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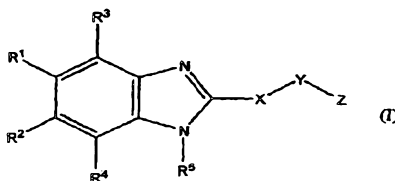
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(54) Title: NOVEL CYCLIC BENZIMIDAZOLE DERIVATIVES USEFUL ANTI-DIABETIC AGENTS



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



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TITLE OF THE INVENTION

NOVEL CYCLIC BENZIMIDAZOLE DERIVATIVES USEFUL ANTI-DIABETIC AGENTS

BACKGROUND OF THE INVENTION

5 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
10 having 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,
15 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
20 patient may 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).

25 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,
30 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
35 referred to as Syndrome X or Metabolic Syndrome. Patients with Metabolic Syndrome have an increased risk of developing 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
5 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, englitazone, balaglitazone, MCC-555, netoglitazone, T-131, LY-300512, LY-818 and
10 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
15 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
20 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
25 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
30 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
35 and muscle via glycerol-3-phosphate acyltransferase (Muoio, D. M. et.al., Biochem. J. 338:783 (1999)). Another substrate of AMPK, hepatocyte nuclear factor-4 α , 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*
 5 *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)
 10 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
 15 (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
 20 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.*
 25 108: 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
 30 and fatty acid oxidation with resulting improvement of glucose homeostasis, and an improvement in insulin action. Finally, the resulting increase in energy expenditure should 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
 35 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.,

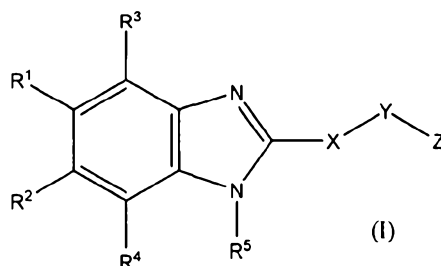
J. Neurochem. 73: 1674 (1999)); to prevent damage from reactive oxygen species (Zhou, M. et.al., Am. J. Physiol. Endocrinol. Metab. 279: E622 (2000)); and to improve local circulatory systems (Chen, Z.-P., et.al. AMP-activated protein kinase phosphorylation of endothelial NO synthase. FEBS Letters 443: 285 (1999)).

Compounds that activate AMPK are expected to 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 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.

SUMMARY OF THE INVENTION

A first aspect of the invention provides for a compound of structural formula I:



or a pharmaceutically acceptable salt thereof, wherein:

X is selected from:

- (1) -S-,
- (2) -O-,
- (3) -O-CH₂-, and
- (4) -NH-,

wherein CH₂ is unsubstituted or substituted with 1 or 2 substituents selected from: hydroxy, halogen, NH₂, C₁-6alkyl, CO₂H, CO₂C₁-6alkyl, COC₁-6alkyl, phenyl and -CH₂phenyl, and wherein NH is unsubstituted or substituted with 1 substituent selected from: C₁-6alkyl, CO₂H, CO₂C₁-6alkyl, COC₁-6alkyl, phenyl and -CH₂phenyl;

Y is selected from:

- (1) $-C_{2-10}$ cycloheteroalkenyl,
- (2) aryl, and
- (3) heteroaryl,

5 wherein cycloheteroalkenyl, aryl and heteroaryl are unsubstituted or substituted with 1, 2, 3 or 4 substituents selected from R^b ;

Z is selected from:

- (1) oxo,
- (2) $-CN$,
- 10 (3) $-(CH_2)_nCO_2H$,
- (4) $-(CH_2)_nCO_2R^i$,
- (5) $-(CH_2)_nOH$,
- (6) $-(CH_2)_nC(O)NHR^g$,
- (7) $-(CH_2)_nNHC(O)C_{1-6}alkyl$,
- 15 (8) $-(CH_2)_nSO_2NHR^g$,
- (9) $-(CH_2)_nSO_2NHC(O)R^i$,
- (10) $-(CH_2)_nC(O)NHSO_2R^i$,
- (11) $-(CH_2)_nNHC(O)N(R^g)_2$,
- (12) $-(CH_2)_nC_{3-10}cycloalkyl-CO_2R^e$,
- 20 (13) heteroaryl,
- (14) $-C_{2-10}$ cycloheteroalkenyl, and
- (15) $-C_{2-10}$ cycloheteroalkyl,

wherein each CH_2 is unsubstituted or substituted with 1 or 2 substituents selected from $C_{1-6}alkyl$, $-OH$ and $-NH_2$, wherein each NH is unsubstituted or substituted with
25 1 substituent selected from R^c , and wherein each alkyl, cycloalkyl, cycloheteroalkyl, cycloheteroalkenyl, aryl and heteroaryl is unsubstituted or substituted with 1, 2, 3 or 4 substituents selected from R^c ;

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

- (1) halogen,
- 30 (2) $-CN$,
- (3) $-CF_3$,
- (4) $-C_{1-6}alkyl$,
- (5) $-(CH_2)_paryl$,

- (6) biphenyl,
- (7) $-(CH_2)_p$ heteroaryl,
- (8) $-C_{2-6}$ alkenyl-aryl,
- (9) $-C_{2-6}$ alkynyl-alkyl,
- 5 (10) $-C_{2-6}$ alkynyl-aryl,
- (11) $-C_{2-6}$ alkynyl-heteroaryl,
- (12) $-C_{2-6}$ alkynyl- C_{3-7} cycloalkyl,
- (13) $-C_{2-6}$ alkynyl- C_{2-7} cycloheteroalkyl, and
- (14) $-C_{2-6}$ alkynyl- C_{2-7} cycloheteroalkenyl,

10 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 $-N(C_{1-6}alkyl)_2$,

wherein alkyl, alkenyl and alkynyl is unsubstituted or substituted with 1, 2 or 3 substituents selected from: halogen, CF_3 , $-OH$, $-NH_2$, $-C_{1-6}$ alkyl, $-OC_{1-6}$ alkyl,
15 $-NHC_{1-6}$ alkyl, and $-N(C_{1-6}alkyl)_2$, and wherein each 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: halogen, $-CN$, $-CF_3$, and $-C_{1-6}$ alkyl;

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

- (1) hydrogen,
- (2) halogen,
- (3) $-C_{1-6}$ alkyl,
- (4) $-CN$,
- 25 (5) $-CF_3$,
- (6) $-OH$,
- (7) $-OC_{1-6}$ alkyl,
- (8) $-SOC_{1-6}$ alkyl, and
- (9) $-SO_2C_{1-6}$ alkyl;

R⁵ is selected from:

- (1) hydrogen,
- (2) -C₁₋₆alkyl,
- (3) -CH₂CO₂H, and
- (4) -CH₂CO₂C₁₋₆alkyl;

R^a is independently selected from the group consisting of:

- (1) halogen,
- (2) oxo,
- (3) -(CH₂)_mOH,
- (4) -(CH₂)_mN(R^j)₂,
- (5) -CN,
- (6) -C₁₋₆alkyl,
- (7) -(CH₂)_mCF₃,
- (8) -OCF₃,
- (9) -C(=N-OH)N(R^j)₂,
- (10) -OC₁₋₆alkyl,
- (11) -SC₁₋₆alkyl,
- (12) -S(O)C₁₋₆alkyl,
- (13) -C(O)C₁₋₆alkyl,
- (14) -C(O)C₂₋₆cycloheteroalkyl,
- (15) -C(O)NH₂,
- (16) -C(O)N(C₁₋₆alkyl)₂,
- (17) -CO₂H, -OC(O)H,
- (18) -CO₂C₁₋₆alkyl,
- (19) -OC(O)C₁₋₆alkyl,
- (20) -(CH₂)_mC₃₋₇cycloalkyl,
- (21) -C₂₋₆cycloheteroalkyl,
- (22) -C₂₋₆cycloheteroalkenyl,
- (23) aryl, and
- (24) heteroaryl,

wherein each CH₂ is unsubstituted or substituted with 1 or 2 substituents selected from: oxo, -(CH₂)₀₋₃OH, -CN, -NH₂, -NH(C₁₋₆alkyl), -N(C₁₋₆alkyl)₂, -C₁₋₆alkyl, -OC₁₋₆alkyl, halogen, -CH₂F, -CHF₂, -CF₃, -CO₂H, -CO₂C₁₋₆alkyl, -C₃₋₇cycloalkyl, phenyl, and CH₂phenyl, and wherein alkyl, cycloalkyl, cycloheteroalkyl, aryl and heteroaryl are unsubstituted or substituted with 1, 2, 3 or 4 substituents selected from: oxo, -(CH₂)₀₋₃OH, -CN, -NH₂, -NH(C₁₋₆alkyl), -N(C₁₋₆alkyl)₂, -C₁₋₆alkyl, -OC₁₋₆alkyl, halogen, -CH₂F, -CHF₂, -CF₃, -CO₂H, -CO₂C₁₋₆alkyl, -C₃₋₇cycloalkyl, phenyl, and CH₂phenyl;

each R^b is independently selected from:

- (1) hydrogen,
- (2) -C₁₋₆alkyl,
- (3) -C₃₋₆cycloalkyl,
- (4) -C₃₋₆cycloalkenyl,
- (5) -C₂₋₆cycloheteroalkyl,
- (6) aryl,
- (7) heteroaryl,
- (8) halogen,
- (9) -OH,
- (10) -NO₂,
- (11) -NH₂,
- (12) -NH(C₁₋₆alkyl),
- (13) -N(C₁₋₆alkyl)₂,
- (14) -OC₁₋₆alkyl,
- (15) -(CH₂)_qCO₂H,
- (16) -(CH₂)_qCO₂C₁₋₆alkyl,
- (17) -CF₃,
- (18) -CN,
- (19) -SO₂C₁₋₆alkyl, and
- (20) -(CH₂)_qCON(R^e)₂,

wherein each CH₂ is unsubstituted or substituted with 1 or 2 halogens, and wherein each alkyl, cycloalkyl, cycloalkenyl, cycloheteroalkyl, aryl and heteroaryl is unsubstituted or substituted with 1, 2 or 3 halogens;

each R^c is independently selected from:

- (1) halogen,
- (2) oxo,
- (3) -(CH₂)_rOH,
- 5 (4) -(CH₂)_rN(R^e)₂,
- (5) -(CH₂)_rCN,
- (6) -C₁₋₆alkyl,
- (7) -CF₃,
- (8) -C₁₋₆alkyl-OH,
- 10 (9) -OCH₂OC₁₋₆alkyl,
- (10) -(CH₂)_rOC₁₋₆alkyl,
- (11) -OCH₂aryl,
- (12) -(CH₂)_rSC₁₋₆alkyl,
- (13) -(CH₂)_rC(O)R^f,
- 15 (14) -(CH₂)_rC(O)N(R^e)₂,
- (15) -(CH₂)_rCO₂H,
- (16) -(CH₂)_rCO₂R^f,
- (17) -(CH₂)_rC₃₋₇cycloalkyl,
- (18) -(CH₂)_rC₂₋₆cycloheteroalkyl,
- 20 (19) -(CH₂)_raryl, and
- (20) -(CH₂)_rheteroaryl,

wherein each CH₂ is unsubstituted or substituted with 1 or 2 substituents selected from: oxo, -OH, -CN, -N(R^h)₂, -C₁₋₆alkyl, -OC₁₋₆alkyl, halogen, -CH₂F, -CHF₂, -CF₃, -CO₂H, -CO₂C₁₋₆alkyl, -C₃₋₇cycloalkyl and heteroaryl, and wherein alkyl, cycloalkyl, 25 cycloheteroalkyl, aryl and heteroaryl are unsubstituted or substituted with 1, 2, 3 or 4 substituents selected from: oxo, -OH, -CN, -N(R^h)₂, -C₁₋₆alkyl, -OC₁₋₆alkyl, halogen, -CH₂F, -CHF₂, -CF₃, -CO₂H, -CO₂C₁₋₆alkyl, -C₃₋₇cycloalkyl and heteroaryl;

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

- (1) hydrogen, and
- 30 (2) C₁₋₆alkyl,

wherein alkyl is unsubstituted or substituted with 1, 2, 3 or 4 substituents selected from: -OH, oxo, halogen, C₁₋₆alkyl, -OC₁₋₆alkyl, -NH₂, -NH(C₁₋₆alkyl), and -N(C₁₋₆alkyl)₂;

each R^j is independently selected from:

- (1) hydrogen,
- 35 (2) C₁₋₆alkyl,

- (3) C₃₋₆cycloalkyl,
- (4) -C(O)Rⁱ, and
- (5) -SO₂Rⁱ,

wherein alkyl and cycloalkyl are unsubstituted or substituted with 1, 2, 3 or 4 substituents selected from: -OH, oxo, halogen, C₁₋₆alkyl, -OC₁₋₆alkyl, -NH₂, -NH(C₁₋₆alkyl), and -N(C₁₋₆alkyl)₂;

each R^f and Rⁱ is independently selected from:

- (1) C₁₋₆alkyl,
- (2) C₄₋₇cycloalkyl,
- (3) C₄₋₇cycloalkenyl,
- (4) C₃₋₇cycloheteroalkyl,
- (5) C₃₋₇cycloheteroalkenyl,
- (6) aryl, and
- (7) 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, -NH₂, -C₁₋₆alkyl, -OC₁₋₆alkyl, halogen, -CH₂F, -CHF₂, -CF₃, -CO₂H, -CO₂C₁₋₆alkyl, -C₃₋₇cycloalkyl, 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; and

r is 0, 1 or 2.

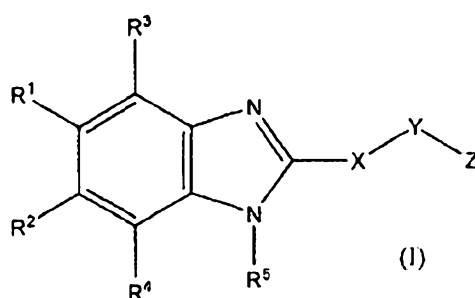
A second aspect of the invention provides for a composition comprising a compound according to the first aspect of the invention, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

A third aspect of the invention provides for a composition comprising a compound according to the first aspect of the invention, or a pharmaceutically acceptable salt thereof, and a compound selected from simvastatin, ezetimibe, taranabant and sitagliptin; and a pharmaceutically acceptable carrier.

A fourth aspect of the invention provides for the use of a compound according to the first aspect of the invention, or a pharmaceutically acceptable salt thereof, for the preparation of a medicament useful for the treatment of a disorder, condition, or disease responsive to the activation of AMP-activated protein kinase in a mammal in need thereof.

A fifth aspect of the invention provides for a method of treating a disorder, condition or disease 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 the first aspect of the invention, or a pharmaceutically acceptable salt thereof, or a composition of the second aspect of the invention.

