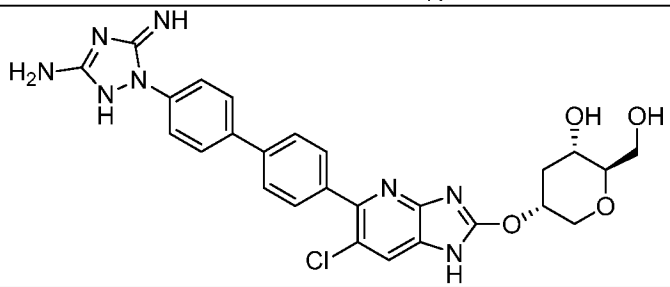
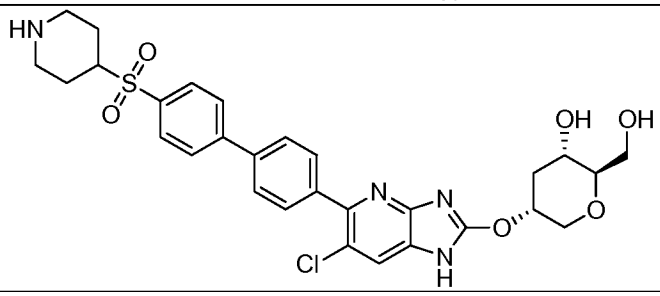
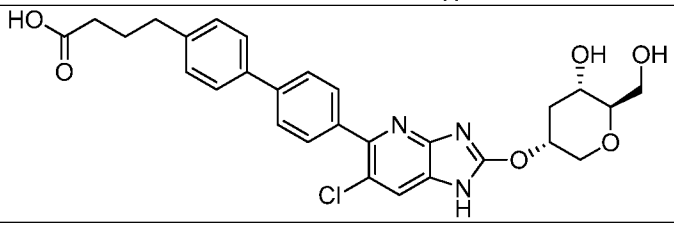
EXAMPLE 83



4'-(6-chloro-2-(((3R,5S,6R)-5-hydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-3-yl)oxy)-1H-imidazo[4,5-b]pyridin-5-yl)-2-fluoro-[1,1'-biphenyl]-4-carbonitrile Placed 4-bromo-3-fluorobenzonitrile (15 mg, 0.075 mmol) and chloro[(tri-*tert*-butylphosphine)-2-(2-aminobiphenyl)] palladium(II) (6 mg, 0.012 mmol) into a reaction vessel in a dry-glove box. Then 6-chloro-2-(((4aR,7R,8aS)-2-phenylhexahydropyrano-[3,2-d][1,3]dioxin-7-yl)oxy)-5-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazo[4,5-b]pyridine (45 mg, 0.062 mmol) was added as a solution in anhydrous dioxane (0.50 mL) which had been degassed. To this mixture was added a solution of degassed, aqueous 1N K_3PO_4 (0.19 mL, 0.19 mmol). The reaction vessel was sealed and heated to 80°C with stirring. After 16 hours, the mixture was allowed to cool to room temperature, then diluted with DCM (2.0 mL) and water (1.0 mL), and vigorously stirred for 30 minutes. The organic layer was separated and concentrated under reduced pressure. The resultant oil was dissolved in DCM (1.0 mL), and SiliaMetS® Dimercaptotriazine (100 mg) was added. The resulting suspension was stirred for 2 hours at 35°C. After cooling to room temperature, the mixture was filtered and concentrated under reduced pressure. The resultant residue was dissolved in DCM (0.50 mL) and TFA (0.50 mL) and stirred at room temperature. After 3 hours the mixture was concentrated under reduced pressure. The resultant oil was dissolved in methanol (0.50 mL), then a 5N aqueous solution of NaOH (0.10 mL) was added and the mixture was allowed to stir at room temperature. After 15 minutes the solution was acidified with a few drops of formic acid and diluted with DMSO. The resulting mixture was filtered to remove solids and purified via reverse phase preparatory HPLC using MeCN/water/formic acid as the mobile phase. The fractions containing product were combined and concentrated under reduced pressure to provide the title compound as a white solid. LC-MS: calculated for $C_{25}H_{20}ClFN_4O_4$ 494.12, observed m/e: 495.12 $(M+H)^+$ (Rt 0.48/2 min).

Table 14. Compounds prepared according to the methods described in Example 83.

Example Number	Structure	HPLC-mass spectrum m/e
84		546.15
85		535.14
86		534.15
87		535.14
88		534.15

89		519.14
90		535.13
91		535.14
92		549.17
93		599.16
94		538.17

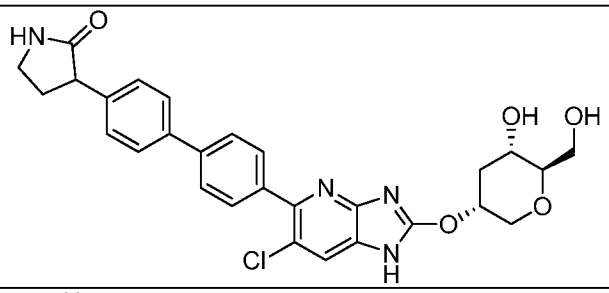
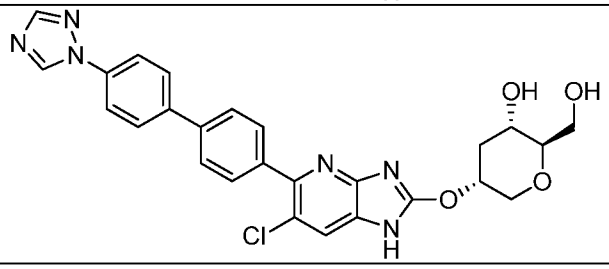
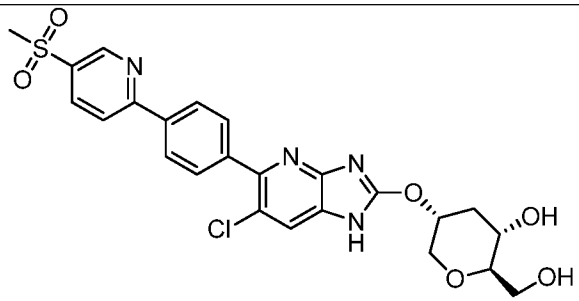
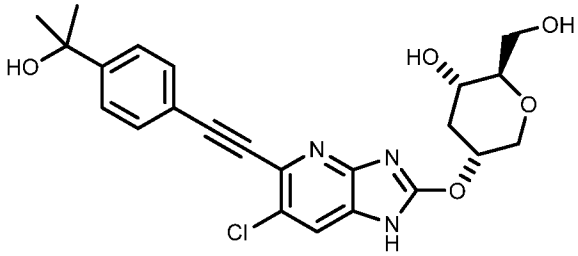
95		535.17
96		519.15

Table 15. Compounds prepared according to the methods in Example 1.

Example Number	Structure	LCMS M+H
97		531.4

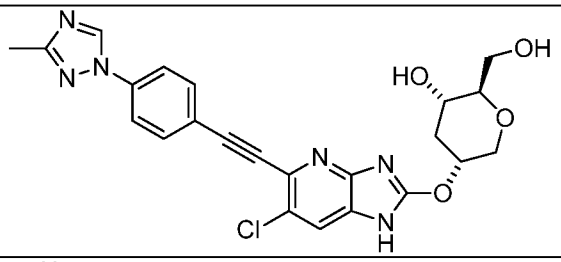
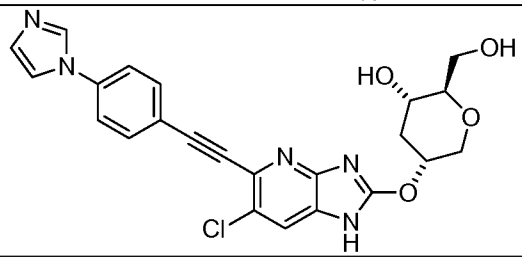
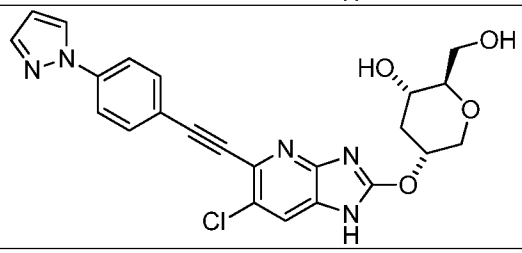
EXAMPLE 98