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



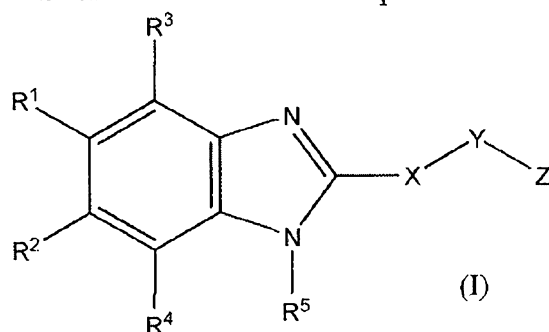
and pharmaceutically acceptable salts thereof. The compounds of structural formula I, and embodiments thereof, are activators of AMP-activated protein kinase (AMPK) and are useful in the treatment, prevention and suppression of diseases, disorders and conditions mediated by activation of AMP-activated protein kinase, such as 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 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 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 known to be 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:



or a pharmaceutically acceptable salt thereof, wherein:

X is absent or selected from:

- (1) -CH₂-,
- (2) -CHF-,
- (3) -CF₂-,
- (4) -S-,
- (5) -O-,
- (6) -O-CH₂-,
- (7) -NH-,
- (8) -C(O)-,
- (9) -NHC(O)-,
- (10) -C(O)NH-,
- (11) -NHSO₂-,
- (12) -SO₂NH-, and
- (13) -CO₂-,

wherein each CH₂ is unsubstituted or substituted with 1 or 2 substituents selected from:

hydroxy, halogen, NH₂, C₁₋₆alkyl, CO₂H, CO₂C₁₋₆alkyl, COC₁₋₆alkyl, phenyl and -CH₂phenyl, and wherein each NH is unsubstituted or substituted with 1 substituent selected

from: C₁₋₆alkyl, CO₂H, CO₂C₁₋₆alkyl, COC₁₋₆alkyl, phenyl and -CH₂phenyl;

Y is selected from:

- (1) C₃₋₁₀cycloalkyl,
- (2) C₃₋₁₀cycloalkenyl,
- 5 (3) C₂₋₁₀cycloheteroalkyl,
- (4) C₂₋₁₀cycloheteroalkenyl,
- (5) aryl, and
- (6) heteroaryl,

wherein cycloalkyl, cycloalkenyl, cycloheteroalkyl, cycloheteroalkenyl, aryl and heteroaryl are
 10 unsubstituted or substituted with 1, 2, 3 or 4 substituents selected from R^b;

Z is selected from:

- (1) oxo,
- (2) -CN,
- (3) -(CH₂)_nCO₂H,
- 15 (4) -(CH₂)_nCO₂Rⁱ,
- (5) -(CH₂)_nOH,
- (6) -(CH₂)_nC(O)NHR^g,
- (7) -(CH₂)_nNHC(O)C₁₋₆alkyl,
- (8) -(CH₂)_nNHSO₂Rⁱ,
- 20 (9) -(CH₂)_nSO₂NHR^g,
- (10) -(CH₂)_nSO₂NHC(O)Rⁱ,
- (11) -(CH₂)_nSO₂NHCO₂Rⁱ,
- (12) -(CH₂)_nSO₂NHCON(R^g)₂,
- (13) -(CH₂)_nC(O)NHSO₂Rⁱ,
- 25 (14) -(CH₂)_nNHC(O)N(R^g)₂,
- (15) -(CH₂)_nC₃₋₁₀cycloalkyl-CO₂R^e,
- (16) heteroaryl,
- (17) -C₂₋₁₀cycloheteroalkenyl, and
- (18) -C₂₋₁₀cycloheteroalkyl,

30 wherein each CH₂ is unsubstituted or substituted with 1 or 2 substituents selected from C₁₋₆alkyl, -OH and -NH₂, wherein each NH is unsubstituted or substituted with 1 substituent selected from R^c, and wherein each alkyl, cycloalkyl, cycloheteroalkyl, cycloheteroalkenyl, aryl and heteroaryl is unsubstituted or substituted with 1, 2, 3 or 4 substituents selected from R^c;
 each R¹ and R² is independently selected from:

- 35 (1) hydrogen,
- (2) halogen,
- (3) -CN,

- (4) -CF₃,
 (5) -C₁₋₆alkyl,
 (6) -C₂₋₆alkenyl,
 (7) -C₂₋₆alkynyl,
 5 (8) -(CH₂)_pC₃₋₁₀cycloalkyl,
 (9) -(CH₂)_pC₃₋₇cycloalkyl-aryl,
 (10) -(CH₂)_pC₃₋₇cycloalkyl-heteroaryl,
 (11) -(CH₂)_pC₄₋₁₀cycloalkenyl,
 (12) -(CH₂)_pC₄₋₇cycloalkenyl-aryl,
 10 (13) -(CH₂)_pC₄₋₇cycloalkenyl-heteroaryl,
 (14) -(CH₂)_pC₂₋₁₀cycloheteroalkyl,
 (15) -(CH₂)_pC₂₋₁₀cycloheteroalkenyl,
 (16) -(CH₂)_paryl,
 (17) biphenyl,
 15 (18) -(CH₂)_pheteroaryl,
 (19) -C₂₋₆alkenyl-alkyl,
 (20) -C₂₋₆alkenyl-aryl,
 (21) -C₂₋₆alkenyl-heteroaryl,
 (22) -C₂₋₆alkenyl-C₃₋₇cycloalkyl,
 20 (23) -C₂₋₆alkenyl-C₃₋₇cycloalkenyl,
 (24) -C₂₋₆alkenyl-C₂₋₇cycloheteroalkyl,
 (25) -C₂₋₆alkenyl-C₂₋₇cycloheteroalkenyl,
 (26) -C₂₋₆alkynyl-(CH₂)₁₋₃-O-aryl,
 (27) -C₂₋₆alkynyl-alkyl,
 25 (28) -C₂₋₆alkynyl-aryl,
 (29) -C₂₋₆alkynyl-heteroaryl,
 (30) -C₂₋₆alkynyl-C₃₋₇cycloalkyl,
 (31) -C₂₋₆alkynyl-C₃₋₇cycloalkenyl,
 (32) -C₂₋₆alkynyl-C₂₋₇cycloheteroalkyl,
 30 (33) -C₂₋₆alkynyl-C₂₋₇cycloheteroalkenyl, and
 (34) -C(O)NH-(CH₂)₀₋₃phenyl,

wherein each CH₂ is unsubstituted or substituted with 1 or 2 substituents selected from: halogen, CF₃, -OH, -NH₂, -C₁₋₆alkyl, -OC₁₋₆alkyl, -NHC₁₋₆alkyl, and -N(C₁₋₆alkyl)₂, wherein each alkyl, alkenyl and alkynyl is unsubstituted or substituted with 1, 2 or 3 substituents selected from:
 35 halogen, CF₃, -OH, -NH₂, -C₁₋₆alkyl, -OC₁₋₆alkyl, -NHC₁₋₆alkyl, and -N(C₁₋₆alkyl)₂, and wherein each 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, -CF₃, -C₁₋₆alkyl, -C₂₋₆alkenyl and -C₂₋₆alkynyl, and provided that if R^1 or R^2 is hydrogen, then at least one of R^3 and R^4 is not hydrogen;

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

- 5 (1) hydrogen,
- (2) halogen,
- (3) -C₁₋₆alkyl,
- (4) -C₂₋₆alkenyl,
- (5) -C₂₋₆alkynyl,
- 10 (6) -C₃₋₁₀cycloalkyl,
- (7) -C₃₋₁₀cycloalkenyl,
- (8) aryl,
- (9) heteroaryl,
- (10) -CN,
- 15 (11) -CF₃,
- (12) -OH,
- (13) -OC₁₋₆alkyl,
- (14) -NH₂,
- (15) -NHC₁₋₆alkyl,
- 20 (16) -N(C₁₋₆alkyl)₂,
- (17) -SC₁₋₆alkyl,
- (18) -SOC₁₋₆alkyl,
- (19) -SO₂C₁₋₆alkyl,
- (20) -NHSO₂C₁₋₆alkyl,
- 25 (21) -NHC(O)C₁₋₆alkyl,
- (22) -SO₂NHC₁₋₆alkyl, and
- (23) -C(O)NHC₁₋₆alkyl;

R^5 is selected from:

- 30 (1) hydrogen,
- (2) -C₁₋₆alkyl,
- (3) -CH₂CO₂H, and
- (4) -CH₂CO₂C₁₋₆alkyl;

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

- 35 (1) halogen,
- (2) oxo,
- (3) -(CH₂)_mOH,
- (4) -(CH₂)_mN(R^j)₂,

- (5) $-(CH_2)_mNO_2$,
 (6) $-(CH_2)_mCN$,
 (7) $-C_{1-6}alkyl$,
 (8) $-(CH_2)_mCF_3$,
 5 (9) $-(CH_2)_mOCF_3$,
 (10) $-OCH_2OC_{1-6}alkyl$,
 (11) $-OCH_2-aryl$,
 (12) $-(CH_2)_mC(=N-OH)N(R^j)_2$,
 (13) $-(CH_2)_mOC_{1-6}alkyl$,
 10 (14) $-(CH_2)_mO-aryl$,
 (15) $-OCH_2phenyl$,
 (16) $-(CH_2)_mSC_{1-6}alkyl$,
 (17) $-(CH_2)_mS(O)C_{1-6}alkyl$,
 (18) $-(CH_2)_mS(O)_2C_{1-6}alkyl$,
 15 (19) $-(CH_2)_mNHS(O)_2C_{1-6}alkyl$,
 (20) $-(CH_2)_mC(O)R^f$,
 (21) $-(CH_2)_mC(O)N(R^j)_2$,
 (22) $-(CH_2)_mN(R^j)C(O)R^f$,
 (23) $-(CH_2)_mN(R^j)C(O)N(R^j)_2$,
 20 (24) $-(CH_2)_mCO_2H$,
 (25) $-(CH_2)_mOC(O)H$,
 (26) $-(CH_2)_mCO_2R^f$,
 (27) $-(CH_2)_mOC(O)R^f$,
 (28) $-(CH_2)_mC_{3-7}cycloalkyl$,
 25 (29) $-(CH_2)_mC_{3-7}cycloalkenyl$,
 (30) $-(CH_2)_mC_{2-6}cycloheteroalkyl$,
 (31) $-(CH_2)_mC_{2-6}cycloheteroalkenyl$,
 (32) $-(CH_2)_maryl$, and
 (33) $-(CH_2)_mheteroaryl$,
 30 wherein each CH_2 is unsubstituted or substituted with 1 or 2 substituents selected from: oxo, -
 $(CH_2)_{0-3}OH$, $-CN$, $-NH_2$, $-NH(C_{1-6}alkyl)$, $-N(C_{1-6}alkyl)_2$, $-C_{1-6}alkyl$, $-OC_{1-6}alkyl$, halogen, -
 CH_2F , $-CHF_2$, $-CF_3$, $-CO_2H$, $-CO_2C_{1-6}alkyl$, $-C_{3-7}cycloalkyl$, phenyl, $CH_2phenyl$, heteroaryl
 and $CH_2heteroaryl$, and wherein alkyl, cycloalkyl, cycloheteroalkyl, phenyl, aryl and heteroaryl
 are unsubstituted or substituted with 1, 2, 3 or 4 substituents selected from: oxo, $-(CH_2)_{0-3}OH$, -
 35 CN , $-NH_2$, $-NH(C_{1-6}alkyl)$, $-N(C_{1-6}alkyl)_2$, $-C_{1-6}alkyl$, $-OC_{1-6}alkyl$, halogen, $-CH_2F$, $-CHF_2$,
 $-CF_3$, $-CO_2H$, $-CO_2C_{1-6}alkyl$, $-C_{3-7}cycloalkyl$, phenyl, $CH_2phenyl$, heteroaryl and
 $CH_2heteroaryl$;

each R^b is independently selected from:

- (1) hydrogen,
- (2) -C₁₋₆alkyl,
- (3) -C₃₋₆cycloalkyl,
- 5 (4) -C₃₋₆cycloalkenyl,
- (5) -C₂₋₆cycloheteroalkyl,
- (6) aryl,
- (7) heteroaryl,
- (8) halogen,
- 10 (9) -OH,
- (10) -NO₂,
- (11) -NH₂,
- (12) -NH(C₁₋₆alkyl),
- (13) -N(C₁₋₆alkyl)₂,
- 15 (14) -OC₁₋₆alkyl,
- (15) -(CH₂)_qCO₂H,
- (16) -(CH₂)_qCO₂C₁₋₆alkyl,
- (17) -CF₃,
- (18) -CN,
- 20 (19) -SO₂C₁₋₆alkyl, and
- (20) -(CH₂)_qCON(R^e)₂,

wherein each CH₂ is unsubstituted or substituted with 1 or 2 halogens, and wherein each alkyl, cycloalkyl, cycloalkenyl, cycloheteroalkyl, aryl and heteroaryl is unsubstituted or substituted with 1, 2 or 3 halogens;

25 each R^c is independently selected from:

- (1) halogen,
- (2) oxo,
- (3) -(CH₂)_rOH,
- (4) -(CH₂)_rN(R^e)₂,
- 30 (5) -(CH₂)_rCN,
- (6) -C₁₋₆alkyl,
- (7) -CF₃,
- (8) -C₁₋₆alkyl-OH,
- (9) -OCH₂OC₁₋₆alkyl,
- 35 (10) -(CH₂)_rOC₁₋₆alkyl,
- (11) -OCH₂aryl,
- (12) -(CH₂)_rSC₁₋₆alkyl,

- (13) $-(CH_2)_rC(O)R^f$,
 (14) $-(CH_2)_rC(O)N(R^e)_2$,
 (15) $-(CH_2)_rCO_2H$,
 (16) $-(CH_2)_rCO_2R^f$,
 5 (17) $-(CH_2)_rC_3-7cycloalkyl$,
 (18) $-(CH_2)_rC_2-6cycloheteroalkyl$,
 (19) $-(CH_2)_raryl$, and
 (20) $-(CH_2)_rheteroaryl$,

wherein each CH_2 is unsubstituted or substituted with 1 or 2 substituents selected from: oxo, -
 10 OH, -CN, $-N(R^h)_2$, $-C_1-6alkyl$, $-OC_1-6alkyl$, halogen, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CO_2H$, $-CO_2C_1-6alkyl$, $-C_3-7cycloalkyl$ 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, $-N(R^h)_2$, $-C_1-6alkyl$, $-OC_1-6alkyl$, halogen, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CO_2H$, $-CO_2C_1-6alkyl$, $-C_3-7cycloalkyl$ and heteroaryl;

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

- (1) hydrogen, and
 (2) $C_1-6alkyl$,

wherein alkyl is unsubstituted or substituted with 1, 2, 3 or 4 substituents selected from: -OH, oxo, halogen, $C_1-6alkyl$, $-OC_1-6alkyl$, $-NH_2$, $-NH(C_1-6alkyl)$, and $-N(C_1-6alkyl)_2$;

20 each R^j is independently selected from:

- (1) hydrogen,
 (2) $C_1-6alkyl$,
 (3) $C_3-6cycloalkyl$,
 (4) $-C(O)R^i$, and
 25 (5) $-SO_2R^i$,

wherein alkyl and cycloalkyl are unsubstituted or substituted with 1, 2, 3 or 4 substituents selected from: -OH, oxo, halogen, $C_1-6alkyl$, $-OC_1-6alkyl$, $-NH_2$, $-NH(C_1-6alkyl)$, and $-N(C_1-6alkyl)_2$;

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

- 30 (1) $C_1-6alkyl$,
 (2) $C_4-7cycloalkyl$,
 (3) $C_4-7cycloalkenyl$,
 (4) $C_3-7cycloheteroalkyl$,
 (5) $C_3-7cycloheteroalkenyl$,
 35 (6) aryl, and
 (7) 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, -NH₂, -C₁-alkyl, -OC₁-alkyl, halogen, -CH₂F, -CHF₂, -CF₃, -CO₂H, -CO₂C₁-alkyl, -C₃-7cycloalkyl, and heteroaryl;

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

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

p is 0, 1, 2, or 3;

q is 0, 1, 2, 3 or 4; and

r is 0, 1 or 2.