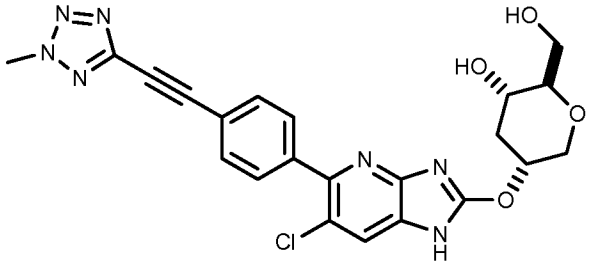
(2R,3S,5R)-5-((6-chloro-5-((4-(2-hydroxypropan-2-yl)phenyl)ethynyl)-1H-imidazo[4,5-b]pyridin-2-yl)oxy)-2-(hydroxymethyl)tetrahydro-2H-pyran-3-ol A mixture of (2R,3S,5R)-5-((6-chloro-5-iodo-1H-imidazo[4,5-b]pyridin-2-yl)oxy)-2-(hydroxymethyl)tetrahydro-2H-pyran-3-ol (50 mg, 0.120 mmol), 2-(4-ethynylphenyl)propan-2-ol (28.2 mg, 0.176 mmol), $Pd(Ph_3P)_4$ (13.58 mg, 0.012 mmol), copper(I) iodide (2.237 mg, 0.012 mmol) and diisopropylethylamine

(0.062 ml, 0.360 mmol) in dioxane (2 ml) was charged in a reaction tube. Then the tube was sealed and N_2 was bubbled through for 5 min. The mixture was heated at 80 C for 2 h, and then concentrated. The resulting residue was purified on reverse phase HPLC eluting with 10-70% CH_3CN/H_2O with TFA as an additive to give the title compound. LC-MS m/e =458.35 $(M+H)^+$ (Rt 1.70/4.0 min); ^1H NMR δ (ppm) (CD_3OD): 7.83 (s, 1H), 7.58-7.54 (m, 4H), 5.13 (septet, 1H, J = 5 Hz)), 4.34 (ddd 1H, J = 12, 5, 2Hz), 3.89 (dd, 1 H, J = 12, 2 Hz), 3.64 (dd, 1H, J = 12, 6 Hz)), 3.61 (dd, 1H, J = 12, 5Hz), 3.37 (t, 1H, J = 11 Hz), 3.19-3.15 (m, 1H), 2.77-2.73 (m, 1H), 1.70 (dd, 1H, J = 23, 12 Hz), 1.55 (s, 6H).

Table 16. Compounds prepared according to the methods in Example 98

Example Number	Structure	HPLC-mass spectum m/e
99		481.33
100		466.35
101		466.34

EXAMPLE 102



(2R,3S,5R)-5-((6-chloro-5-(4-((2-methyl-2H-tetrazol-5-yl)ethynyl)phenyl)-1H-imidazo[4,5-b]pyridin-2-yl)oxy)-2-(hydroxymethyl)tetrahydro-2H-pyran-3-ol A mixture of (2R,3S,5R)-5-((6-chloro-5-(4-ethynylphenyl)-1H-imidazo[4,5-b]pyridin-2-yl)- oxy)-2-(hydroxymethyl)tetrahydro-2H-pyran-3-ol(60 mg, 0.150 mmol), $Pd(Ph_3P)_4$(17.34 mg, 0.015 mmol), copper(I) iodide (2.85 mg, 0.015 mmol), 5-bromo-2-methyl-2H-tetrazole (48.9 mg, 0.300 mmol) and diisopropylethylamine (0.210 ml, 0.450 mmol) in dioxane (2 ml) was charged in a reaction tube. The tube was sealed and N_2 was bubbled through for 5 min. The reaction was heated at 80 C for 18 h, and then concentrated. The resulting residue was purified on reverse phase HPLC eluting with 10-70% CH_3CN/H_2O with TFA as an additive to give the title compound. LC-MS: m/e: 481.97.53 $(M+H)^+$ (Rt 1.70/ 4 min); ^1H NMR δ (ppm) (CD_3OD): 7.84-7.75 (m, 4H), 5.11 (septet, 1H, J = 5 Hz)), 4.38-4.31 (m, 1H), 4.24 (s, 3H), 3.89 (dd, 1 H, J = 12, 2 Hz), 3.69-3.59 (m, 2H), 3.37 (t, 1H, J = 11 Hz), 3.20-3.15 (m, 1H), 2.79-2.72 (m, 1H), 1.70 (dd, 1H, J = 23, 12 Hz),

BIOLOGICAL EXAMPLE 1

AMPKSAMSF (in vitro AMPK activation assay)

The recombinant human AMPK complex 1 (containing α1β1γ1) or AMPK complex 7 (containing α2β1γ1) was obtained from baculovirus expression system. Recombinant viruses were generated by cotransfection of AMPK/pBacPak9 clones with Baculogold baculovirus DNA (Pharmingen) in spodoptera frugiperda 21 cells according to the manufacturer's instructions. Each round of virus amplification was performed for 5 days in Grace's medium containing 10% serum. Virus that had been subjected to three rounds of amplification was used for all protein production procedures. To express the AMPK complex, sf21 cells were adapted to serum free medium (SF900 II, Invitrogen) by sequential dilution from serum containing stocks into SF900II medium and maintained in shaker flasks at 90 rpm at 27°C. The recombinant AMPK enzyme complex was produced by triple infection, one recombinant virus for each of the subunits, in sf21 cells under serum free conditions. Cells were infected in log phase, 1 x 10^6 cells/ml, at a multiplicity of infection of ~5. Cells were harvested by centrifugation at 10,000 x g for 15 minutes after 72 hours of infection with viruses. The insect cell pellet from 2 liters of culture was resuspended in 50 ml lysis buffer (20 mM Tris-HCl, 50 mM NaCl, 50 mM NaF, 30 mM Na PPi, 0.25 M sucrose, 10 mM $ZnCl_2$, 2 mM DTT, 0.4 mg/ml digitonin) and subjected to two cycles of freeze-thaw lysis in a dry-ice ethanol bath. Insoluble material was removed by centrifugation at 10,000 x g and the supernatant was fractionated with use of polyethylene glycol (PEG). The protein fraction precipitating between 2.5 and 6% PEG was used for further purification using a Blue-Sepharose step

(Zhou et al, J. Clin. Invest. 108, 1167-1174, 2001).

The in vitro AMPK activation assay is performed in a volume of 30 µl in a 384-well plate. Enzyme reactions were assembled in the microtiter plate by adding 15 µl of 2X enzyme in assay buffer (20 mM HEPES, pH 7.3, 5 mM $MgCl_2$, 3mM DTT, 0.01% Brij 35 and CamK Kinase, to activate AMPK) to wells which contained either DMSO or compound. The reaction was initiated with the addition of 15 µl 2X substrate mixture containing 200 µM ATP, and 3.0 µM fluorescently labeled SAMS (5-FAM-HMRSAMSGLHLVKRR-COOH) in assay buffer. After 45-minute incubation at 25°C, the reaction was stopped by the addition of 70 µl stop buffer (100mM HEPES, pH 7.3, 40mM EDTA, 0.015% Brij 35). Phosphorylated 5-FAM SAMS product is assessed using a Caliper EZ Reader LabChip microfluidics reader. Product conversion is determined by calculating the peak heights of the substrate and product and reporting the product/(product + substrate) peak ratio. The 10-point titration data were expressed as % maximum AMP activation. The results were plotted using 4 parameter fit and the inflection point reflecting 50% of the maximum activation was reported as the EC_{50}. The % maximum AMP activation for selected compounds is provided in the table below.

The compounds of present invention, including the compounds of Examples 1 - 102, were tested in the in vitro AMPK activation assay using recombinant human AMPK complex 1 (containing $\alpha1\beta1\gamma1$) or AMPK complex 7 (containing $\alpha2\beta1\gamma1$), and were found to have greater than 50% maximum AMP activation of human AMPK complex 1 (containing $\alpha1\beta1\gamma1$) or AMPK complex 7 (containing $\alpha2\beta1\gamma1$), and EC_{50} values of less than 50 micromolar. Preferred compounds of the present invention were found to have EC_{50} values of less than 0.1 micromolar in the in vitro AMPK activation assay using recombinant human AMPK complex 1 or AMPK complex 7.

Maximum AMP Activation for Selected Compounds

Example No.	% Maximum AMP Activation of human AMPK Complex 1	EC_{50} (nM)
1	574	128
34	367	19
35	489	18
37	473	22
39	379	4
45	417	3

46	619	15
47	590	25
48	615	2
49	464	9
54	767	9
55	752	8
56	392	11
61	568	36
62	545	17
66	410	13
67	418	3
68	419	6
70	417	31
71	443	6
72	504	8
73	249	8
74	460	25
77	494	15

BIOLOGICAL EXAMPLE 2

Phosphoroylation of Acetyl CoA Carboxylase by AMPK activators in db/+ Mice:

To assess the potential for AMPK activators to increase the phosphorylation of Acetyl COA Carboxylase (ACC) in liver and skeletal muscle, db/+ mice are dosed with AMPK activators at either 2 or 7 h prior to evaluation where phosphorylated ACC (p-ACC)/ total ACC levels are compared in the tissues of vehicle and compound treated mice. Briefly, mice are anesthetized using gas anesthesia with 1-4% isoflurane administered to effect via nose cone. Once anesthetized, samples of liver and skeletal muscle (gastrocnemius) are removed, snap frozen in liquid nitrogen, and homogenized. Homogenates are analyzed for protein concentration and equal amounts of protein are assayed for total and phosphorylated ACC (p-ACC) levels using Meso Scale Discovery's Multi-array assay kit. MSD assay plates contain an electrode surface that is coated with streptavidin. Protein sample binds to streptavidin. The primary ACC or p-ACC specific antibody binds to protein and a secondary antibody labeled with MSD SULFO-TAG then binds to the primary antibody. The electrode surface of the MSD plate responds to an electrical stimulus and causes the SULFO-TAG labels bound to ACC and p-ACC to emit a light signal in proportion to the amount of p-ACC or total ACC present. The ratio of p-ACC/ total ACC levels are determined for each sample and the ratio of p-ACC/ total ACC levels for mice treated with AMPK activators is significantly elevated compared to the ratio of those treated

with the vehicle control (significant elevations are described as differences where $p < 0.05$).

BIOLOGICAL EXAMPLE 3

Inhibition of Fatty Acid Synthesis (FAS) by AMPK activators in db/+ Mice:

To determine the effect of AMPK activators on Fatty Acid Synthesis (FAS) in the liver, the effect of oral pre-dosing of compounds on the amount of ^3H incorporated into hepatic triglyceride is determined as described by Sakurai T, Miyazawa S, Shindo Y, and T. Hashimoto (Biochim Biophys Acta. 1974 Sep 19; 360 (3):275-88). Briefly, mice (db/+, Jackson Laboratory, Maine) are orally dosed with AMPK activators at time = -8 h. Then at time = -1 h, mice are injected with 0.5 ml of 0.15 M NaCl containing 0.2 mCi of ^3H water per 100 g of body weight. At time 0, mice are sacrificed via cervical dislocation and livers are harvested for FAS analysis. To analyze livers for FAS, samples of liver are heated at 90 °C for 5 hours in a 4 M KOH / 50% ethanol solution. Then the alkaline hydrolysate of liver is extracted with hexane and acidified to a pH <2 with 10 M H_2SO_4. The fatty acids of liver are then extracted from acidified hydrolysate with additional hexane, dried down with a stream of warm air, then re-suspended in scintillation fluid, and counted on a beta counter. The amount of fatty acids synthesized per gram of liver is calculated based on the amount of ^3H incorporated into hepatic triglyceride. The amount of ^3H radiolabelled fatty acids synthesized in mice with treated with an AMPK activator is significantly less than the amount of ^3H radiolabelled fatty acids synthesized in the control mice.

BIOLOGICAL EXAMPLE 4

In vivo study for therapy with an AMPK activator in Mice (Glucose Tolerance Test):

DIO mice are treated simultaneously with an effective dose of an AMPK-activated protein kinase activator.

Materials and Methods: Male C57BL/6NT mice (Taconic, 16-18 weeks old at the beginning of the drug administration) are used. Mice are given water and high fat diet D12492 (Research Diet Inc.) ad libitum. They are kept in an animal room which is maintained at 23 ± 2 C temperature, 55 ± 15 % relative humidity and on a 12-hr light-dark cycle (7:00-19:00) during a quarantine and acclimatization period of 1 week. Animals are then administered vehicle (5ml/kg of 0.5% methylcellulose in distilled water) by oral gavage twice-daily at 9 AM and 5 PM. After 9 days, stable body weight is observed. The following day (day -1), the mice are fasted for 4 hours and tail bled to determine the glucose and insulin levels. Animals are sorted into groups based on plasma glucose, insulin levels and body weight (n=8). The body weight and food in the hopper are recorded on day 0 before compound dosing is initiated. One of the groups is orally administered vehicle while the second group is administered an AMPK-activated protein kinase activator of the present invention at a dose of 30 mg/kg (5 ml/kg) twice-daily for 12 days by

gavage. Body weight and food intake are measured every other day. On day 5, the animals are fasted 4 hours for measuring plasma glucose and insulin levels after morning dosing. At day 12, body weight and food intake are measured and animals receive their last morning dose. Mice again are fasted 4 hours, blood is collected at a set time point (t = 0 min), and then challenged with dextrose orally (2 g/kg) Plasma glucose and insulin levels are determined from tail bleeds taken at 20 and 90 minutes after dextrose challenge. The plasma glucose and insulin excursion profile from t = 0 to t = 90 min is used to integrate an area under the curve (AUC) for each treatment. Percent inhibition values for each treatment are generated from the AUC data normalized to the C57BL/6NT mice feed with D7012. Preferred compounds of the present invention significantly reduce day 12 glucose and/or insulin AUC during the Oral Glucose Tolerance Test after an oral dose in the range of 0.1 to 100 mg/kg.

BIOLOGICAL EXAMPLE 5

Acute food intake studies in Diet Induced Obese (DIO) mice: General Procedure

Adult DIO mice are used in these studies. After at least 2 days of acclimation to the vivarium conditions (controlled humidity and temperature, lights on for 12 hours out of 24 hours) food (D12492 (Research Diet Inc.) is removed from rodent cages. An AMPK activator of the present invention or the vehicle is administered orally, intraperitoneally, subcutaneously or intravenously before the return of a known amount of food to cage. The optimal interval between dosing and food presentation is based on the half-life of the compound based on when brain concentrations of the compound is the highest. Food remaining is measured at several intervals. Food intake is calculated as grams of food eaten per gram of body weight within each time interval and the appetite-suppressant effect of the AMPK activator is compared to the effect of the vehicle. The food intake of mice treated with an AMPK activator is significantly less than the food intake of control mice.

BIOLOGICAL EXAMPLE 6

Chronic weight reduction studies in Diet Induced Obese (DIO) mice: General Procedure

Adult DIO mice are used in these studies. Upon or soon after weaning, rats or mice are made obese due to exclusive access to diets containing fat and sucrose in higher proportions than in the control diet. The diet used to induce obesity is Research Diets D12451 chow (45% fat). The rodents ingest chow until they are significantly heavier and have a higher proportion of body fat than control diet rats, often 9 weeks. The rodents receive injections (1 to 4 per day) or continuous infusions of an AMPK activator of the present invention or the vehicle either orally, intraperitoneally, subcutaneously or intravenously. Food intake and body weights are measured daily or more frequently. Food intake is calculated as grams of food eaten per gram of body weight within each time interval and the appetite-suppressant and weight loss effect of the

AMPK activator of the present invention is compared to the effect of the vehicle. The weight loss of mice treated with an AMPK activator is significantly greater than the weight loss of control mice.

BIOLOGICAL EXAMPLE 7

ASSAY FOR TRIGLYCERIDES

Adult DIO mice are used in these studies. Upon or soon after weaning, rats or mice are made obese due to exclusive access to diets containing fat and sucrose in higher proportions than in the control diet. The diet used to induce obesity is Research Diets D12451 chow (45% fat). The rodents ingest chow until they are significantly heavier and have a higher proportion of body fat than control diet rats, often 9 weeks. The rodents receive injections (1 to 4 per day) or continuous infusions of an AMPK activator of the present invention or the vehicle either orally, intraperitoneally, subcutaneously or intravenously. Food intake and body weights are measured daily or more frequently. Food intake is calculated as grams of food eaten per gram of body weight within each time interval and the appetite-suppressant and weight loss effect of the AMPK activator of the present invention is compared to the effect of the vehicle. The weight loss of mice treated with an AMPK activator is significantly greater than the weight loss of control mice.

BIOLOGICAL EXAMPLE 8

ASSAY FOR LOW HDL and/or HIGH LDL

Adult DIO mice are used in these studies. Upon or soon after weaning, rats or mice are made obese due to exclusive access to diets containing fat and sucrose in higher proportions than in the control diet. The diet used to induce obesity is Research Diets D12451 chow (45% fat). The rodents ingest chow until they are significantly heavier and have a higher proportion of body fat than control diet rats, often 9 weeks. The rodents receive injections (1 to 4 per day) or continuous infusions of an AMPK activator of the present invention or the vehicle either orally, intraperitoneally, subcutaneously or intravenously. Food intake and body weights are measured daily or more frequently. Food intake is calculated as grams of food eaten per gram of body weight within each time interval and the appetite-suppressant and weight loss effect of the AMPK activator of the present invention is compared to the effect of the vehicle. The weight loss of mice treated with an AMPK activator is significantly greater than the weight loss of control mice.

BIOLOGICAL EXAMPLE 9

ASSAY FOR SARCOPENIA

Adult DIO mice are used in these studies. Upon or soon after weaning, rats or mice are

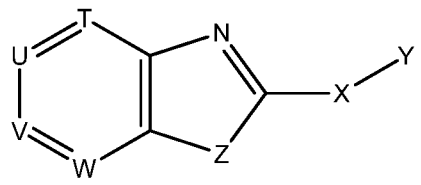
made obese due to exclusive access to diets containing fat and sucrose in higher proportions than in the control diet. The diet used to induce obesity is Research Diets D12451 chow (45% fat). The rodents ingest chow until they are significantly heavier and have a higher proportion of body fat than control diet rats, often 9 weeks. The rodents receive injections (1 to 4 per day) or continuous infusions of an AMPK activator of the present invention or the vehicle either orally, intraperitoneally, subcutaneously or intravenously. Food intake and body weights are measured daily or more frequently. Food intake is calculated as grams of food eaten per gram of body weight within each time interval and the appetite-suppressant and weight loss effect of the AMPK activator of the present invention is compared to the effect of the vehicle. The weight loss of mice treated with an AMPK activator is significantly greater than the weight loss of control mice.