In one embodiment of the present invention, X is absent.

10 In another embodiment of the present invention, X is selected from: -CH₂-, -CHF-, -CF₂-, -S-, -O-, -O-CH₂-, -NH-, -C(O)-, -NHC(O)-, -C(O)NH-, -NHSO₂-, -SO₂NH-, and -CO₂-, wherein each CH₂ is unsubstituted or substituted with 1 or 2 substituents selected from: hydroxy, halogen, NH₂, C₁-alkyl, CO₂H, CO₂C₁-alkyl, COC₁-alkyl, phenyl and -CH₂phenyl, and wherein each NH is unsubstituted or substituted with 1 substituent selected
15 from: C₁-alkyl, CO₂H, CO₂C₁-alkyl, COC₁-alkyl, phenyl and -CH₂phenyl. In a class of this embodiment, X is selected from: -CH₂-, -CF₂-, -S-, -O-, -O-CH₂-, -NH-, and -C(O)-, wherein each CH₂ is unsubstituted or substituted with 1 or 2 substituents selected from: hydroxy, halogen, NH₂, C₁-alkyl, CO₂H, CO₂C₁-alkyl, COC₁-alkyl, phenyl and -CH₂phenyl, and wherein each NH is unsubstituted or substituted with 1 substituent selected
20 from: C₁-alkyl, CO₂H, CO₂C₁-alkyl, COC₁-alkyl, phenyl and -CH₂phenyl. In another class of this embodiment, X is selected from: -S-, -O-, -O-CH₂-, and -NH-, wherein CH₂ is unsubstituted or substituted with 1 or 2 substituents selected from: hydroxy, halogen, NH₂, C₁-alkyl, CO₂H, CO₂C₁-alkyl, COC₁-alkyl, phenyl and -CH₂phenyl, and wherein NH is unsubstituted or substituted with 1 substituent selected from: C₁-alkyl, CO₂H, CO₂C₁-alkyl,
25 COC₁-alkyl, phenyl and -CH₂phenyl.

In another embodiment of the present invention, X is selected from: -CH₂-, -CHF-, -CF₂-, -S-, -O-, -O-CH₂-, -NH-, -C(O)-, -NHC(O)-, -C(O)NH-, -NHSO₂-, -SO₂NH-, and -CO₂-. In a class of this embodiment, X is selected from: -CH₂-, -CF₂-, -S-, -O-, -O-CH₂-, -NH-, and -C(O)-. In another class of this embodiment, X is selected from: -S-, -O-, -O-CH₂-, and -NH-.

30 In another embodiment of the present invention, X is selected from: -CH₂-, wherein CH₂ is unsubstituted or substituted with 1 or 2 substituents selected from: hydroxy, halogen, NH₂, C₁-alkyl, CO₂H, CO₂C₁-alkyl, COC₁-alkyl, phenyl and -CH₂phenyl. In another embodiment of the present invention, X is: -CHF-. In another embodiment of the present invention, X is -CF₂-. In another embodiment of the present invention, X is -S-. In another
35 embodiment of the present invention, X is -O-. In another embodiment of the present invention, X is -O-CH₂-, wherein CH₂ is unsubstituted or substituted with 1 or 2 substituents selected from: hydroxy, halogen, NH₂, C₁-alkyl, CO₂H, CO₂C₁-alkyl, COC₁-alkyl, phenyl and -

CH₂phenyl. In another embodiment of the present invention, X is -NH-, wherein NH is unsubstituted or substituted with 1 or 2 substituents selected from: C₁-6alkyl, CO₂H, CO₂C₁-6alkyl, COC₁-6alkyl, phenyl and -CH₂phenyl. In another embodiment of the present invention, X is -C(O)-. In another embodiment of the present invention, X is -NHC(O)-, wherein NH is unsubstituted or substituted with 1 or 2 substituents selected from: C₁-6alkyl, CO₂H, CO₂C₁-6alkyl, COC₁-6alkyl, phenyl and -CH₂phenyl. In another embodiment of the present invention, X is -C(O)NH-, wherein NH is unsubstituted or substituted with 1 or 2 substituents selected from: C₁-6alkyl, CO₂H, CO₂C₁-6alkyl, COC₁-6alkyl, phenyl and -CH₂phenyl. In another embodiment of the present invention, X is -NHSO₂-, wherein NH is unsubstituted or substituted with 1 or 2 substituents selected from: C₁-6alkyl, CO₂H, CO₂C₁-6alkyl, -COC₁-6alkyl, phenyl and -CH₂phenyl. In another embodiment of the present invention, X is -SO₂NH-, wherein NH is unsubstituted or substituted with 1 or 2 substituents selected from: C₁-6alkyl, CO₂H, CO₂C₁-6alkyl, -COC₁-6alkyl, phenyl and -CH₂phenyl. In another embodiment of the present invention, X is -CO₂-.

In another embodiment of the present invention, Y is selected from: -C₃-10cycloalkyl, -C₃-10cycloalkenyl, -C₂-10cycloheteroalkyl, -C₂-10cycloheteroalkenyl, aryl, and heteroaryl, wherein cycloalkyl, cycloalkenyl, cycloheteroalkyl, cycloheteroalkenyl, aryl and heteroaryl are unsubstituted or substituted with 1, 2, 3 or 4 substituents selected from R^b. In a class of this embodiment, Y is unsubstituted or substituted with 1, 2 or 3 substituents selected from R^b. In another class of this embodiment, Y is unsubstituted or substituted with 1 or 2 substituents selected from R^b. In a class of this embodiment, Y is selected from: -C₂-10cycloheteroalkenyl, aryl, and heteroaryl, wherein cycloheteroalkenyl, aryl and heteroaryl are unsubstituted or substituted with 1, 2, 3 or 4 substituents selected from R^b. In a subclass of this class, Y is unsubstituted or substituted with 1, 2 or 3 substituents selected from R^b. In another subclass of this class, Y is unsubstituted or substituted with 1 or 2 substituents selected from R^b. In a subclass of this class, Y is selected from: benzodihydrofuran, phenyl, benzoimidazole, benzofuran, pyridine, indole, and tetrazole, wherein Y is unsubstituted or substituted with 1, 2, 3 or 4 substituents selected from R^b. In a subclass of this subclass, Y is unsubstituted or substituted with 1, 2 or 3 substituents selected from R^b. In another subclass of this subclass, Y is unsubstituted or substituted with 1 or 2 substituents selected from R^b. In another subclass of this class of this embodiment, Y is selected from: benzodihydrofuran, phenyl, pyridine, indole, and tetrazole, wherein Y is unsubstituted or substituted with 1, 2, 3 or 4 substituents selected from R^b. In a subclass of this subclass, Y is unsubstituted or substituted with 1, 2 or 3 substituents selected from R^b. In another subclass of this subclass, Y is unsubstituted or substituted with 1 or 2 substituents selected from R^b. In another class of this embodiment, Y is selected from: aryl, and heteroaryl, wherein cycloalkyl, cycloalkenyl, cycloheteroalkyl, cycloheteroalkenyl, aryl and heteroaryl are unsubstituted or substituted with 1, 2, 3 or 4 substituents selected from R^b. In a

subclass of this class, Y is unsubstituted or substituted with 1, 2 or 3 substituents selected from R^b. In another subclass of this class, Y is unsubstituted or substituted with 1 or 2 substituents selected from R^b. In a subclass of this class, Y is selected from: phenyl, benzoimidazole, benzofuran, pyridine, indole, and tetrazole, wherein Y is unsubstituted or substituted with 1, 2, 3 or 4 substituents selected from R^b. In a subclass of this subclass, Y is unsubstituted or substituted with 1, 2 or 3 substituents selected from R^b. In another subclass of this subclass, Y is unsubstituted or substituted with 1 or 2 substituents selected from R^b. In another subclass of this class, Y is selected from: phenyl, pyridine, indole, and tetrazole, wherein Y is unsubstituted or substituted with 1, 2, 3 or 4 substituents selected from R^b. In a subclass of this subclass, Y is unsubstituted or substituted with 1, 2 or 3 substituents selected from R^b. In another subclass of this subclass, Y is unsubstituted or substituted with 1 or 2 substituents selected from R^b.

In class of this embodiment, Y is selected from: aryl, and heteroaryl, wherein aryl and heteroaryl are unsubstituted or substituted with 1, 2, 3 or 4 substituents selected from R^b. In a subclass of this class, Y is phenyl or pyridine, wherein phenyl and pyridine are unsubstituted or substituted with 1, 2 or 3 substituents selected from R^b. In another subclass of this class, Y is phenyl or pyridine, wherein phenyl and pyridine are unsubstituted or substituted with 1 or 2 substituents selected from R^b. In another subclass of this class, Y is phenyl or pyridine, wherein phenyl and pyridine are unsubstituted or substituted with 1 substituent selected from R^b. In yet another subclass of this class, Y is phenyl or pyridine.

In another class of this embodiment, Y is aryl, wherein aryl is unsubstituted or substituted with 1, 2, 3 or 4 substituents selected from R^b. In a subclass of this class, Y is phenyl, wherein phenyl is unsubstituted or substituted with 1, 2, 3 or 4 substituents selected from R^b. In another subclass of this class, Y is phenyl, wherein phenyl is unsubstituted or substituted with 1, 2 or 3 substituents selected from R^b. In another subclass of this class, Y is phenyl, wherein phenyl is unsubstituted or substituted with 1 or 2 substituents selected from R^b. In another subclass of this class, Y is phenyl, wherein phenyl is unsubstituted or substituted with 1 substituent selected from R^b.

In another class of this embodiment, Y is heteroaryl, wherein heteroaryl is unsubstituted or substituted with 1, 2, 3 or 4 substituents selected from R^b. In a subclass of this class, Y is selected from benzoimidazole, benzofuran, pyridine, indole and tetrazole, wherein Y is unsubstituted or substituted with 1, 2 or 3 substituents selected from R^b. In another subclass of this class, Y is selected from pyridine, indole and tetrazole, wherein Y is unsubstituted or substituted with 1, 2 or 3 substituents selected from R^b. In another subclass of this class, Y is pyridine, wherein Y is unsubstituted or substituted with 1, 2 or 3 substituents selected from R^b.

In another class of this embodiment, Y is C₂₋₁₀cycloheteroalkenyl, wherein cycloheteroalkenyl is unsubstituted or substituted with 1, 2, 3 or 4 substituents selected from R^b. In a subclass of this class, Y is benzodihydrofuran, wherein Y is unsubstituted or substituted with

1, 2, 3 or 4 substituents selected from R^b.

In another embodiment of the present invention, Y is -C₃₋₁₀cycloalkyl, wherein cycloalkyl is unsubstituted or substituted with 1, 2, 3 or 4 substituents selected from R^b. In a class of this embodiment, Y is unsubstituted or substituted with 1, 2 or 3 substituents selected from R^b. In another class of this embodiment, Y is unsubstituted or substituted with 1 or 2 substituents selected from R^b. In another embodiment of the present invention, Y is -C₃₋₁₀cycloalkenyl, wherein cycloalkenyl is unsubstituted or substituted with 1, 2, 3 or 4 substituents selected from R^b. In a class of this embodiment, Y is unsubstituted or substituted with 1, 2 or 3 substituents selected from R^b. In another class of this embodiment, Y is unsubstituted or substituted with 1 or 2 substituents selected from R^b. In another embodiment of the present invention, Y is -C₂₋₁₀cycloheteroalkyl, wherein cycloheteroalkyl is unsubstituted or substituted with 1, 2, 3 or 4 substituents selected from R^b. In a class of this embodiment, Y is unsubstituted or substituted with 1, 2 or 3 substituents selected from R^b. In another class of this embodiment, Y is unsubstituted or substituted with 1 or 2 substituents selected from R^b. In another embodiment of the present invention, Y is -C₂₋₁₀cycloheteroalkenyl, wherein cycloheteroalkenyl is unsubstituted or substituted with 1, 2, 3 or 4 substituents selected from R^b. In a class of this embodiment, Y is unsubstituted or substituted with 1, 2 or 3 substituents selected from R^b. In another class of this embodiment, Y is unsubstituted or substituted with 1 or 2 substituents selected from R^b. In another embodiment of the present invention, Y is aryl, wherein aryl is unsubstituted or substituted with 1, 2, 3 or 4 substituents selected from R^b. In a class of this embodiment, Y is unsubstituted or substituted with 1, 2 or 3 substituents selected from R^b. In another class of this embodiment, Y is unsubstituted or substituted with 1 or 2 substituents selected from R^b. In another embodiment of the present invention, Y is heteroaryl, wherein heteroaryl is unsubstituted or substituted with 1, 2, 3 or 4 substituents selected from R^b. In a class of this embodiment, Y is unsubstituted or substituted with 1, 2 or 3 substituents selected from R^b. In another class of this embodiment, 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: oxo, -CN, -(CH₂)_nCO₂H, -(CH₂)_nCO₂Rⁱ, -(CH₂)_nOH, -(CH₂)_nC(O)NHR^g, -(CH₂)_nNHC(O)C₁₋₆alkyl, -(CH₂)_nNHSO₂Rⁱ, -(CH₂)_nSO₂NHR^g, -(CH₂)_nSO₂NHC(O)Rⁱ, -(CH₂)_nSO₂NHCO₂Rⁱ, -(CH₂)_nSO₂NHCON(R^g)₂, -(CH₂)_nC(O)NHSO₂Rⁱ, -(CH₂)_nNHC(O)N(R^g)₂, -(CH₂)_nC₃₋₁₀cycloalkyl-CO₂R^e, heteroaryl, -C₂₋₁₀cycloheteroalkenyl, and -C₂₋₁₀cycloheteroalkyl, wherein each CH₂ is unsubstituted or substituted with 1 or 2 substituents selected from C₁₋₆alkyl, -OH and -NH₂, wherein each NH is unsubstituted or substituted with 1 substituent selected from R^c, and wherein alkyl, cycloalkyl, cycloheteroalkyl, cycloheteroalkenyl, aryl and heteroaryl is unsubstituted or substituted with 1, 2, 3 or 4 substituents selected from R^c. In a subclass of this class, each CH₂ is unsubstituted or substituted with 1 substituent selected from

C₁₋₆alkyl, -OH and -NH₂; each NH is unsubstituted or substituted with 1 substituent selected from R^c; and each alkyl, cycloalkyl, cycloheteroalkyl, cycloheteroalkenyl, aryl and heteroaryl is unsubstituted or substituted with 1 or 2 substituents selected from R^c.