The scope of the claims should not be limited by the preferred embodiments set forth in the examples, but should be given the broadest interpretation consistent with the description as a whole.

While the invention has been described and illustrated with reference to certain particular embodiments thereof, those skilled in the art will appreciate that various changes, modifications and substitutions can be made therein without departing from the scope of the invention. For example, effective dosages other than the particular dosages as set forth herein above may be applicable as a consequence of variations in the responsiveness of the mammal being treated for any of the indications for the compounds of the invention indicated above. Likewise, the specific pharmacological responses observed may vary according to and depending upon the particular active compound selected or whether there are present pharmaceutical carriers, as well as the type of formulation and mode of administration employed, and such expected variations or differences in the results are contemplated in accordance with the objects and practices of the present invention.

WHAT IS CLAIMED IS:

1. A compound of structural formula I:



(I)

or a pharmaceutically acceptable salt thereof, wherein:

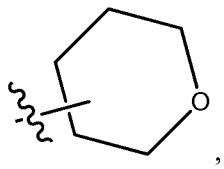
T is selected from the group consisting of: CR^3, N and N-oxide;
U is selected from the group consisting of: CR^1, N and N-oxide;
V is selected from the group consisting of: CR^2, N and N-oxide;
W is selected from the group consisting of: CR^4, N and N-oxide,
provided that at least one of T, U, V and W is N or N-oxide;

X is selected from:

(1) $-CH_2-$,
(2) -CHF-,
(3) $-CF_2-$,
(4) -S-,
(5) -O-,
(6) $-O-CH_2-$,
(7) $-O-CH_2CH_2-$,
(8) -NH-,
(9) -C(O)-,
(10) -NHC(O)-,
(11) -C(O)NH-,
(12) $-NHSO_2-$,
(13) $-SO_2NH-$, and
(14) $-CO_2-$,

wherein each CH_2 is unsubstituted or substituted with 1 or 2 substituents selected from: hydroxy, halogen, NH_2, C_{1-6}alkyl, CO_2H, CO_2C_{1-6}alkyl, COC_{1-6}alkyl, phenyl and -CH_2phenyl, and wherein each NH is unsubstituted or substituted with 1 substituent selected from: C_{1-6}alkyl, CO_2H, CO_2C_{1-6}alkyl, COC_{1-6}alkyl, phenyl and -CH_2phenyl;

Y is selected from:



,

wherein Y is unsubstituted or substituted with 1, 2, 3, 4 or 5 substituents selected from R^b;

Z is selected from:

(1) NR^5,
(2) -S-, and
(3) -O-;

each R^1 and R^2 is independently selected from:

(1) hydrogen,
(2) halogen,
(3) CN,
(4) CF_3,
(5) -C_{1-6}alkyl,
(6) -C_{2-6}alkenyl,
(7) -C_{2-6}alkynyl,
(8) -$(CH_2)_pC_{3-10}$cycloalkyl,
(9) -$(CH_2)_pC_{3-7}$cycloalkyl-aryl,
(10) -$(CH_2)_pC_{3-7}$cycloalkyl-heteroaryl,
(11) -$(CH_2)_pC_{4-10}$cycloalkenyl,
(12) -$(CH_2)_pC_{4-7}$cycloalkenyl-aryl,
(13) -$(CH_2)_pC_{4-7}$cycloalkenyl-heteroaryl,
(14) -$(CH_2)_pC_{2-10}$cycloheteroalkyl,
(15) -$(CH_2)_pC_{2-10}$cycloheteroalkenyl,
(16) -$(CH_2)_p$aryl,
(17) -$(CH_2)_p$aryl-C_{1-8}alkyl,
(18) -$(CH_2)_p$aryl-C_{2-8}alkenyl,
(19) -$(CH_2)_p$aryl-C_{2-8}alkynyl-C_{1-8}alkyl,
(20) -$(CH_2)_p$aryl-C_{2-8}alkynyl-C_{3-7}cycloalkyl,
(21) -$(CH_2)_p$aryl-C_{2-8}alkynyl-C_{3-7}cycloalkenyl,
(22) -$(CH_2)_p$aryl-C_{2-8}alkynyl-C_{2-10}cycloheteroalkyl,
(23) -$(CH_2)_p$aryl-C_{2-8}alkynyl-C_{2-10}cycloheteroalkenyl,
(24) -$(CH_2)_p$aryl-C_{2-8}alkynyl-aryl,

(25) -$(CH_2)_p$aryl-C_{2-8}alkynyl-heteroaryl,
(26) -$(CH_2)_p$aryl-C_{3-7}cycloalkyl,
(27) -$(CH_2)_p$aryl-C_{2-10}cycloheteroalkyl,
(28) -$(CH_2)_p$aryl-C_{2-10}cycloheteroalkenyl,
(29) -$(CH_2)_p$aryl-aryl,
(30) -$(CH_2)_p$aryl-heteroaryl,
(31) -$(CH_2)_p$heteroaryl,
(32) -$(CH_2)_p$heteroaryl-C_{3-7}cycloalkyl,
(33) -$(CH_2)_p$heteroaryl-C_{2-10}cycloheteroalkyl,
(34) -$(CH_2)_p$heteroaryl-C_{2-10}cycloheteroalkenyl,
(35) -$(CH_2)_p$heteroaryl-aryl,
(36) -$(CH_2)_p$heteroaryl-heteroaryl,
(37) -C_{2-6}alkenyl-alkyl,
(38) -C_{2-6}alkenyl-aryl,
(39) -C_{2-6}alkenyl-heteroaryl,
(40) -C_{2-6}alkenyl-C_{3-7}cycloalkyl,
(41) -C_{2-6}alkenyl-C_{3-7}cycloalkenyl,
(42) -C_{2-6}alkenyl-C_{2-7}cycloheteroalkyl,
(43) -C_{2-6}alkenyl-C_{2-7}cycloheteroalkenyl,
(44) -C_{2-6} alkynyl-$(CH_2)_{1-3}$-O-aryl,
(45) -C_{2-6}alkynyl-alkyl,
(46) -C_{2-6}alkynyl-aryl,
(47) -C_{2-6}alkynyl-heteroaryl,
(48) -C_{2-6}alkynyl-C_{3-7}cycloalkyl,
(49) -C_{2-6}alkynyl-C_{3-7}cycloalkenyl,
(50) -C_{2-6}alkynyl-C_{2-7}cycloheteroalkyl,
(51) -C_{2-6}alkynyl-C_{2-7}cycloheteroalkenyl, and
(52) –C(O)NH-$(CH_2)_{0-3}$phenyl,

wherein each CH_2 is unsubstituted or substituted with 1 or 2 substituents selected from: halogen, CF_3, -OH, $-NH_2$, –C_{1-6}alkyl, -OC_{1-6}alkyl, –NHC_{1-6}alkyl, and –N(C_{1-6}alkyl)$_2$, and wherein each alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloheteroalkyl, cycloheteroalkenyl, phenyl, aryl and heteroaryl is unsubstituted or substituted with 1, 2, 3 or 4 substituents independently selected from R^a,

provided that at least one of and only one of R^1 and R^2 is selected from the group consisting of: hydrogen, halogen, -CN, $-CF_3$, -C_{1-6}alkyl, –C_{2-6}alkenyl and–C_{2-6}alkynyl;

R^3 and R^4 are each independently selected from:

(1) hydrogen,
(2) halogen,
(3) –C_{1-6}alkyl,
(4) –C_{2-6}alkenyl,
(5) –C_{2-6}alkynyl,
(6) –C_{3-10}cycloalkyl,
(7) –C_{3-10}cycloalkenyl,
(8) aryl,
(9) heteroaryl,
(10) –CN,
(11) –CF_3,
(12) –OH,
(13) -OC_{1-6}alkyl,
(14) –NH_2,
(15) –NHC_{1-6}alkyl,
(16) –N(C_{1-6}alkyl)$_2$,
(17) -SC_{1-6}alkyl,
(18) -SOC_{1-6}alkyl,
(19) –SO_2C_{1-6}alkyl,
(20) –NHSO_2C_{1-6}alkyl,
(21) –NHC(O)C_{1-6}alkyl,
(22) –SO_2NHC_{1-6}alkyl, and
(23) –C(O)NHC_{1-6}alkyl;