In a class of this embodiment, Z is selected from: oxo, -CN, -(CH₂)_nCO₂H, -
 5 (CH₂)_nCO₂Rⁱ, -(CH₂)_nOH, -(CH₂)_nC(O)NHR^g, -(CH₂)_nNHC(O)C₁₋₆alkyl, -
 (CH₂)_nSO₂NHR^g, -(CH₂)_nSO₂NHC(O)Rⁱ, -(CH₂)_nC(O)NHSO₂Rⁱ, -(CH₂)_nNHC(O)N(R^g)₂,
 -(CH₂)_nC₃₋₁₀cycloalkyl-CO₂R^e, heteroaryl, -C₂₋₁₀cycloheteroalkenyl, and -C₂₋₁₀
 10 cycloheteroalkyl, wherein each CH₂ is unsubstituted or substituted with 1 or 2 substituents
 selected from C₁₋₆alkyl, -OH and -NH₂, wherein each NH is unsubstituted or substituted with 1
 substituent selected from R^c, and wherein each alkyl, cycloalkyl, cycloheteroalkyl,
 cycloheteroalkenyl, aryl and heteroaryl is unsubstituted or substituted with 1, 2, 3 or 4
 substituents selected from R^c. In a subclass of this class, each CH₂ is unsubstituted or
 substituted with 1 substituent selected from C₁₋₆alkyl, -OH and -NH₂; each NH is unsubstituted
 15 or substituted with 1 substituent selected from R^c; and each alkyl, cycloalkyl, cycloheteroalkyl,
 cycloheteroalkenyl, aryl and heteroaryl is unsubstituted or substituted with 1 or 2 substituents
 selected from R^c.

In a subclass of this class, Z is selected from: oxo, -CN, -(CH₂)_nCO₂H, -
 (CH₂)_nCO₂C₁₋₆alkyl, -(CH₂)_nOH, -(CH₂)_nC(O)NHR^g, -NHC(O)C₁₋₆alkyl, -SO₂NHR^g, -
 20 SO₂NHC(O)C₁₋₆alkyl, -C(O)NHSO₂C₁₋₆alkyl, -C(O)NHSO₂aryl, -NHC(O)N(R^g)₂, -C₃₋₁₀
 cycloalkyl-CO₂R^e, heteroaryl, -C₂₋₁₀cycloheteroalkenyl, and -C₂₋₁₀cycloheteroalkyl,
 wherein each CH₂ is unsubstituted or substituted with 1 or 2 substituents selected from C₁₋₆
 6alkyl, -OH and -NH₂, wherein each NH is unsubstituted or substituted with 1 substituent
 selected from R^c, and wherein each alkyl, cycloalkyl, cycloheteroalkyl, cycloheteroalkenyl, aryl
 and heteroaryl is unsubstituted or substituted with 1, 2, 3 or 4 substituents selected from R^c. In a
 25 subclass of this class, each CH₂ is unsubstituted or substituted with 1 substituent selected from
 C₁₋₆alkyl, -OH and -NH₂; each NH is unsubstituted or substituted with 1 or 2 substituents
 selected from R^c; and each alkyl, cycloalkyl, cycloheteroalkyl, cycloheteroalkenyl, aryl and
 heteroaryl is unsubstituted or substituted with 1 or 2 substituents selected from R^c.

In another subclass of this class, Z is selected from: oxo, -CN, -CO₂H, -CH₂CO₂H, -
 30 (CH₂)₂CO₂H, -CO₂CH₃, -CO₂CH₂CH₃, -CH₂CO₂CH₂CH₃, -CH₂OH, -CH₂C(O)NH₂, -
 C(O)NH₂, -NHC(O)CH₃, -SO₂NH₂, -SO₂NHC(O)CH₃, -C(O)NHSO₂CH₃, -
 C(O)NHSO₂phenyl, -NHC(O)NH₂, -cyclopropyl-CO₂H, -cyclopropyl-CO₂CH₃, tetrazole,
 dihydro-1,3,4-oxadiazole and imidazolidine, wherein each CH₂ is unsubstituted or substituted
 with 1 or 2 substituents selected from C₁₋₆alkyl, -OH and -NH₂, wherein each NH is
 35 unsubstituted or substituted with 1 substituent selected from R^c, and wherein each alkyl,
 cycloalkyl, cycloheteroalkyl, cycloheteroalkenyl, aryl and heteroaryl is unsubstituted or
 substituted with 1, 2, 3 or 4 substituents selected from R^c. In a subclass of this class, each CH₂

is unsubstituted or substituted with 1 substituent selected from C₁₋₆alkyl, -OH and -NH₂; each NH is unsubstituted or substituted with 1 substituent selected from R^C; and each alkyl, cycloalkyl, cycloheteroalkyl, cycloheteroalkenyl, aryl and heteroaryl is unsubstituted or substituted with 1 or 2 substituents selected from R^C.

5 In another class of this embodiment, Z is selected from: $-(CH_2)_nCO_2H$, and $-(CH_2)_nCO_2C_{1-6}alkyl$, wherein each CH₂ and alkyl is unsubstituted or substituted with 1 or 2 substituents selected from C₁₋₆alkyl, -OH and -NH₂. In a subclass of this class, Z is selected from: $-(CH_2)_nCO_2H$, and $-(CH_2)_nCO_2C_{1-6}alkyl$, wherein each CH₂ is unsubstituted or substituted with 1 or 2 substituents selected from C₁₋₆alkyl, -OH and -NH₂. In another subclass
10 of this class, each CH₂ is unsubstituted or substituted with 1 substituent selected from C₁₋₆alkyl, -OH and -NH₂.

In another subclass of this class, Z is $-(CH_2)_nCO_2H$, wherein each CH₂ is unsubstituted or substituted with 1 or 2 substituents selected from C₁₋₆alkyl, -OH and -NH₂. In a subclass of this class, each CH₂ is unsubstituted or substituted with 1 substituent selected from C₁₋₆alkyl, -
15 OH and -NH₂. In a subclass of this subclass, Z is selected from: $-CO_2H$, $-CH_2CO_2H$, and $-(CH_2)_2CO_2H$, wherein each CH₂ is unsubstituted or substituted with 1 or 2 substituents selected from C₁₋₆alkyl, -OH and -NH₂. In a subclass of this class, each CH₂ is unsubstituted or substituted with 1 substituent selected from C₁₋₆alkyl, -OH and -NH₂. In another subclass of this subclass, Z is $-CO_2H$. In another subclass of this subclass, Z is $-CH_2CO_2H$. In another
20 subclass of this subclass, Z is $-(CH_2)_2CO_2H$.

In another subclass of this class, Z is $-(CH_2)_nCO_2C_{1-6}alkyl$, wherein each CH₂ and alkyl is unsubstituted or substituted with 1 or 2 substituents selected from C₁₋₆alkyl, -OH and -
NH₂. In a subclass of this class, Z is $-(CH_2)_nCO_2C_{1-6}alkyl$, wherein each CH₂ is unsubstituted or substituted with 1 or 2 substituents selected from C₁₋₆alkyl, -OH and -NH₂. In another
25 subclass of this subclass, each CH₂ is unsubstituted or substituted with 1 substituent selected from C₁₋₆alkyl, -OH and -NH₂. In another subclass of this subclass, Z is selected from: $-CO_2CH_3$, $-CO_2CH_2CH_3$, and $-CH_2CO_2CH_2CH_3$, wherein each CH₂ is unsubstituted or substituted with 1 or 2 substituents selected from C₁₋₆alkyl, -OH and -NH₂. In another subclass of this subclass, each CH₂ is unsubstituted or substituted with 1 substituent selected from C₁₋₆alkyl, -OH and -NH₂. In another subclass of this subclass, Z is selected from: $-CO_2CH_3$, $-CO_2CH_2CH_3$, and $-CH_2CO_2CH_2CH_3$.
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In another embodiment of the present invention, Z is $-(CH_2)_nCO_2H$, wherein each CH₂ is unsubstituted or substituted with 1 or 2 substituents selected from C₁₋₆alkyl, -OH and -NH₂. In a class of this embodiment, Z is $-CO_2H$. In another class of this embodiment, Z is $-CH_2CO_2H$, wherein CH₂ is unsubstituted or substituted with 1 or 2 substituents selected from
35 C₁₋₆alkyl, -OH and -NH₂. In a subclass of this class, each CH₂ is unsubstituted or substituted with 1 substituent selected from C₁₋₆alkyl, -OH and -NH₂. In another class of this embodiment,

Z is $-(CH_2)_2CO_2H$, wherein each CH_2 is unsubstituted or substituted with 1 or 2 substituents selected from $C_{1-6}alkyl$, $-OH$ and $-NH_2$. In a subclass of this class, each CH_2 is unsubstituted or substituted with 1 substituent selected from $C_{1-6}alkyl$, $-OH$ and $-NH_2$. In another class of this embodiment, Z is $-CH_2CO_2H$. In yet another class of this embodiment, Z is $-CO_2H$.

- 5 In another embodiment of the present invention, each R^1 and R^2 is independently selected from: hydrogen, halogen, $-CN$, $-CF_3$, $-C_{1-6}alkyl$, $-C_{2-6}alkenyl$, $-C_{2-6}alkynyl$, $-(CH_2)_pC_{3-10}cycloalkyl$, $-(CH_2)_pC_{3-7}cycloalkyl-aryl$, $-(CH_2)_pC_{3-7}cycloalkyl-heteroaryl$, $-(CH_2)_pC_{4-10}cycloalkenyl$, $-(CH_2)_pC_{4-7}cycloalkenyl-aryl$, $-(CH_2)_pC_{4-7}cycloalkenyl-heteroaryl$, $-(CH_2)_pC_{2-10}cycloheteroalkyl$, $-(CH_2)_pC_{2-10}cycloheteroalkenyl$, $-(CH_2)_paryl$,
 10 biphenyl, $-(CH_2)_p heteroaryl$, $-C_{2-6}alkenyl-alkyl$, $-C_{2-6}alkenyl-aryl$, $-C_{2-6}alkenyl-heteroaryl$, $-C_{2-6}alkenyl-C_{3-7}cycloalkyl$, $-C_{2-6}alkenyl-C_{3-7}cycloalkenyl$, $-C_{2-6}alkenyl-C_{2-7}cycloheteroalkyl$, $-C_{2-6}alkenyl-C_{2-7}cycloheteroalkenyl$, $-C_{2-6}alkynyl-alkyl$, $-C_{2-6}alkynyl-aryl$, $-C_{2-6}alkynyl-heteroaryl$, $-C_{2-6}alkynyl-C_{3-7}cycloalkyl$, $-C_{2-6}alkynyl-C_{3-7}cycloalkenyl$, $-C_{2-6}alkynyl-C_{2-7}cycloheteroalkyl$, $-C_{2-6}alkynyl-C_{2-7}cycloheteroalkenyl$, and $-C(O)NH-$
 15 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 $-N(C_{1-6}alkyl)_2$, wherein each alkyl, alkenyl and alkynyl is unsubstituted or substituted with 1, 2 or 3 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 cycloalkyl, cycloalkenyl, cycloheteroalkyl, cycloheteroalkenyl,
 20 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 $-C_{2-6}alkynyl$, and provided that if R^1 or R^2 is hydrogen, then at least one of R^3 and R^4 is not hydrogen. In a class of this embodiment, at least one of and only one of R^1 and R^2 is
 25 selected from the group consisting of: hydrogen, halogen, $-CN$, $-CF_3$, and $-C_{1-6}alkyl$. In another class of this embodiment, at least one of and only one of R^1 and R^2 is selected from the group consisting of: hydrogen, Cl, F, Br, CN, CF_3 , and CH_3 . In another class of this embodiment, at least one of and only one of R^1 and R^2 is selected from the group consisting of: halogen, $-CN$, $-CF_3$, $-C_{1-6}alkyl$, $-C_{2-6}alkenyl$ and $-C_{2-6}alkynyl$. In another class of this embodiment, at least
 30 one of and only one of R^1 and R^2 is selected from the group consisting of: halogen, $-CN$, $-CF_3$, and $-C_{1-6}alkyl$. In another class of this embodiment, at least one of and only one of R^1 and R^2 is selected from the group consisting of: Cl, F, Br, CN, CF_3 , and CH_3 .

- In another embodiment of the present invention, each R^1 and R^2 is independently selected from: halogen, $-CN$, $-CF_3$, $-C_{1-6}alkyl$, $-C_{2-6}alkenyl$, $-C_{2-6}alkynyl$, $-(CH_2)_pC_{3-10}cycloalkyl$, $-(CH_2)_pC_{3-7}cycloalkyl-aryl$, $-(CH_2)_pC_{3-7}cycloalkyl-heteroaryl$, $-(CH_2)_pC_{4-10}cycloalkenyl$, $-(CH_2)_pC_{4-7}cycloalkenyl-aryl$, $-(CH_2)_pC_{4-7}cycloalkenyl-heteroaryl$, $-(CH_2)_pC_{2-10}cycloheteroalkyl$, $-(CH_2)_pC_{2-10}cycloheteroalkenyl$, $-(CH_2)_paryl$, biphenyl, $-$
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(CH₂)_pheteroaryl, -C₂-6alkenyl-alkyl, -C₂-6alkenyl-aryl, -C₂-6alkenyl-heteroaryl, -C₂-6alkenyl-C₃-7cycloalkyl, -C₂-6alkenyl-C₃-7cycloalkenyl, -C₂-6alkenyl-C₂-7cycloheteroalkyl, -C₂-6alkenyl-C₂-7cycloheteroalkenyl, -C₂-6alkynyl-alkyl, -C₂-6alkynyl-aryl, -C₂-6alkynyl-heteroaryl, -C₂-6alkynyl-C₃-7cycloalkyl, -C₂-6alkynyl-C₃-7cycloalkenyl, -C₂-6alkynyl-C₂-7cycloheteroalkyl, -C₂-6alkynyl-C₂-7cycloheteroalkenyl, and -C(O)NH-phenyl, wherein each CH₂ is unsubstituted or substituted with 1 or 2 substituents selected from: halogen, CF₃, -OH, -NH₂, -C₁-6alkyl, -OC₁-6alkyl, -NHC₁-6alkyl, and -N(C₁-6alkyl)₂, wherein each alkyl, alkenyl and alkynyl is unsubstituted or substituted with 1, 2 or 3 substituents selected from: halogen, CF₃, -OH, -NH₂, -C₁-6alkyl, -OC₁-6alkyl, -NHC₁-6alkyl, and -N(C₁-6alkyl)₂, and wherein each 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 R¹ and R² is selected from the group consisting of: halogen, -CN, -CF₃, -C₁-6alkyl, -C₂-6alkenyl and -C₂-6alkynyl. In a class of this embodiment, at least one of and only one of R¹ and R² is selected from the group consisting of: halogen, -CN, -CF₃, and -C₁-6alkyl. In another class of this embodiment, at least one of and only one of R¹ and R² is selected from the group consisting of: Cl, F, Br, CN, CF₃, and CH₃.