R^5 is selected from:
(1) hydrogen,
(2) -C_{1-6}alkyl,
(3) -C_{1-6}alkenyl,
(4) -$(CH_2)_u$OH,
(5) -CH_2CO_2H, and
(6) -$CH_2CO_2C_{1-6}$alkyl;

each R^a is independently selected from the group consisting of:
(1) -$(CH_2)_m$-halogen,
(2) oxo,
(3) -$(CH_2)_m$OH,
(4) -$(CH_2)_m$N(Rj)$_2$,

(5) $-(CH_2)_mNO_2$,
(6) $-(CH_2)_mCN$,
(7) $-C_{1-6}$alkyl,
(8) $-(CH_2)_mCF_3$,
(9) $-(CH_2)_mOCF_3$,
(10) $-O-(CH_2)_m-OC_{1-6}$ alkyl,
(11) $-(CH_2)_mN(R^j)C(O)R^f$,
(12) $-(CH_2)_mN(R^j)CO_2R^f$,
(13) $-(CH_2)_mC(=N-OH)N(R^j)_2$,
(14) $-(CH_2)_mOC_{1-6}$alkyl,
(15) $-(CH_2)_mO-(CH_2)_m-C_{3-7}$cycloalkyl,
(16) $-(CH_2)_mO-(CH_2)_m-C_{2-7}$cycloheteroalkyl,
(17) $-(CH_2)_mO-(CH_2)_m$-aryl,
(18) $-(CH_2)_mO-(CH_2)_m$-heteroaryl,
(19) $-(CH_2)_mSC_{1-6}$alkyl,
(20) $-(CH_2)_mS(O)C_{1-6}$alkyl,
(21) $-(CH_2)_mSO_2C_{1-6}$alkyl,
(22) $-(CH_2)_mSO_2(CH_2)_m-C_{3-7}$cycloalkyl,
(23) $-(CH_2)_mSO_2(CH_2)_m-C_{2-7}$cycloheteroalkyl,
(24) $-(CH_2)_mSO_2(CH_2)_m$-aryl,
(25) $-(CH_2)_mSO_2(CH_2)_m$-heteroaryl,
(26) $-(CH_2)_mSO_2NH_2$,
(27) $-(CH_2)_mSO_2NHC_{1-6}$alkyl,
(28) $-(CH_2)_mSO_2NHC_{3-7}$cycloalkyl,
(29) $-(CH_2)_mSO_2NHC_{2-7}$cycloheteroalkyl,
(30) $-(CH_2)_mSO_2NH$-aryl,
(31) $-(CH_2)_mSO_2NH$-heteroaryl,
(32) $-(CH_2)_mNHSO_2C_{1-6}$alkyl,
(33) $-(CH_2)_mNHSO_2-C_{3-7}$cycloalkyl,
(34) $-(CH_2)_mNHSO_2-C_{2-7}$cycloheteroalkyl,
(35) $-(CH_2)_mNHSO_2$-aryl,
(36) $-(CH_2)_mNHSO_2NH$-heteroaryl,
(37) $-(CH_2)_mN(R^j)-C_{1-6}$alkyl,
(38) $-(CH_2)_mN(R^j)-C_{3-7}$cycloalkyl,
(39) $-(CH_2)_mN(R^j)-C_{2-7}$cycloheteroalkyl,
(40) $-(CH_2)_mN(R^j)-C_{2-7}$cycloheteroalkenyl,
(41) $-(CH_2)_mN(R^j)$-aryl,

(42) -$(CH_2)_mN(R^j)$-heteroaryl,
(43) -$(CH_2)_mC(O)R^f$,
(44) -$(CH_2)_mC(O)N(R^j)_2$,
(45) -$(CH_2)_mN(R^j)C(O)N(R^j)_2$,
(46) -$(CH_2)_mCO_2H$,
(47) -$(CH_2)_mOCOH$,
(48) -$(CH_2)_mCO_2R^f$,
(49) -$(CH_2)_mOCOR^f$,
(50) -$(CH_2)_mC_{3-7}$cycloalkyl,
(51) -$(CH_2)_mC_{3-7}$cycloalkenyl,
(52) -$(CH_2)_mC_{2-6}$cycloheteroalkyl,
(53) -$(CH_2)_mC_{2-6}$cycloheteroalkenyl,
(54) -$(CH_2)_m$aryl, and
(55) -$(CH_2)_m$heteroaryl,

wherein each CH_2 is unsubstituted or substituted with 1 or 2 substituents selected from: oxo, -OH, -$(CH_2)_{1-3}$OH, -CN, -NH_2, -NH(C_{1-6}alkyl), -N(C_{1-6}alkyl)$_2$, oxo, -C_{1-6}alkyl, -C_{1-6}alkyl substituted with 1-5 OH, -OC_{1-6}alkyl, halogen, -CH_2F, -CHF_2, -CF_3, -CO_2H, -CO_2C_{1-6}alkyl, -C_{3-7}cycloalkyl, phenyl, CH_2phenyl, heteroaryl and CH_2heteroaryl, and wherein alkyl, cycloalkyl, cycloalkenyl, cycloheteroalkyl, cycloheteroalkenyl, aryl and heteroaryl are unsubstituted or substituted with 1, 2, 3 or 4 substituents selected from: oxo, -OH, -$(CH_2)_{1-5}$OH, -$(CH_2)_{1-5}$CN, -CN, -NH_2, -NH(C_{1-6}alkyl), -N(C_{1-6}alkyl)$_2$, -C_{1-6}alkyl, -C_{1-6}alkyl substituted with 1-5 OH, -OC_{1-6}alkyl, halogen, -CH_2F, -CHF_2, -CF_3, -$(CH_2)_{1-5}CF_3$ optionally substituted with 1, 2 or 3 -OH, -CO_2H, -CO_2C_{1-6}alkyl, -SO_2C_{1-6}alkyl, -C_{3-7}cycloalkyl, phenyl, CH_2phenyl, heteroaryl and CH_2heteroaryl;

each R^b is independently selected from:

(1) hydrogen,
(2) -C_{1-6}alkyl,
(3) -C_{1-6}alkenyl,
(4) -$(CH_2)_nC_{3-10}$cycloalkyl,
(5) -$(CH_2)_nC_{3-10}$cycloalkenyl,
(6) -$(CH_2)_nC_{2-10}$cycloheteroalkyl,
(7) -$(CH_2)_nC_{2-10}$cycloheteroalkenyl,
(8) -$(CH_2)_n$aryl,
(9) -$(CH_2)_n$heteroaryl,
(10) oxo,
(11) -$(CH_2)_nCF_3$,

(12) -$(CH_2)_nCN$,
(13) -(CH_2)t-halogen,
(14) -(CH_2)s-OH,
(15) -$(CH_2)_nNO_2$,
(16) -$(CH_2)_nNH_2$,
(17) -$(CH_2)_nNH(C_{1-6}alkyl)$,
(18) -$(CH_2)_nN(C_{1-6}alkyl)_2$,
(19) -$(CH_2)_nNHCO_2H$,
(20) -$(CH_2)_nOC_{1-6}alkyl$,
(21) -$(CH_2)_nOC_{1-6}alkenyl$,
(22) –$(CH_2)_nCOC_{1-6}alkyl$,
(23) –$(CH_2)_nCO_2H$,
(24) –$(CH_2)_nOCOH$,
(25) –$(CH_2)_nCO_2R^i$,
(26) –$(CH_2)_nOC(O)R^i$,
(27) -$(CH_2)qC(O)N(R^e)_2$,
(28) -$(CH_2)qCO_2N(R^e)_2$,
(29) –$(CH_2)_nC(O)(CH_2)_nN(Rg)_2$,
(30) –$(CH_2)_nOC(O)(CH_2)_nN(Rg)_2$,
(31) -$(CH_2)nN(R^e)C(O)C_{1-6}alkyl$,
(32) –$(CH_2)_nN(R^e)SO_2R^i$,
(33) –$(CH_2)_nSO_2C_{1-6}alkyl$,
(34) –$(CH_2)_nSO_2N(R^e)Rg$,
(35) –$(CH_2)_nSO_2N(R^e)C(O)R^i$,
(36) –$(CH_2)_nSO_2N(R^e)CO_2R^i$,
(37) –$(CH_2)_nSO_2N(R^e)CON(Rg)_2$,
(38) –$(CH_2)_nC(O)N(R^e)SO_2R^i$,
(39) –$(CH_2)_nN(R^e)C(O)N(Rg)_2$,
(40) =N(OH), and
(41) =$N(OC_{1-6}alkyl)$,

wherein each CH_2 is unsubstituted or substituted with 1 or 2 substituents selected from: -C_{1-6}alkyl, -OH, halogen and -NH_2 wherein each NH is unsubstituted or substituted with 1 substituent selected from R^c, and wherein each alkyl, cycloalkyl, cycloalkenyl, cycloheteroalkyl, cycloheteroalkenyl, aryl and heteroaryl is unsubstituted or substituted with 1, 2, 3 or 4 substituents selected from R^c, or

wherein two R^b substituents and the carbon to which they are attached may form a 3 to 6 membered cycloalkyl ring, a 3-6 membered cycloalkenyl ring, a 3-6 membered cycloheteroalkyl

ring or a 3-6 membered cycloheteroalkenyl ring, wherein the ring is unsubstituted or substituted with 1, 2, 3 or 4 substituents selected from R^c;

each R^c is independently selected from:

(1) halogen,
(2) oxo,
(3) $-(CH_2)_rOH$,
(4) $-(CH_2)_rN(R^e)_2$,
(5) $-(CH_2)_rCN$,
(6) $-C_{1-6}$alkyl,
(7) $-CF_3$,
(8) $-C_{1-6}$alkyl-OH,
(9) $-OCH_2OC_{1-6}$alkyl,
(10) $-(CH_2)_rOC_{1-6}$alkyl,
(11) $-OCH_2$aryl,
(12) $-(CH_2)_rSC_{1-6}$alkyl,
(13) $-(CH_2)_rC(O)R^f$,
(14) $-(CH_2)_rC(O)N(R^e)_2$,
(15) $-(CH_2)_rCO_2H$,
(16) $-(CH_2)_rCO_2R^f$,
(17) $-(CH_2)_rC_{3-7}$cycloalkyl,
(18) $-(CH_2)_rC_{2-6}$cycloheteroalkyl,
(19) $-(CH_2)_r$aryl, and
(20) $-(CH_2)_r$heteroaryl,

wherein each CH_2 is unsubstituted or substituted with 1 or 2 substituents selected from: oxo, –OH, -CN, $-N(R^h)_2$, $-C_{1-6}$alkyl, $-OC_{1-6}$alkyl, halogen, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CO_2H$, $-CO_2C_{1-6}$alkyl, $-C_{3-7}$cycloalkyl and heteroaryl, and wherein alkyl, cycloalkyl, cycloheteroalkyl, aryl and heteroaryl are unsubstituted or substituted with 1, 2, 3 or 4 substituents selected from: oxo, –OH, -CN, $-N(R^h)_2$, $-C_{1-6}$alkyl, $-OC_{1-6}$alkyl, halogen, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CO_2H$, $-CO_2C_{1-6}$alkyl, $-C_{3-7}$cycloalkyl and heteroaryl;

each R^e, R^g and R^h is independently selected from:

(1) hydrogen,
(2) $-C_{1-6}$alkyl, and
(3) $-O-C_{1-6}$alkyl,

wherein alkyl is unsubstituted or substituted with 1, 2, 3 or 4 substituents selected from: -OH, oxo, halogen, C_{1-6}alkyl, $-OC_{1-6}$alkyl, $-NH_2$, $-NH(C_{1-6}$alkyl), and $-N(C_{1-6}$alkyl$)_2$;

each R^j is independently selected from:

(1) hydrogen,
(2) C_{1-6}alkyl,
(3) C_{3-6}cycloalkyl,
(4) $-C(O)R^i$,
(5) $-CO_2R^i$, and
(6) $-SO_2R^i$,

wherein alkyl and cycloalkyl are unsubstituted or substituted with 1, 2, 3 or 4 substituents selected from: -OH, oxo, halogen, C_{1-6}alkyl, -OC_{1-6}alkyl, $-NH_2$, -NH(C_{1-6}alkyl), and -N(C_{1-6}alkyl)$_2$;

each R^f and R^i is independently selected from:

(1) C_{1-6}alkyl,
(2) -$(CH_2)_r$$C_{4-7}$cycloalkyl,
(3) -$(CH_2)_r$$C_{4-7}$cycloalkenyl,
(4) -$(CH_2)_r$$C_{3-7}$cycloheteroalkyl,
(5) -$(CH_2)_r$$C_{3-7}$cycloheteroalkenyl,
(6) -$(CH_2)_r$aryl, and
(7) -$(CH_2)_r$heteroaryl,

wherein alkyl, cycloalkyl, cycloalkenyl, cycloheteroalkyl, cycloheteroalkenyl, aryl and heteroaryl are unsubstituted or substituted with 1, 2, 3 or 4 substituents selected from: oxo, -OH, -CN, $-NH_2$, -NH(C_{1-6}alkyl), -N(C_{1-6}alkyl)$_2$, -C_{1-6}alkyl, -OC_{1-6}alkyl, halogen, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CO_2H$, -CO_2C_{1-6}alkyl, -C_{3-7}cycloalkyl, and heteroaryl;

n is 0, 1, 2, 3 or 4;
m is 0, 1, 2, 3 or 4;
p is 0, 1, 2, or 3;
q is 0, 1, 2, 3 or 4;
r is 0, 1 or 2;
s is 0, 1, 2, 3 or 4;
t is 0, 1, 2, 3 or 4; and
u is 0, 1, 2, 3 or 4.

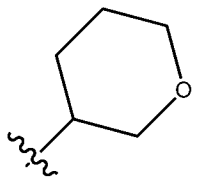
2. The compound according to Claim 1 wherein one of T, V and W is N or N-oxide, and U is $-CR^1$-; or a pharmaceutically acceptable salt thereof.

3. The compound according to Claims 1- 2 wherein T is N or N-oxide; U is -CR^1-; V is -CR^2-; and W is -CR^4-; or a pharmaceutically acceptable salt thereof.

4. The compound according to Claims 1- 3 wherein T is N; U is -CR^1-; V is -CR^2-; and W is -CR^4-; or a pharmaceutically acceptable salt thereof.

5. The compound according to Claims 1- 4, wherein X is -O-; or a pharmaceutically acceptable salt thereof.

6. The compound according to Claims 1- 5, wherein Y is:



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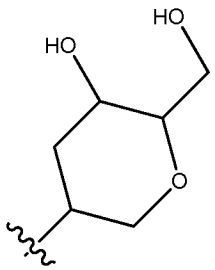
wherein Y is unsubstituted or substituted with 1, 2, 3, 4 or 5 substituents selected from R^b; or a pharmaceutically acceptable salt thereof.

7. The compound according to Claims 1- 6, wherein Y is:



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wherein Y is unsubstituted or substituted with 1, 2 or 3 substituents selected from R^b; or a pharmaceutically acceptable salt thereof.

8. The compound according to Claims 1- 7, wherein Z is NR^5; or a pharmaceutically acceptable salt thereof.

9. The compound according to Claims 1 - 8, each R^1 and R^2 is independently selected from:

(1) halogen,

(2) aryl-C_{2-8}alkynyl-heteroaryl,

(3) -C_{2-6}alkynyl-aryl,
(4) aryl,
(5) aryl-C_{3-7}cycloalkyl,
(6) aryl-C_{2-10}cycloheteroalkyl,
(7) aryl-aryl,
(8) aryl-heteroaryl, and
(9) heteroaryl,

wherein each alkynyl, cycloalkyl, cycloheteroalkyl, aryl and heteroaryl is unsubstituted or substituted with 1, 2, 3 or 4 substituents independently selected from R^a, provided that at least one of and only one of R^1 and R^2 is selected from halogen; or a pharmaceutically acceptable salt thereof.

10. The compound according to Claims 1-9, wherein each R^1 is independently selected from:

(1) aryl-C_{2-8}alkynyl-heteroaryl,
(2) -C_{2-6}alkynyl-aryl,
(3) aryl,
(4) aryl-C_{3-7}cycloalkyl,
(5) aryl-C_{2-10}cycloheteroalkyl,
(6) aryl-aryl,
(7) aryl-heteroaryl, and
(8) heteroaryl,

wherein each alkynyl, cycloalkyl, cycloheteroalkyl, aryl and heteroaryl is unsubstituted or substituted with 1, 2, 3 or 4 substituents independently selected from R^a; and
R^2 is selected from halogen;
or a pharmaceutically acceptable salt thereof.

11. The compound according to Claims 1-10, wherein each R^1 is independently selected from:

(1) aryl,
(2) aryl-C_{2-10}cycloheteroalkyl,
(3) aryl-aryl, and
(4) aryl-heteroaryl,

wherein each cycloheteroalkyl, aryl and heteroaryl is unsubstituted or substituted with 1, 2, 3 or 4 substituents independently selected from R^a, and
R^2 is selected from halogen;
or a pharmaceutically acceptable salt thereof.

12. The compound according to Claims 1- 11, wherein each R^1 is independently selected from:

(1) phenyl,

(2) phenyl-pyrrolidine,

(3) biphenyl, and

(4) phenyl-pyridine,

wherein each pyrrolidine, phenyl, and pyridine is unsubstituted or substituted with 1, 2, 3 or 4 substituents independently selected from R^a, and

R^2 is halogen;

or a pharmaceutically acceptable salt thereof.

13. The compound according to Claims 1- 12, wherein R^3 is hydrogen or absent; R^4 is hydrogen; and R^5 is hydrogen; or a pharmaceutically acceptable salt thereof.

14. The compound according to Claims 1- 13, wherein R^3 is hydrogen or absent; R^4 is hydrogen; R^5 is hydrogen; and R^2 is halogen; or a pharmaceutically acceptable salt thereof.