In another embodiment of the present invention, each R¹ and R² is independently selected from: hydrogen, halogen, -CN, -CF₃, -C₁-6alkyl, -(CH₂)_paryl, biphenyl, -(CH₂)_pheteroaryl, -C₂-6alkenyl-aryl, -C₂-6alkynyl-alkyl, -C₂-6alkynyl-aryl, -C₂-6alkynyl-heteroaryl, -C₂-6alkynyl-C₃-7cycloalkyl, -C₂-6alkynyl-C₂-7cycloheteroalkyl, and -C₂-6alkynyl-C₂-7cycloheteroalkenyl, wherein each CH₂ is unsubstituted or substituted with 1 or 2 substituents selected from: halogen, CF₃, -OH, -NH₂, -C₁-6alkyl, -OC₁-6alkyl, -NHC₁-6alkyl, and -N(C₁-6alkyl)₂, wherein each alkyl, alkenyl and alkynyl is unsubstituted or substituted with 1, 2 or 3 substituents selected from: halogen, CF₃, -OH, -NH₂, -C₁-6alkyl, -OC₁-6alkyl, -NHC₁-6alkyl, and -N(C₁-6alkyl)₂, and wherein each 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 R¹ and R² is selected from the group consisting of: hydrogen, halogen, -CN, -CF₃, and -C₁-6alkyl, and provided that if R¹ or R² is hydrogen, then at least one of R³ and R⁴ is not hydrogen. In a subclass of this class, at least one of and only one of R¹ and R² is selected from the group consisting of: hydrogen, Cl, F, Br, CN, CF₃, and CH₃. In another subclass of this class, at least one of and only one of R¹ and R² is selected from the group consisting of: halogen, -CN, -CF₃, and -C₁-6alkyl. In another subclass of this class, at least one of and only one of R¹ and R² is selected from the group consisting of: Cl, F, Br, CN, CF₃, and CH₃.

In another class of this embodiment, each R¹ and R² is independently selected from: halogen, -CN, -CF₃, -C₁-6alkyl, -(CH₂)_paryl, biphenyl, -(CH₂)_pheteroaryl, -C₂-6alkenyl-aryl, -C₂-6alkynyl-alkyl, -C₂-6alkynyl-aryl, -C₂-6alkynyl-heteroaryl, -C₂-6alkynyl-C₃-7cycloalkyl,

-C₂-6alkynyl-C₂-7cycloheteroalkyl, and -C₂-6alkynyl-C₂-7cycloheteroalkenyl, wherein each CH₂ is unsubstituted or substituted with 1 or 2 substituents selected from: halogen, CF₃, -OH, -NH₂, -C₁-6alkyl, -OC₁-6alkyl, -NHC₁-6alkyl, and -N(C₁-6alkyl)₂, wherein alkyl, alkenyl and alkynyl is unsubstituted or substituted with 1, 2 or 3 substituents selected from: halogen, CF₃, -OH, -NH₂, -C₁-6alkyl, -OC₁-6alkyl, -NHC₁-6alkyl, and -N(C₁-6alkyl)₂, and wherein each 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 R¹ and R² is selected from the group consisting of: halogen, -CN, -CF₃, and -C₁-6alkyl. In a subclass of this class, at least one of and only one of R¹ and R² is selected from the group consisting of: Cl, F, Br, CN, CF₃, and CH₃.

In another class of this embodiment, each R¹ and R² is independently selected from: hydrogen, halogen, -CN, -CF₃, -C₁-6alkyl, -(CH₂)_paryl, biphenyl, heteroaryl, -C₂-6alkenyl-aryl, -C₂-6alkynyl-alkyl, -C₂-6alkynyl-aryl, -C₂-6alkynyl-heteroaryl, -C₂-6alkynyl-C₃-7cycloalkyl, -C₂-6alkynyl-C₂-7cycloheteroalkyl, and -C₂-6alkynyl-C₂-7cycloheteroalkenyl, wherein each CH₂ is unsubstituted or substituted with 1 or 2 substituents selected from: halogen, CF₃, -OH, -NH₂, -C₁-6alkyl, -OC₁-6alkyl, -NHC₁-6alkyl, and -N(C₁-6alkyl)₂, wherein each alkyl, alkenyl and alkynyl is unsubstituted or substituted with 1, 2 or 3 substituents selected from: halogen, CF₃, -OH, -NH₂, -C₁-6alkyl, -OC₁-6alkyl, -NHC₁-6alkyl, and -N(C₁-6alkyl)₂, and wherein each 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 R¹ and R² is selected from the group consisting of: hydrogen, halogen, -CN, -CF₃, and -C₁-6alkyl, and provided that if R¹ or R² is hydrogen, then at least one of R³ and R⁴ is not hydrogen. In a subclass of this class, at least one of and only one of R¹ and R² is selected from the group consisting of: hydrogen, Cl, F, Br, CN, CF₃, and CH₃.

In another subclass of this class, at least one of and only one of R¹ and R² is selected from the group consisting of: halogen, -CN, -CF₃, and -C₁-6alkyl. In another subclass of this class, at least one of and only one of R¹ and R² is selected from the group consisting of: Cl, F, Br, CN, CF₃, and CH₃.

In another class of this embodiment, each R¹ and R² is independently selected from: halogen, -CN, -CF₃, -C₁-6alkyl, -(CH₂)_paryl, biphenyl, heteroaryl, -C₂-6alkenyl-aryl, -C₂-6alkynyl-alkyl, -C₂-6alkynyl-aryl, -C₂-6alkynyl-heteroaryl, -C₂-6alkynyl-C₃-7cycloalkyl, -C₂-6alkynyl-C₂-7cycloheteroalkyl, and -C₂-6alkynyl-C₂-7cycloheteroalkenyl, wherein each CH₂ is unsubstituted or substituted with 1 or 2 substituents selected from: halogen, CF₃, -OH, -NH₂, -C₁-6alkyl, -OC₁-6alkyl, -NHC₁-6alkyl, and -N(C₁-6alkyl)₂, each alkyl, alkenyl and alkynyl is unsubstituted or substituted with 1, 2 or 3 substituents selected from: halogen, CF₃, -OH, -NH₂, -C₁-6alkyl, -OC₁-6alkyl, -NHC₁-6alkyl, and -N(C₁-6alkyl)₂, and wherein each 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 R¹ and R² is selected from the group consisting of: halogen, -CN, -CF₃, and -C₁₋₆alkyl. In a subclass of this class, at least one of and only one of R¹ and R² is selected from the group consisting of: Cl, F, Br, CN, CF₃, and CH₃.

5 In another class of this embodiment, each R¹ and R² is independently selected from: hydrogen, halogen, -CN, -CF₃, -C₁₋₆alkyl, -(CH₂)_paryl, biphenyl, heteroaryl, -C₂₋₆alkenyl-aryl, -C₂alkynyl-alkyl, -C₂alkynyl-aryl, -C₂alkynyl-heteroaryl, -C₂alkynyl-C₅₋₆cycloalkyl, -C₂alkynyl-C₄₋₅cycloheteroalkyl, and -C₂alkynyl-C₄₋₅cycloheteroalkenyl, wherein each CH₂ is unsubstituted or substituted with 1 or 2 substituents selected from: halogen, CF₃, -OH, -NH₂, -C₁₋₆alkyl, -OC₁₋₆alkyl, -NHC₁₋₆alkyl, and -N(C₁₋₆alkyl)₂, each alkyl and alkenyl is
 10 unsubstituted or substituted with 1, 2 or 3 substituents selected from: halogen, CF₃, -OH, -NH₂, -C₁₋₆alkyl, -OC₁₋₆alkyl, -NHC₁₋₆alkyl, and -N(C₁₋₆alkyl)₂, and wherein each 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
 15 one of and only one of R¹ and R² is selected from the group consisting of: hydrogen, halogen, -CN, -CF₃, and -C₁₋₆alkyl. In a subclass of this class, at least one of and only one of R¹ and R² is selected from the group consisting of: hydrogen, Cl, F, Br, CN, CF₃, and CH₃, and provided that if R¹ or R² is hydrogen, then at least one of R³ and R⁴ is not hydrogen. In another subclass of this class, at least one of and only one of R¹ and R² is selected from the group consisting of:
 20 halogen, -CN, -CF₃, and -C₁₋₆alkyl. In another subclass of this class, at least one of and only one of R¹ and R² is selected from the group consisting of: Cl, F, Br, CN, CF₃, and CH₃.

In another class of this embodiment, each R¹ and R² is independently selected from: halogen, -CN, -CF₃, -C₁₋₆alkyl, -(CH₂)_paryl, biphenyl, heteroaryl, -C₂₋₆alkenyl-aryl, -C₂alkynyl-alkyl, -C₂alkynyl-aryl, -C₂alkynyl-heteroaryl, -C₂alkynyl-C₅₋₆cycloalkyl, -C₂alkynyl-C₄₋₅cycloheteroalkyl, and -C₂alkynyl-C₄₋₅cycloheteroalkenyl, wherein each CH₂ is
 25 unsubstituted or substituted with 1 or 2 substituents selected from: halogen, CF₃, -OH, -NH₂, -C₁₋₆alkyl, -OC₁₋₆alkyl, -NHC₁₋₆alkyl, and -N(C₁₋₆alkyl)₂, each alkyl and alkenyl is unsubstituted or substituted with 1, 2 or 3 substituents selected from: halogen, CF₃, -OH, -NH₂, -C₁₋₆alkyl, -OC₁₋₆alkyl, -NHC₁₋₆alkyl, and -N(C₁₋₆alkyl)₂, and wherein each 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
 30 one of and only one of R¹ and R² is selected from the group consisting of: halogen, -CN, -CF₃, and -C₁₋₆alkyl. In a subclass of this class, at least one of and only one of R¹ and R² is selected from the group consisting of: Cl, F, Br, CN, CF₃, and CH₃.

35 In another class of this embodiment, each R¹ and R² is independently selected from: hydrogen, Cl, F, Br, -CN, -CF₃, -CH₃, -(CH₂)₂phenyl, phenyl, naphthalene, indane, 5,6,7,8-tetrahydronaphthalene, biphenyl, 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, [1,2,4]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, 1,2,3,6-tetrahydropyridine, -C₂alkenyl-phenyl, -C₂alkynyl-isopropyl, -C₂alkynyl-phenyl, -C₂alkynyl-naphthalene, -C₂alkynyl-imidazole, -C₂alkynyl-pyridine, -C₂alkynyl-cyclopentyl, -C₂alkynyl-pyrrolidine, -C₂alkynyl-dihydropyridine, and 1,6-dihydro-pyridin-3-ylethynyl, wherein each CH₂ is unsubstituted or substituted with 1 or 2 substituents selected from: halogen, CF₃, -OH, -NH₂, -C₁-6alkyl, -OC₁-6alkyl, -NHC₁-6alkyl, and -N(C₁-6alkyl)₂, each alkyl and alkenyl is unsubstituted or substituted with 1 or 2 substituents selected from: halogen, CF₃, -OH, -NH₂, -C₁-6alkyl, -OC₁-6alkyl, -NHC₁-6alkyl, and -N(C₁-6alkyl)₂, and wherein each cycloalkyl, cycloalkenyl, cycloheteroalkyl, cycloheteroalkenyl, phenyl, aryl and heteroaryl is unsubstituted or substituted with 1, 2, 3 or 4 substituents independently selected from R¹, provided that at least one of and only one of R¹ and R² is selected from the group consisting of: hydrogen, Cl, F, Br, CN, CF₃, and CH₃, and provided that if R¹ or R² is hydrogen, then at least one of R³ and R⁴ is not hydrogen. In a subclass of this class, at least one of and only one of R¹ and R² is selected from the group consisting of: halogen, -CN, -CF₃, and -C₁-6alkyl. In another subclass of this class, at least one of and only one of R¹ and R² is selected from the group consisting of: Cl, F, Br, CN, CF₃, and CH₃.

In another class of this embodiment, each R¹ and R² is independently selected from: Cl, F, Br, -CN, -CF₃, -CH₃, -(CH₂)₂phenyl, phenyl, naphthalene, indane, 5,6,7,8-tetrahydronaphthalene, biphenyl, 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, [1,2,4]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, 1,2,3,6-tetrahydropyridine, -C₂alkenyl-phenyl, -C₂alkynyl-isopropyl, -C₂alkynyl-phenyl, -C₂alkynyl-naphthalene, -C₂alkynyl-imidazole, -C₂alkynyl-pyridine, -C₂alkynyl-cyclopentyl, -C₂alkynyl-pyrrolidine, -C₂alkynyl-dihydropyridine, and 1,6-dihydro-pyridin-3-ylethynyl, wherein each CH₂ is unsubstituted or substituted with 1 or 2 substituents selected from: halogen, CF₃, -OH, -NH₂, -C₁-6alkyl, -OC₁-6alkyl, -NHC₁-6alkyl, and -N(C₁-6alkyl)₂, each alkyl and alkenyl is unsubstituted or substituted with 1, 2 or 3 substituents selected from: halogen, CF₃, -OH, -NH₂, -C₁-6alkyl, -OC₁-6alkyl, -NHC₁-6alkyl, and -N(C₁-6alkyl)₂, and wherein each

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 R¹ and R² is selected from the group consisting of: Cl, F, Br, CN, CF₃, and CH₃.

5 In another embodiment of the present invention, R¹ is selected from: -(CH₂)_pC₃-10cycloalkyl, -(CH₂)_pC₃-7cycloalkyl-aryl, -(CH₂)_pC₃-7cycloalkyl-heteroaryl, -(CH₂)_pC₄-10cycloalkenyl, -(CH₂)_pC₄-7cycloalkenyl-aryl, -(CH₂)_pC₄-7cycloalkenyl-heteroaryl, -(CH₂)_pC₂-10cycloheteroalkyl, -(CH₂)_pC₂-10cycloheteroalkenyl, -(CH₂)_paryl, biphenyl, -(CH₂)_pheteroaryl, -C₂-6alkenyl-alkyl, -C₂-6alkenyl-aryl, -C₂-6alkenyl-heteroaryl, -C₂-6alkenyl-C₃-7cycloalkyl, -C₂-6alkenyl-C₃-7cycloalkenyl, -C₂-6alkenyl-C₂-7cycloheteroalkyl, -C₂-6alkenyl-C₂-7cycloheteroalkenyl, -C₂-6alkynyl-alkyl, -C₂-6alkynyl-aryl, -C₂-6alkynyl-heteroaryl, -C₂-6alkynyl-C₃-7cycloalkyl, -C₂-6alkynyl-C₃-7cycloalkenyl, -C₂-6alkynyl-C₂-7cycloheteroalkyl, -C₂-6alkynyl-C₂-7cycloheteroalkenyl, and -C(O)NH-phenyl, wherein each CH₂ is unsubstituted or substituted with 1 or 2 substituents selected from: halogen, CF₃, -OH, -NH₂, -C₁-6alkyl, -OC₁-6alkyl, -NHC₁-6alkyl, and -N(C₁-6alkyl)₂, wherein each alkyl, alkenyl and alkynyl is unsubstituted or substituted with 1, 2 or 3 substituents selected from: halogen, CF₃, -OH, -NH₂, -C₁-6alkyl, -OC₁-6alkyl, -NHC₁-6alkyl, and -N(C₁-6alkyl)₂, and wherein each cycloalkyl, cycloalkenyl, cycloheteroalkyl, cycloheteroalkenyl, phenyl, aryl and heteroaryl is unsubstituted or substituted with 1, 2, 3 or 4 substituents independently selected from R^a; and R² is selected from the group consisting of: hydrogen, halogen, -CN, -CF₃, -C₁-6alkyl, -C₂-6alkenyl and -C₂-6alkynyl, and provided that if R² is hydrogen, then at least one of R³ and R⁴ is not hydrogen. In a class of this embodiment, R² is selected from the group consisting of: hydrogen, halogen, -CN, -CF₃, and -C₁-6alkyl. In another class of this embodiment, R² is selected from the group consisting of: hydrogen, Cl, F, Br, CN, CF₃, and CH₃. In another class of this embodiment, R² is selected from the group consisting of: halogen, -CN, -CF₃, -C₁-6alkyl, -C₂-6alkenyl and -C₂-6alkynyl. In another class of this embodiment, R² is selected from the group consisting of: halogen, -CN, -CF₃, and -C₁-6alkyl. In another class of this embodiment, R² is selected from the group consisting of: Cl, F, Br, CN, CF₃, and CH₃.

10 In another embodiment of the present invention, each R¹ is selected from: -(CH₂)_pC₃-10cycloalkyl, -(CH₂)_pC₃-7cycloalkyl-aryl, -(CH₂)_pC₃-7cycloalkyl-heteroaryl, -(CH₂)_pC₄-10cycloalkenyl, -(CH₂)_pC₄-7cycloalkenyl-aryl, -(CH₂)_pC₄-7cycloalkenyl-heteroaryl, -(CH₂)_pC₂-10cycloheteroalkyl, -(CH₂)_pC₂-10cycloheteroalkenyl, -(CH₂)_paryl, biphenyl, -(CH₂)_pheteroaryl, -C₂-6alkenyl-alkyl, -C₂-6alkenyl-aryl, -C₂-6alkenyl-heteroaryl, -C₂-6alkenyl-C₃-7cycloalkyl, -C₂-6alkenyl-C₃-7cycloalkenyl, -C₂-6alkenyl-C₂-7cycloheteroalkyl, -C₂-6alkenyl-C₂-7cycloheteroalkenyl, -C₂-6alkynyl-alkyl, -C₂-6alkynyl-aryl, -C₂-6alkynyl-heteroaryl, -C₂-6alkynyl-C₃-7cycloalkyl, -C₂-6alkynyl-C₃-7cycloalkenyl, -C₂-6alkynyl-C₂-7cycloheteroalkyl, -C₂-6alkynyl-C₂-7cycloheteroalkenyl, and -C(O)NH-phenyl, wherein each

CH₂ is unsubstituted or substituted with 1 or 2 substituents selected from: halogen, CF₃, -OH, -NH₂, -C₁-6alkyl, -OC₁-6alkyl, -NHC₁-6alkyl, and -N(C₁-6alkyl)₂, wherein each alkyl, alkenyl and alkynyl is unsubstituted or substituted with 1, 2 or 3 substituents selected from: halogen, CF₃, -OH, -NH₂, -C₁-6alkyl, -OC₁-6alkyl, -NHC₁-6alkyl, and -N(C₁-6alkyl)₂, and wherein
 5 each cycloalkyl, cycloalkenyl, cycloheteroalkyl, cycloheteroalkenyl, phenyl, aryl and heteroaryl is unsubstituted or substituted with 1, 2, 3 or 4 substituents independently selected from R^a; and R² is selected from the group consisting of: halogen, -CN, -CF₃, -C₁-6alkyl, -C₂-6alkenyl and -C₂-6alkynyl. In a class of this embodiment, R² is selected from the group consisting of: halogen, -CN, -CF₃, and -C₁-6alkyl. In another class of this embodiment, R² is selected from the group
 10 consisting of: Cl, F, Br, CN, CF₃, and CH₃.

In a class of this embodiment, R¹ is selected from: -(CH₂)_paryl, biphenyl, -(CH₂)_pheteroaryl, -C₂-6alkenyl-aryl, -C₂-6alkynyl-alkyl, -C₂-6alkynyl-aryl, -C₂-6alkynyl-heteroaryl, -C₂-6alkynyl-C₃-7cycloalkyl, -C₂-6alkynyl-C₂-7cycloheteroalkyl, and -C₂-6alkynyl-C₂-7cycloheteroalkenyl, wherein each CH₂ is unsubstituted or substituted with 1 or 2
 15 substituents selected from: halogen, CF₃, -OH, -NH₂, -C₁-6alkyl, -OC₁-6alkyl, -NHC₁-6alkyl, and -N(C₁-6alkyl)₂, wherein each alkyl, alkenyl and alkynyl is unsubstituted or substituted with 1, 2 or 3 substituents selected from: halogen, CF₃, -OH, -NH₂, -C₁-6alkyl, -OC₁-6alkyl, -NHC₁-6alkyl, and -N(C₁-6alkyl)₂, and wherein each cycloalkyl, cycloalkenyl, cycloheteroalkyl, cycloheteroalkenyl, phenyl, aryl and heteroaryl is unsubstituted or substituted with 1, 2, 3 or 4
 20 substituents independently selected from R^a; and R² is selected from the group consisting of: hydrogen, halogen, -CN, -CF₃, and -C₁-6alkyl, and provided that if R² is hydrogen, then at least one of R³ and R⁴ is not hydrogen. In a subclass of this class, R² is selected from the group consisting of: hydrogen, Cl, F, Br, CN, CF₃, and CH₃. In another subclass of this class, R² is selected from the group consisting of: halogen, -CN, -CF₃, and -C₁-6alkyl. In another subclass
 25 of this class, R² is selected from the group consisting of: Cl, F, Br, CN, CF₃, and CH₃.

In another class of this embodiment, R¹ is selected from: -(CH₂)_paryl, biphenyl, -(CH₂)_pheteroaryl, -C₂-6alkenyl-aryl, -C₂-6alkynyl-alkyl, -C₂-6alkynyl-aryl, -C₂-6alkynyl-heteroaryl, -C₂-6alkynyl-C₃-7cycloalkyl, -C₂-6alkynyl-C₂-7cycloheteroalkyl, and -C₂-6alkynyl-C₂-7cycloheteroalkenyl, wherein each CH₂ is unsubstituted or substituted with 1 or 2
 30 substituents selected from: halogen, CF₃, -OH, -NH₂, -C₁-6alkyl, -OC₁-6alkyl, -NHC₁-6alkyl, and -N(C₁-6alkyl)₂, wherein each alkyl, alkenyl and alkynyl is unsubstituted or substituted with 1, 2 or 3 substituents selected from: halogen, CF₃, -OH, -NH₂, -C₁-6alkyl, -OC₁-6alkyl, -NHC₁-6alkyl, and -N(C₁-6alkyl)₂, and wherein each cycloalkyl, cycloalkenyl, cycloheteroalkyl, cycloheteroalkenyl, phenyl, aryl and heteroaryl is unsubstituted or substituted with 1, 2, 3 or 4
 35 substituents independently selected from R^a; and R² is selected from the group consisting of: halogen, -CN, -CF₃, and -C₁-6alkyl. In a subclass of this class, R² is selected from the group consisting of: Cl, F, Br, CN, CF₃, and CH₃.

In another class of this embodiment, each R¹ is selected from: -(CH₂)_paryl, biphenyl, heteroaryl, -C₂-6alkenyl-aryl, -C₂-6alkynyl-alkyl, -C₂-6alkynyl-aryl, -C₂-6alkynyl-heteroaryl, -C₂-6alkynyl-C₃-7cycloalkyl, -C₂-6alkynyl-C₂-7cycloheteroalkyl, and -C₂-6alkynyl-C₂-7cycloheteroalkenyl, wherein each CH₂ is unsubstituted or substituted with 1 or 2 substituents selected from: halogen, CF₃, -OH, -NH₂, -C₁-6alkyl, -OC₁-6alkyl, -NHC₁-6alkyl, and -N(C₁-6alkyl)₂, wherein each alkyl, alkenyl and alkynyl is unsubstituted or substituted with 1, 2 or 3 substituents selected from: halogen, CF₃, -OH, -NH₂, -C₁-6alkyl, -OC₁-6alkyl, -NHC₁-6alkyl, and -N(C₁-6alkyl)₂, and wherein each cycloalkyl, cycloalkenyl, cycloheteroalkyl, cycloheteroalkenyl, phenyl, aryl and heteroaryl is unsubstituted or substituted with 1, 2, 3 or 4 substituents independently selected from R^a; and R² is selected from the group consisting of: hydrogen, halogen, -CN, -CF₃, and -C₁-6alkyl, and provided that if R² is hydrogen, then at least one of R³ and R⁴ is not hydrogen. In a subclass of this class, R² is selected from the group consisting of: hydrogen, Cl, F, Br, CN, CF₃, and CH₃. In another subclass of this class, R² is selected from the group consisting of: halogen, -CN, -CF₃, and -C₁-6alkyl. In another subclass of this class, R² is selected from the group consisting of: Cl, F, Br, CN, CF₃, and CH₃.

In another class of this embodiment, each R¹ is selected from: -(CH₂)_paryl, biphenyl, heteroaryl, -C₂-6alkenyl-aryl, -C₂-6alkynyl-alkyl, -C₂-6alkynyl-aryl, -C₂-6alkynyl-heteroaryl, -C₂-6alkynyl-C₃-7cycloalkyl, -C₂-6alkynyl-C₂-7cycloheteroalkyl, and -C₂-6alkynyl-C₂-7cycloheteroalkenyl, wherein each CH₂ is unsubstituted or substituted with 1 or 2 substituents selected from: halogen, CF₃, -OH, -NH₂, -C₁-6alkyl, -OC₁-6alkyl, -NHC₁-6alkyl, and -N(C₁-6alkyl)₂, wherein each alkyl, alkenyl and alkynyl is unsubstituted or substituted with 1, 2 or 3 substituents selected from: halogen, CF₃, -OH, -NH₂, -C₁-6alkyl, -OC₁-6alkyl, -NHC₁-6alkyl, and -N(C₁-6alkyl)₂, and wherein each cycloalkyl, cycloalkenyl, cycloheteroalkyl, cycloheteroalkenyl, phenyl, aryl and heteroaryl is unsubstituted or substituted with 1, 2, 3 or 4 substituents independently selected from R^a; and R² is selected from the group consisting of: halogen, -CN, -CF₃, and -C₁-6alkyl. In a subclass of this class, R² is selected from the group consisting of: Cl, F, Br, CN, CF₃, and CH₃.

In another class of this embodiment, each R¹ is selected from: -(CH₂)_paryl, biphenyl, heteroaryl, -C₂-6alkenyl-aryl, -C₂-alkynyl-alkyl, -C₂-alkynyl-aryl, -C₂-alkynyl-heteroaryl, -C₂-alkynyl-C₅-6cycloalkyl, -C₂-alkynyl-C₄-5cycloheteroalkyl, and -C₂-alkynyl-C₄-5cycloheteroalkenyl, wherein each CH₂ is unsubstituted or substituted with 1 or 2 substituents selected from: halogen, CF₃, -OH, -NH₂, -C₁-6alkyl, -OC₁-6alkyl, -NHC₁-6alkyl, and -N(C₁-6alkyl)₂, wherein each alkyl and alkenyl is unsubstituted or substituted with 1, 2 or 3 substituents selected from: halogen, CF₃, -OH, -NH₂, -C₁-6alkyl, -OC₁-6alkyl, -NHC₁-6alkyl, and -N(C₁-6alkyl)₂, and wherein each cycloalkyl, cycloalkenyl, cycloheteroalkyl, cycloheteroalkenyl, phenyl, aryl and heteroaryl is unsubstituted or substituted with 1, 2, 3 or 4 substituents independently selected from R^a; and R² is selected from the group consisting of: hydrogen,

halogen, -CN, -CF₃, and -C₁₋₆alkyl, and provided that if R² is hydrogen, then at least one of R³ and R⁴ is not hydrogen. In a subclass of this class, R² is selected from the group consisting of: hydrogen, Cl, F, Br, CN, CF₃, and CH₃. In another subclass of this class, R² is selected from the group consisting of: halogen, -CN, -CF₃, and -C₁₋₆alkyl. In another subclass of this class, R² is selected from the group consisting of: Cl, F, Br, CN, CF₃, and CH₃.

In another class of this embodiment, each R¹ is selected from: -(CH₂)_paryl, biphenyl, heteroaryl, -C₂₋₆alkenyl-aryl, -C₂alkynyl-alkyl, -C₂alkynyl-aryl, -C₂alkynyl-heteroaryl, -C₂alkynyl-C₅₋₆cycloalkyl, -C₂alkynyl-C₄₋₅cycloheteroalkyl, and -C₂alkynyl-C₄₋₅cycloheteroalkenyl, wherein each CH₂ is unsubstituted or substituted with 1 or 2 substituents selected from: halogen, CF₃, -OH, -NH₂, -C₁₋₆alkyl, -OC₁₋₆alkyl, -NHC₁₋₆alkyl, and -N(C₁₋₆alkyl)₂, wherein each alkyl and alkenyl is unsubstituted or substituted with 1, 2 or 3 substituents selected from: halogen, CF₃, -OH, -NH₂, -C₁₋₆alkyl, -OC₁₋₆alkyl, -NHC₁₋₆alkyl, and -N(C₁₋₆alkyl)₂, and wherein each cycloalkyl, cycloalkenyl, cycloheteroalkyl, cycloheteroalkenyl, phenyl, aryl and heteroaryl is unsubstituted or substituted with 1, 2, 3 or 4 substituents independently selected from R^a; and R² is selected from the group consisting of: halogen, -CN, -CF₃, and -C₁₋₆alkyl. In a subclass of this class, R² is selected from the group consisting of: Cl, F, Br, CN, CF₃, and CH₃.