15. The compound according to Claim 1 wherein:

T is N;

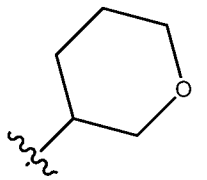
U is $-CR^1-$;

V is $-CR^2-$;

W is $-CR^4-$;

X is -O-;

Y is:



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wherein Y is unsubstituted or substituted with 1, 2, 3, 4 or 5 substituents selected from R^b;

Z is NR^5;

each R^1 is independently selected from:

(1) aryl-C_{2-8}alkynyl-heteroaryl,

(2) -C_{2-6}alkynyl-aryl,

(3) aryl,

(4) aryl-C_{3-7}cycloalkyl,

(5) aryl-C_{2-10}cycloheteroalkyl,

(6) aryl-aryl,

(7) aryl-heteroaryl, and

(8) heteroaryl,

wherein each alkynyl, cycloalkyl, cycloheteroalkyl, aryl and heteroaryl is unsubstituted or substituted with 1, 2, 3 or 4 substituents independently selected from R^a;

R^2 is halogen;

R^4 is hydrogen; and

R^5 is hydrogen;

or a pharmaceutically acceptable salt thereof.

16. The compound according to Claim 1 wherein:

T is N;

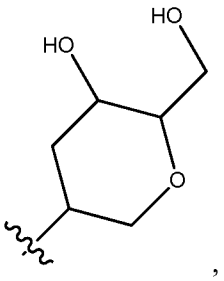
U is $-CR^1-$;

V is $-CR^2-$;

W is $-CR^4-$;

X is -O-;

Y is:



,

wherein Y is unsubstituted or substituted with 1, 2 or 3 substituents selected from R^b;

Z is NR^5;

each R^1 is independently selected from:

(1) aryl,

(2) aryl-C_{2-10}cycloheteroalkyl,

(3) aryl-aryl, and

(4) aryl-heteroaryl,

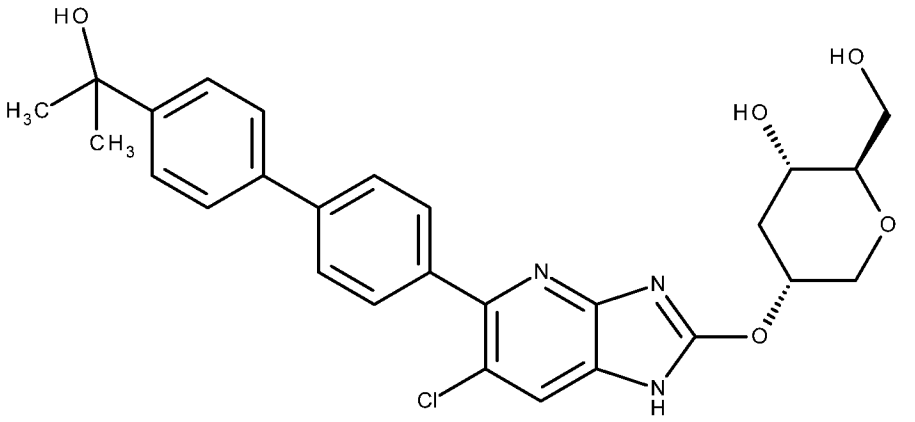
wherein each cycloheteroalkyl, aryl and heteroaryl is unsubstituted or substituted with 1, 2, 3 or 4 substituents independently selected from R^a;

R^2 is halogen;

R^4 is hydrogen; and

R^5 is hydrogen;
or a pharmaceutically acceptable salt thereof.

17. The compound according to Claim 1 selected from:



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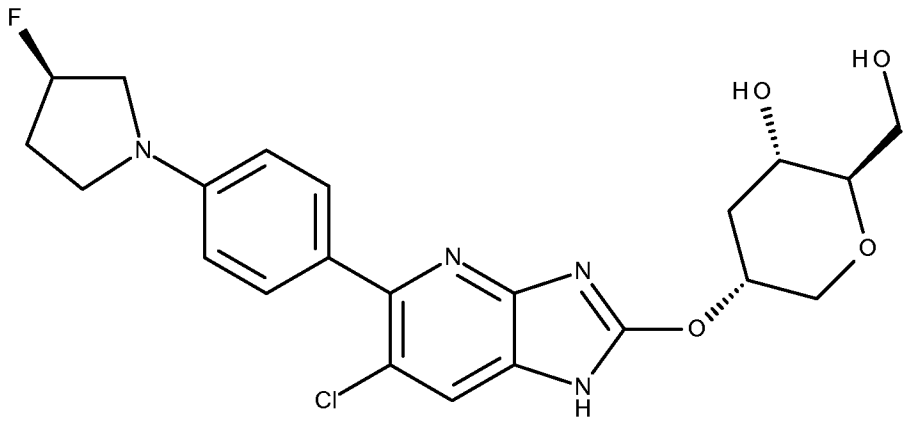

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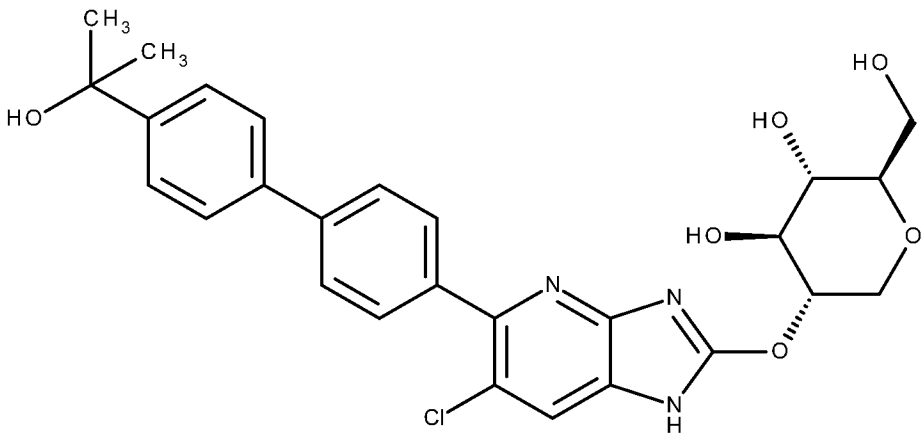

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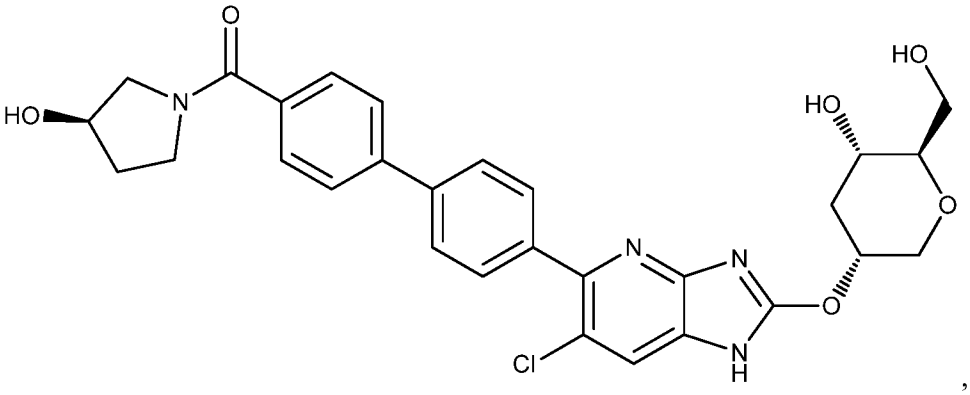

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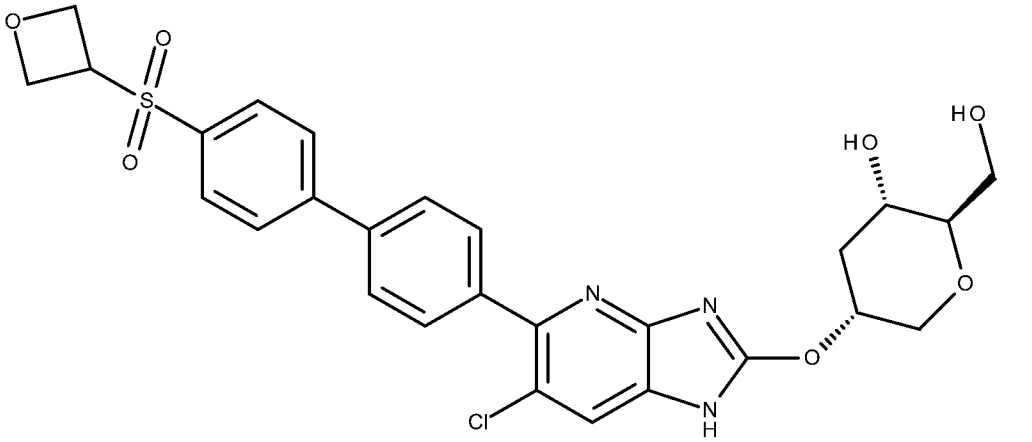