In another class of this embodiment, each R¹ is selected from: -(CH₂)₂phenyl, phenyl, naphthalene, indane, 5,6,7,8-tetrahydronaphthalene, biphenyl, 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, [1,2,4]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, 1,2,3,6-tetrahydropyridine, -C₂alkenyl-phenyl, -C₂alkynyl-isopropyl, -C₂alkynyl-phenyl, -C₂alkynyl-naphthalene, -C₂alkynyl-imidazole, -C₂alkynyl-pyridine, -C₂alkynyl-cyclopentyl, -C₂alkynyl-pyrrolidine, -C₂alkynyl-dihydropyridine, and 1,6-dihydro-pyridin-3-ylethynyl, wherein each CH₂ is unsubstituted or substituted with 1 or 2 substituents selected from: halogen, CF₃, -OH, -NH₂, -C₁₋₆alkyl, -OC₁₋₆alkyl, -NHC₁₋₆alkyl, and -N(C₁₋₆alkyl)₂, wherein each alkyl and alkenyl is unsubstituted or substituted with 1, 2 or 3 substituents selected from: halogen, CF₃, -OH, -NH₂, -C₁₋₆alkyl, -OC₁₋₆alkyl, -NHC₁₋₆alkyl, and -N(C₁₋₆alkyl)₂, and wherein each cycloalkyl, cycloalkenyl, cycloheteroalkyl, cycloheteroalkenyl, phenyl, aryl and heteroaryl is unsubstituted or substituted with 1, 2, 3 or 4 substituents independently selected from R^a; and R² is selected from the group consisting of: hydrogen, Cl, F, Br, CN, CF₃, and CH₃, and provided that if R² is hydrogen, then at least one of R³ and R⁴ is not hydrogen. In a subclass of this class, R² is selected from the group consisting

of: halogen, -CN, -CF₃, and -C₁₋₆alkyl. In another subclass of this class, R² is selected from the group consisting of: Cl, F, Br, CN, CF₃, and CH₃.

In another class of this embodiment, each R¹ is selected from: -(CH₂)₂phenyl, phenyl, naphthalene, indane, 5,6,7,8-tetrahydronaphthalene, biphenyl, 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, [1,2,4]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-dihydrobenzo-imidazole, 1,2-dihydroquinoline, 1,2,3,4-tetrahydroisoquinoline, 1,2,3,4-tetrahydrocyclo-penta[b]indole, 1,2,3,4-tetrahydroquinoxaline, 1,2,3,6-tetrahydropyridine, -C₂alkenyl-phenyl, -C₂alkynyl-isopropyl, -C₂alkynyl-phenyl, -C₂alkynyl-naphthalene, -C₂alkynyl-imidazole, -C₂alkynyl-pyridine, -C₂alkynyl-cyclopentyl, -C₂alkynyl-pyrrolidine, -C₂alkynyl-dihydropyridine, and 1,6-dihydro-pyridin-3-ylethynyl, wherein each CH₂ is unsubstituted or substituted with 1 or 2 substituents selected from: halogen, CF₃, -OH, -NH₂, -C₁₋₆alkyl, -OC₁₋₆alkyl, -NHC₁₋₆alkyl, and -N(C₁₋₆alkyl)₂, wherein each alkyl and alkenyl is unsubstituted or substituted with 1, 2 or 3 substituents selected from: halogen, CF₃, -OH, -NH₂, -C₁₋₆alkyl, -OC₁₋₆alkyl, -NHC₁₋₆alkyl, and -N(C₁₋₆alkyl)₂, and wherein each cycloalkyl, cycloalkenyl, cycloheteroalkyl, cycloheteroalkenyl, phenyl, aryl and heteroaryl is unsubstituted or substituted with 1, 2, 3 or 4 substituents independently selected from R^a; and R² is selected from the group consisting of: Cl, F, Br, CN, CF₃, and CH₃.

In another embodiment of the present invention, R² is selected from the group consisting of: halogen, -CN, -CF₃, and -C₁₋₆alkyl. In a class of this embodiment, R² is selected from the group consisting of: hydrogen, Cl, F, Br, CN, CF₃, and CH₃. In another class of this embodiment, R² is halogen. In a subclass of this class, R² is selected from the group consisting of: Cl, F, and Br. In another subclass of this class, R² is selected from the group consisting of: Cl or F. In another subclass of this class, R² is Cl. In another subclass of this class, R² is F.

In another embodiment of the present invention, R³ and R⁴ are each independently selected from: hydrogen, halogen, -C₁₋₆alkyl, -C₂₋₆alkenyl, -C₂₋₆alkynyl, -C₃₋₁₀cycloalkyl, -C₃₋₁₀cycloalkenyl, aryl, heteroaryl, -CN, -CF₃, -OH, -OC₁₋₆alkyl, -NH₂, -NHC₁₋₆alkyl, -N(C₁₋₆alkyl)₂, -SC₁₋₆alkyl, -SOC₁₋₆alkyl, -SO₂C₁₋₆alkyl, -NHSO₂C₁₋₆alkyl, -NHC(O)C₁₋₆alkyl, -SO₂NHC₁₋₆alkyl, and -C(O)NHC₁₋₆alkyl.

In another embodiment of the present invention, R³ and R⁴ are each independently selected from: hydrogen, halogen, -C₁₋₆alkyl, -C₂₋₆alkenyl, -C₂₋₆alkynyl, -C₃₋₁₀cycloalkyl, -C₃₋₁₀cycloalkenyl, aryl, heteroaryl, -CN, -CF₃, -OH, -OC₁₋₆alkyl, -NH₂, -NHC₁₋₆alkyl, -N(C₁₋₆alkyl)₂, -SC₁₋₆alkyl, -SOC₁₋₆alkyl, -SO₂C₁₋₆alkyl, -NHSO₂C₁₋₆alkyl, and -NHC(O)C₁₋₆alkyl. In a class of this embodiment, R³ and R⁴ are each independently selected

from: hydrogen, halogen, $-C_1$ -6alkyl, $-CN$, $-CF_3$, $-OH$, $-OC_1$ -6alkyl, $-SOC_1$ -6alkyl, and $-SO_2C_1$ -6alkyl. In a subclass of this class, R^3 and R^4 are each independently selected from: hydrogen, and halogen. In another subclass of this class, R^3 and R^4 are each independently selected from: hydrogen, Cl, Br and F. In another subclass of this class, R^3 and R^4 are each independently selected from: hydrogen, and F. In another subclass of this class, R^3 is hydrogen or halogen, and R^4 is hydrogen. In another subclass of this class, R^3 is hydrogen or Cl, Br, F, and R^4 is hydrogen. In another subclass of this class, R^3 is hydrogen or F, and R^4 is hydrogen.

In another embodiment of the present invention, R^3 is selected from: hydrogen, halogen, $-C_1$ -6alkyl, $-C_2$ -6alkenyl, $-C_2$ -6alkynyl, $-C_3$ -10cycloalkyl, $-C_3$ -10cycloalkenyl, aryl, heteroaryl, $-CN$, $-CF_3$, $-OH$, $-OC_1$ -6alkyl, $-NH_2$, $-NHC_1$ -6alkyl, $-N(C_1$ -6alkyl) $_2$, $-SC_1$ -6alkyl, $-SOC_1$ -6alkyl, $-SO_2C_1$ -6alkyl, $-NHSO_2C_1$ -6alkyl, and $-NHC(O)C_1$ -6alkyl. In a class of this embodiment, R^3 is selected from: hydrogen, halogen, $-C_1$ -6alkyl, $-CN$, $-CF_3$, $-OH$, $-OC_1$ -6alkyl, $-SOC_1$ -6alkyl, and $-SO_2C_1$ -6alkyl. In a subclass of this class, R^3 is selected from: hydrogen, and halogen. In another subclass of this class, R^3 is selected from: hydrogen, Cl, Br and F. In another subclass of this class, R^3 is selected from: hydrogen, and F. In another subclass of this class, R^3 is hydrogen. In another subclass of this class, R^3 is F. In another subclass of this class, R^3 is hydrogen or halogen, and R^4 is hydrogen. In another subclass of this class, R^3 is hydrogen or Cl, Br, F, and R^4 is hydrogen. In another subclass of this class, R^3 is hydrogen or F, and R^4 is hydrogen.

In another embodiment of the present invention, R^4 is selected from: hydrogen, halogen, $-C_1$ -6alkyl, $-C_2$ -6alkenyl, $-C_2$ -6alkynyl, $-C_3$ -10cycloalkyl, $-C_3$ -10cycloalkenyl, aryl, heteroaryl, $-CN$, $-CF_3$, $-OH$, $-OC_1$ -6alkyl, $-NH_2$, $-NHC_1$ -6alkyl, $-N(C_1$ -6alkyl) $_2$, $-SC_1$ -6alkyl, $-SOC_1$ -6alkyl, $-SO_2C_1$ -6alkyl, $-NHSO_2C_1$ -6alkyl, and $-NHC(O)C_1$ -6alkyl. In a class of this embodiment, R^4 is selected from: hydrogen, halogen, $-C_1$ -6alkyl, $-CN$, $-CF_3$, $-OH$, $-OC_1$ -6alkyl, $-SOC_1$ -6alkyl, and $-SO_2C_1$ -6alkyl. In a subclass of this class, R^4 is selected from: hydrogen, and halogen. In another subclass of this class, R^4 is selected from: hydrogen, Cl, Br and F. In another subclass of this class, R^4 is selected from: hydrogen, and F. In another subclass of this class, R^4 is hydrogen. In another subclass of this class, R^4 is F. In another subclass of this class, R^3 is hydrogen or halogen, and R^4 is hydrogen. In another subclass of this class, R^3 is hydrogen or Cl, Br, F, and R^4 is hydrogen. In another subclass of this class, R^3 is hydrogen or F, and R^4 is hydrogen.

In another embodiment of the present invention, R^5 is selected from: hydrogen, $-C_1$ -6alkyl, $-CH_2CO_2H$, and $-CH_2CO_2C_1$ -6alkyl. In a class of this embodiment, R^5 is selected from: hydrogen, $-CH_2CO_2H$, and $-CH_2CO_2C_1$ -6alkyl. In another class of this embodiment, R^5 is selected from: hydrogen, $-CH_2CO_2H$, and $-CH_2CO_2CH_3$.

In another embodiment of the present invention, R^a is independently selected from the group consisting of: halogen, oxo, $-(CH_2)_mOH$, $-(CH_2)_mN(R^j)_2$, $-(CH_2)_mCN$, $-C_1$ -6alkyl, $-$

(CH₂)_mCF₃, -(CH₂)_mOCF₃, -OCH₂OC₁₋₆alkyl, -(CH₂)_mC(=N-OH)N(R_j)₂, -(CH₂)_mOC₁₋₆alkyl, -OCH₂phenyl, -(CH₂)_mSC₁₋₆alkyl, -(CH₂)_mS(O)C₁₋₆alkyl, -(CH₂)_mS(O)₂C₁₋₆alkyl, -(CH₂)_mC(O)R^f, -(CH₂)_mC(O)N(R_j)₂, -(CH₂)_mN(R_j)C(O)R^f, -(CH₂)_mCO₂H, -(CH₂)_mOC(O)H, -(CH₂)_mCO₂R^f, -(CH₂)_mOC(O)R^f, -(CH₂)_mC₃₋₇cycloalkyl, -(CH₂)_mC₃₋₇cycloalkenyl, -(CH₂)_mC₂₋₆cycloheteroalkyl, -(CH₂)_mC₂₋₆cycloheteroalkenyl, -(CH₂)_maryl, and -(CH₂)_mheteroaryl, wherein each CH₂ is unsubstituted or substituted with 1 or 2 substituents selected from: oxo, -(CH₂)₀₋₃OH, -CN, -NH₂, -NH(C₁₋₆alkyl), -N(C₁₋₆alkyl)₂, -C₁₋₆alkyl, -OC₁₋₆alkyl, halogen, -CH₂F, -CHF₂, -CF₃, -CO₂H, -CO₂C₁₋₆alkyl, -C₃₋₇cycloalkyl, phenyl, CH₂phenyl and heteroaryl, and wherein alkyl, cycloalkyl, cycloheteroalkyl, phenyl, aryl and heteroaryl are unsubstituted or substituted with 1, 2, 3 or 4 substituents selected from: oxo, -(CH₂)₀₋₃OH, -CN, -NH₂, -NH(C₁₋₆alkyl), -N(C₁₋₆alkyl)₂, -C₁₋₆alkyl, -OC₁₋₆alkyl, halogen, -CH₂F, -CHF₂, -CF₃, -CO₂H, -CO₂C₁₋₆alkyl, -C₃₋₇cycloalkyl, phenyl, CH₂phenyl and heteroaryl. In a class of this embodiment, R^a is independently selected from the group consisting of: halogen, oxo, -(CH₂)_mOH, -(CH₂)_mN(R_j)₂, -(CH₂)_mCN, -C₁₋₆alkyl, -(CH₂)_mCF₃, -(CH₂)_mOCF₃, -OCH₂OC₁₋₆alkyl, -(CH₂)_mC(=N-OH)N(R_j)₂, -(CH₂)_mOC₁₋₆alkyl, -OCH₂phenyl, -(CH₂)_mSC₁₋₆alkyl, -(CH₂)_mS(O)C₁₋₆alkyl, -(CH₂)_mS(O)₂C₁₋₆alkyl, -(CH₂)_mC(O)R^f, -(CH₂)_mC(O)N(R_j)₂, -(CH₂)_mN(R_j)C(O)R^f, -(CH₂)_mCO₂H, -(CH₂)_mOC(O)H, -(CH₂)_mCO₂R^f, -(CH₂)_mOC(O)R^f, -(CH₂)_mC₃₋₇cycloalkyl, -(CH₂)_mC₃₋₇cycloalkenyl, -(CH₂)_mC₂₋₆cycloheteroalkyl, -(CH₂)_mC₂₋₆cycloheteroalkenyl, -(CH₂)_maryl, and -(CH₂)_mheteroaryl, wherein each CH₂ is unsubstituted or substituted with 1 or 2 substituents selected from: oxo, -(CH₂)₀₋₃OH, -CN, -NH₂, -NH(C₁₋₆alkyl), -N(C₁₋₆alkyl)₂, -C₁₋₆alkyl, -OC₁₋₆alkyl, halogen, -CH₂F, -CHF₂, -CF₃, -CO₂H, -CO₂C₁₋₆alkyl, -C₃₋₇cycloalkyl, phenyl, and CH₂phenyl, and wherein alkyl, cycloalkyl, cycloheteroalkyl, phenyl, aryl and heteroaryl are unsubstituted or substituted with 1, 2, 3 or 4 substituents selected from: oxo, -(CH₂)₀₋₃OH, -CN, -NH₂, -NH(C₁₋₆alkyl), -N(C₁₋₆alkyl)₂, -C₁₋₆alkyl, -OC₁₋₆alkyl, halogen, -CH₂F, -CHF₂, -CF₃, -CO₂H, -CO₂C₁₋₆alkyl, -C₃₋₇cycloalkyl, phenyl, and CH₂phenyl.