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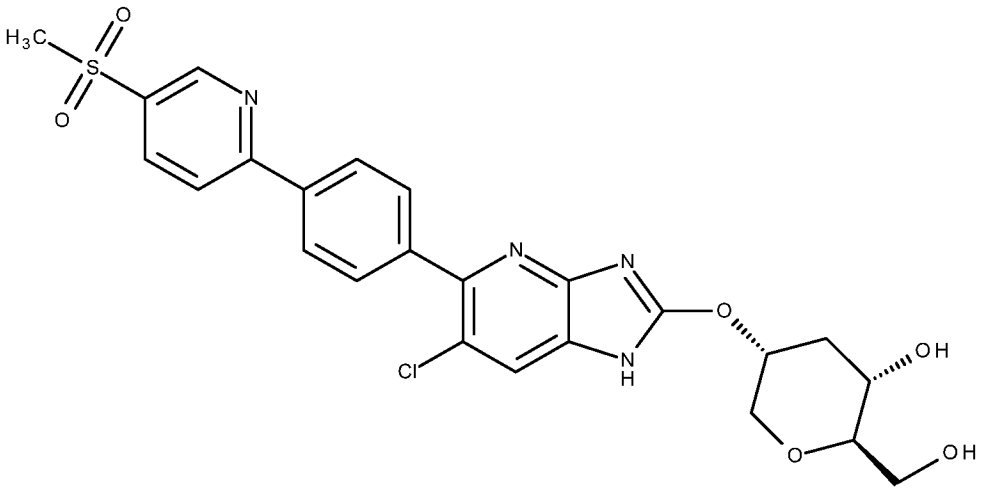

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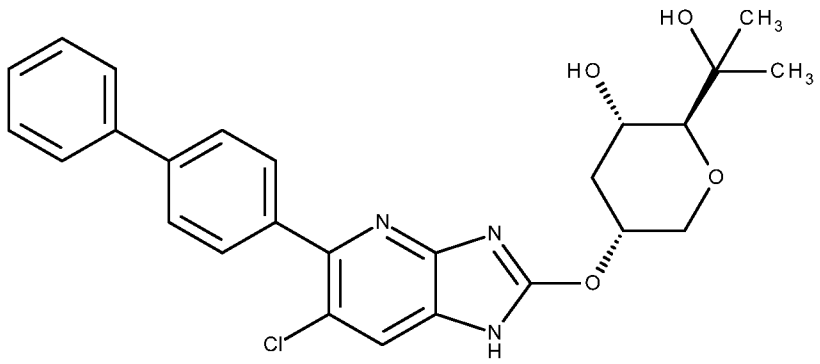

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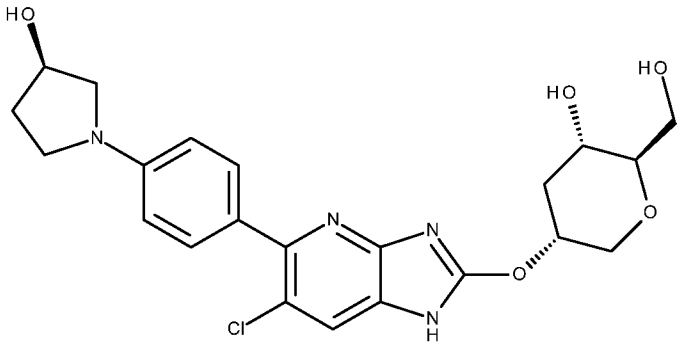

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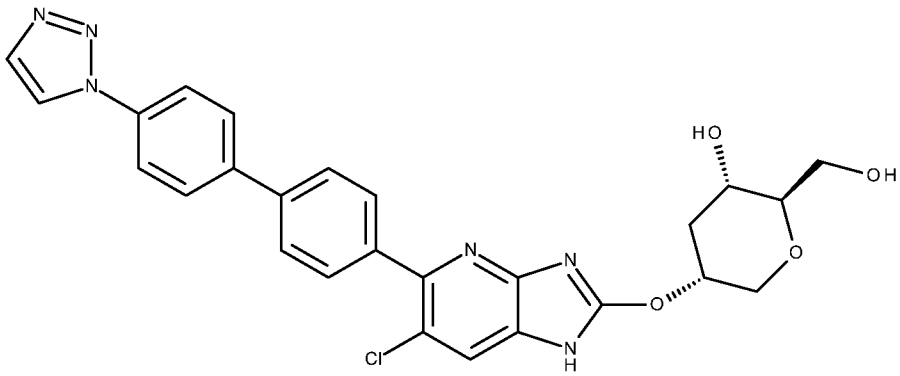
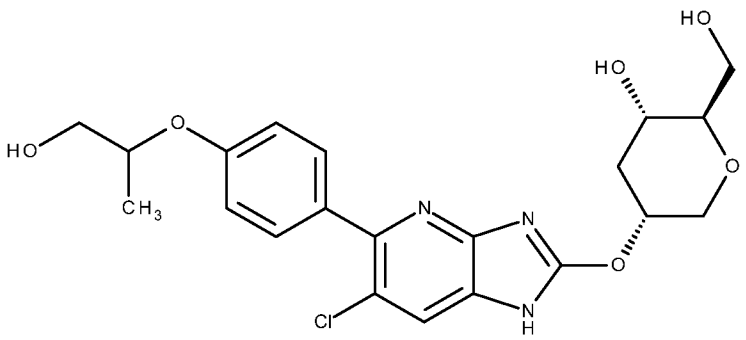


, , and



5 ;

or a pharmaceutically acceptable salt thereof.

18. A composition comprising a compound of Claims 1 – 17, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

19. A composition comprising a compound according to Claims 1 – 17, or a pharmaceutically acceptable salt thereof, and a compound selected from simvastatin, ezetimibe and sitagliptin; and a pharmaceutically acceptable carrier.

20. The use of a compound according to Claims 1 – 17, or a pharmaceutically acceptable salt thereof, for the preparation of a medicament useful for the treatment of a disorder, condition, or disease that is responsive to the activation of AMP-activated protein kinase in a mammal in need thereof.

21. The use according to Claim 20 wherein the disorder, condition, or disease is Type 2 diabetes.

22. The use of a compound of Claims 1 – 17, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of Type 2 diabetes.

23. A compound according to Claims 1 – 17, or a pharmaceutically acceptable salt thereof, for use in therapy.

24. A method of treating or preventing a disorder, condition or disease that is responsive to the activation of AMP-activated protein kinase in a patient in need thereof comprising administration of a therapeutically effective amount of a compound according to Claim 1, or a pharmaceutically acceptable salt thereof.

25. The method of Claim 24 wherein the disorder, condition, or disease is Type 2 diabetes.

26. A method of treating type 2 diabetes mellitus in a patient in need of treatment comprising the administration to the patient of a therapeutically effective amount of a compound of Claim 1, or a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US13/55240

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61P 3/10; A61K 31/4184, 31/415, 31/454 (2013.01)

USPC - 514/234.5, 395; 548/305.1

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC(8): A61P 3/10; A61K 31/4184, 31/415, 31/454, 31/497, 31/4439; A01N 43/52, 43/50 (2013.01)
USPC: 514/234.5, 395, 338, 322, 255.05; 548/305.1; 546/199, 273.7; 544/139, 405

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

MicroPatent (US-G, US-A, EP-A, EP-B, WO, JP-bib, DE-C,B, DE-A, DE-T, DE-U, GB-A, FR-A); Reaxys; IP.com; ProQuest; Google/Google Scholar; Key Words: benzimidazole, tetrahydrofuran, AMP*, activat*, protein*, kinase*, diabet*

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y -- A	WO 2011/106273 A1 (JIANG, J et al.) 01 September 2011; page 98, lines 1-14; page 99, lines 1-10; page 100, lines 1-10; page 101	1-2, 3/1-2, 15, 24-26 ---------- 16, 17
Y -- A	CA 2811025 A1 (TONOGAKI, K et al.) 15 March 2012; claim 6	1-2, 3/1-2, 15, 24-26 ---------- 16, 17
A	IKEHARA, M et al. "Studies of nucleosides and nucleotides—LIV: Purine cyclonucleosides—19. Further investigations on the cleavage of the 8,2'-O-anhydro linkage. A new synthesis of 9-β-D-arabinofuranosyladenine" Tetrahedron, Vol. 28, No. 14, pages 3695-3704, 1972; compound XI, chart 2, page 3700	16, 17
A	US 2011/0195964 A1 (DANG, Q et al.) 11 August 2011; entire document	1-2, 3/1-2, 15-17, 24-26
A	US 2011/0218174 A1 (BAO, J et al.) 8 September 2011; entire document	1-2, 3/1-2, 15-17, 24-26

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
03 January 2014 (03.01.2014)	31 JAN 2014

Name and mailing address of the ISA/US	Authorized officer:
Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Shane Thomas PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US13/55240

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 4-14 and 18-23
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.