In another embodiment of the present invention, each R^a is independently selected from the group consisting of: halogen, oxo, -(CH₂)_mOH, -(CH₂)_mN(R_j)₂, -(CH₂)_mNO₂, -(CH₂)_mCN, -C₁₋₆alkyl, -(CH₂)_mCF₃, -(CH₂)_mOCF₃, -OCH₂OC₁₋₆alkyl, -OCH₂-aryl, -(CH₂)_mC(=N-OH)N(R_j)₂, -(CH₂)_mOC₁₋₆alkyl, -(CH₂)_mO-aryl, -OCH₂phenyl, -(CH₂)_mSC₁₋₆alkyl, -(CH₂)_mS(O)C₁₋₆alkyl, -(CH₂)_mS(O)₂C₁₋₆alkyl, -(CH₂)_mNHS(O)₂C₁₋₆alkyl, -(CH₂)_mC(O)R^f, -(CH₂)_mC(O)N(R_j)₂, -(CH₂)_mN(R_j)C(O)R^f, -(CH₂)_mN(R_j)C(O)N(R_j)₂, -(CH₂)_mCO₂H, -(CH₂)_mOC(O)H, -(CH₂)_mCO₂R^f, -(CH₂)_mOC(O)R^f, -(CH₂)_mC₃₋₇cycloalkyl, -(CH₂)_mC₃₋₇cycloalkenyl, -(CH₂)_mC₂₋₆cycloheteroalkyl, -(CH₂)_mC₂₋₆cycloheteroalkenyl, -(CH₂)_maryl, and -(CH₂)_mheteroaryl, wherein each CH₂ is unsubstituted or substituted with 1 or 2 substituents selected from: oxo, -(CH₂)₀₋₃OH, -CN, -NH₂, -NH(C₁₋₆alkyl),

6alkyl), -N(C₁₋₆alkyl)₂, -C₁₋₆alkyl, -OC₁₋₆alkyl, halogen, -CH₂F, -CHF₂, -CF₃, -CO₂H, -CO₂C₁₋₆alkyl, -C₃₋₇cycloalkyl, phenyl, CH₂phenyl, heteroaryl, and CH₂heteroaryl, and wherein alkyl, cycloalkyl, cycloheteroalkyl, phenyl, aryl and heteroaryl are unsubstituted or substituted with 1, 2, 3 or 4 substituents selected from: oxo, -(CH₂)₀₋₃OH, -CN, -NH₂, -NH(C₁₋₆alkyl), -N(C₁₋₆alkyl)₂, -C₁₋₆alkyl, -OC₁₋₆alkyl, halogen, -CH₂F, -CHF₂, -CF₃, -CO₂H, -CO₂C₁₋₆alkyl, -C₃₋₇cycloalkyl, phenyl, CH₂phenyl, heteroaryl, and CH₂heteroaryl.

In another embodiment of the present invention, each R^a is independently selected from the group consisting of: halogen, oxo, -(CH₂)_mOH, -(CH₂)_mN(R^j)₂, -(CH₂)_mCN, -C₁₋₆alkyl, -(CH₂)_mCF₃, -(CH₂)_mOCF₃, -OCH₂OC₁₋₆alkyl, -(CH₂)_mC(=N-OH)N(R^j)₂, -(CH₂)_mOC₁₋₆alkyl, -OCH₂phenyl, -(CH₂)_mSC₁₋₆alkyl, -(CH₂)_mS(O)C₁₋₆alkyl, -(CH₂)_mC(O)R^f, -(CH₂)_mC(O)N(R^j)₂, -(CH₂)_mN(R^j)C(O)R^f, -(CH₂)_mCO₂H, -(CH₂)_mOC(O)H, -(CH₂)_mCO₂R^f, -(CH₂)_mOC(O)R^f, -(CH₂)_mC₃₋₇cycloalkyl, -(CH₂)_mC₃₋₇cycloalkenyl, -(CH₂)_mC₂₋₆cycloheteroalkyl, -(CH₂)_mC₂₋₆cycloheteroalkenyl, -(CH₂)_maryl, and -(CH₂)_mheteroaryl, wherein each CH₂ is unsubstituted or substituted with 1 or 2 substituents selected from: oxo, -(CH₂)₀₋₃OH, -CN, -NH₂, -NH(C₁₋₆alkyl), -N(C₁₋₆alkyl)₂, -C₁₋₆alkyl, -OC₁₋₆alkyl, halogen, -CH₂F, -CHF₂, -CF₃, -CO₂H, -CO₂C₁₋₆alkyl, -C₃₋₇cycloalkyl, phenyl, CH₂phenyl and heteroaryl, and wherein alkyl, cycloalkyl, cycloheteroalkyl, phenyl, aryl and heteroaryl are unsubstituted or substituted with 1, 2, 3 or 4 substituents selected from: oxo, -(CH₂)₀₋₃OH, -CN, -NH₂, -NH(C₁₋₆alkyl), -N(C₁₋₆alkyl)₂, -C₁₋₆alkyl, -OC₁₋₆alkyl, halogen, -CH₂F, -CHF₂, -CF₃, -CO₂H, -CO₂C₁₋₆alkyl, -C₃₋₇cycloalkyl, phenyl, CH₂phenyl and heteroaryl. In a class of this embodiment, each CH₂ is unsubstituted or substituted with 1 or 2 substituents selected from: oxo, -(CH₂)₀₋₃OH, -CN, -NH₂, -NH(C₁₋₆alkyl), -N(C₁₋₆alkyl)₂, -C₁₋₆alkyl, -OC₁₋₆alkyl, halogen, -CH₂F, -CHF₂, -CF₃, -CO₂H, -CO₂C₁₋₆alkyl, -C₃₋₇cycloalkyl, phenyl, and CH₂phenyl; and alkyl, cycloalkyl, cycloheteroalkyl, phenyl, aryl and heteroaryl are unsubstituted or substituted with 1, 2, 3 or 4 substituents selected from: oxo, -(CH₂)₀₋₃OH, -CN, -NH₂, -NH(C₁₋₆alkyl), -N(C₁₋₆alkyl)₂, -C₁₋₆alkyl, -OC₁₋₆alkyl, halogen, -CH₂F, -CHF₂, -CF₃, -CO₂H, -CO₂C₁₋₆alkyl, -C₃₋₇cycloalkyl, phenyl, and CH₂phenyl. In another class of this embodiment, each CH₂ is unsubstituted or substituted with 1 or 2 substituents selected from: oxo, -CH₂OH, -OH, -CN, -NH₂, -NH(C₁₋₆alkyl), -N(C₁₋₆alkyl)₂, -C₁₋₆alkyl, -OC₁₋₆alkyl, halogen, -CH₂F, -CHF₂, -CF₃, -CO₂H, -CO₂C₁₋₆alkyl, -C₃₋₇cycloalkyl, phenyl, and CH₂phenyl; and alkyl, cycloalkyl, cycloheteroalkyl, phenyl, aryl and heteroaryl are unsubstituted or substituted with 1, 2 or 3 substituents selected from: oxo, -CH₂OH, -OH, -CN, -NH₂, -NH(C₁₋₆alkyl), -N(C₁₋₆alkyl)₂, -C₁₋₆alkyl, -OC₁₋₆alkyl, halogen, -CH₂F, -CHF₂, -CF₃, -CO₂H, -CO₂C₁₋₆alkyl, -C₃₋₇cycloalkyl, phenyl, and CH₂phenyl. In another class of this embodiment, each CH₂ is unsubstituted or substituted with 1 or 2 substituents selected from: oxo, -CH₂OH, -OH, -CN, -NH₂, -CH₃, -OCH₃, F, Cl, -CH₂F, -CO₂H, -CO₂C(CH₃)₃, and cyclopropyl; and alkyl, cycloalkyl, cycloheteroalkyl, phenyl, aryl and

heteroaryl are unsubstituted or substituted with 1, 2 or 3 substituents selected from: oxo, -CH₂OH, -OH, -CN, -NH₂, -CH₃, -OCH₃, F, Cl, -CH₂F, -CO₂H, -CO₂C(CH₃)₃, and cyclopropyl.

In a class of this embodiment, each R^a is independently selected from the group consisting of: halogen, oxo, -(CH₂)_mOH, -(CH₂)_mN(R^j)₂, -(CH₂)_mCN, -C₁₋₆alkyl, -(CH₂)_mCF₃, -(CH₂)_mOCF₃, -(CH₂)_mC(=N-OH)N(R^j)₂, -(CH₂)_mOC₁₋₆alkyl, -(CH₂)_mSC₁₋₆alkyl, -(CH₂)_mS(O)C₁₋₆alkyl, -(CH₂)_mC(O)R^f, -(CH₂)_mC(O)N(R^j)₂, -(CH₂)_mCO₂H, -(CH₂)_mOC(O)H, -(CH₂)_mCO₂R^f, -(CH₂)_mOC(O)R^f, -(CH₂)_mC₃₋₇cycloalkyl, -(CH₂)_mC₂₋₆cycloheteroalkyl, -(CH₂)_mC₂₋₆cycloheteroalkenyl, -(CH₂)_maryl, and -(CH₂)_mheteroaryl, wherein each CH₂ is unsubstituted or substituted with 1 or 2 substituents selected from: oxo, -(CH₂)₀₋₃OH, -CN, -NH₂, -NH(C₁₋₆alkyl), -N(C₁₋₆alkyl)₂, -C₁₋₆alkyl, -OC₁₋₆alkyl, halogen, -CH₂F, -CHF₂, -CF₃, -CO₂H, -CO₂C₁₋₆alkyl, -C₃₋₇cycloalkyl, phenyl, CH₂phenyl and heteroaryl, and wherein alkyl, cycloalkyl, cycloheteroalkyl, aryl and heteroaryl are unsubstituted or substituted with 1, 2, 3 or 4 substituents selected from: oxo, -(CH₂)₀₋₃OH, -CN, -NH₂, -NH(C₁₋₆alkyl), -N(C₁₋₆alkyl)₂, -C₁₋₆alkyl, -OC₁₋₆alkyl, halogen, -CH₂F, -CHF₂, -CF₃, -CO₂H, -CO₂C₁₋₆alkyl, -C₃₋₇cycloalkyl, phenyl, CH₂phenyl and heteroaryl. In a class of this embodiment, each CH₂ is unsubstituted or substituted with 1 or 2 substituents selected from: oxo, -(CH₂)₀₋₃OH, -CN, -NH₂, -NH(C₁₋₆alkyl), -N(C₁₋₆alkyl)₂, -C₁₋₆alkyl, -OC₁₋₆alkyl, halogen, -CH₂F, -CHF₂, -CF₃, -CO₂H, -CO₂C₁₋₆alkyl, -C₃₋₇cycloalkyl, phenyl, and CH₂phenyl; and alkyl, cycloalkyl, cycloheteroalkyl, aryl and heteroaryl are unsubstituted or substituted with 1, 2, 3 or 4 substituents selected from: oxo, -(CH₂)₀₋₃OH, -CN, -NH₂, -NH(C₁₋₆alkyl), -N(C₁₋₆alkyl)₂, -C₁₋₆alkyl, -OC₁₋₆alkyl, halogen, -CH₂F, -CHF₂, -CF₃, -CO₂H, -CO₂C₁₋₆alkyl, -C₃₋₇cycloalkyl, phenyl, and CH₂phenyl. In another class of this embodiment, each CH₂ is unsubstituted or substituted with 1 or 2 substituents selected from: oxo, -CH₂OH, -OH, -CN, -NH₂, -NH(C₁₋₆alkyl), -N(C₁₋₆alkyl)₂, -C₁₋₆alkyl, -OC₁₋₆alkyl, halogen, -CH₂F, -CHF₂, -CF₃, -CO₂H, -CO₂C₁₋₆alkyl, -C₃₋₇cycloalkyl, phenyl, and CH₂phenyl; and alkyl, cycloalkyl, cycloheteroalkyl, aryl and heteroaryl are unsubstituted or substituted with 1, 2 or 3 substituents selected from: oxo, -CH₂OH, -OH, -CN, -NH₂, -NH(C₁₋₆alkyl), -N(C₁₋₆alkyl)₂, -C₁₋₆alkyl, -OC₁₋₆alkyl, halogen, -CH₂F, -CHF₂, -CF₃, -CO₂H, -CO₂C₁₋₆alkyl, -C₃₋₇cycloalkyl, phenyl, and CH₂phenyl. In another class of this embodiment, each CH₂ is unsubstituted or substituted with 1 or 2 substituents selected from: oxo, -CH₂OH, -OH, -CN, -NH₂, -CH₃, -OCH₃, F, Cl, -CH₂F, -CO₂H, -CO₂C(CH₃)₃, and cyclopropyl; and alkyl, cycloalkyl, cycloheteroalkyl, aryl and heteroaryl are unsubstituted or substituted with 1, 2 or 3 substituents selected from: oxo, -CH₂OH, -OH, -CN, -NH₂, -CH₃, -OCH₃, F, Cl, -CH₂F, -CO₂H, -CO₂C(CH₃)₃, and cyclopropyl.

In another class of this embodiment, each R^a is independently selected from the group consisting of: halogen, oxo, -(CH₂)_mOH, -(CH₂)_mN(R^j)₂, -CN, -C₁₋₆alkyl, -(CH₂)_mCF₃,

OCF₃, -C(=N-OH)N(R_i)₂, -OC₁₋₆alkyl, -SC₁₋₆alkyl, -S(O)C₁₋₆alkyl, -(CH₂)_mC(O)C₁₋₆alkyl, -(CH₂)_mC(O)C₂₋₆cycloheteroalkyl, -C(O)N(R_i)₂, -CO₂H, -OC(O)H, -CO₂R^f, -(CH₂)_mOC(O)R^f, -(CH₂)_mC₃₋₇cycloalkyl, -C₂₋₆cycloheteroalkyl, -C₂₋₆cycloheteroalkenyl, aryl, and heteroaryl, wherein each CH₂ is unsubstituted or substituted with 1 or 2 substituents selected from: oxo, -(CH₂)₀₋₃OH, -CN, -NH₂, -NH(C₁₋₆alkyl), -N(C₁₋₆alkyl)₂, -C₁₋₆alkyl, -OC₁₋₆alkyl, halogen, -CH₂F, -CHF₂, -CF₃, -CO₂H, -CO₂C₁₋₆alkyl, -C₃₋₇cycloalkyl, phenyl, CH₂phenyl and heteroaryl, and wherein alkyl, cycloalkyl, cycloheteroalkyl, aryl and heteroaryl are unsubstituted or substituted with 1, 2, 3 or 4 substituents selected from: oxo, -(CH₂)₀₋₃OH, -CN, -NH₂, -NH(C₁₋₆alkyl), -N(C₁₋₆alkyl)₂, -C₁₋₆alkyl, -OC₁₋₆alkyl, halogen, -CH₂F, -CHF₂, -CF₃, -CO₂H, -CO₂C₁₋₆alkyl, -C₃₋₇cycloalkyl, phenyl, CH₂phenyl and heteroaryl. In a class of this embodiment, each CH₂ is unsubstituted or substituted with 1 or 2 substituents selected from: oxo, -(CH₂)₀₋₃OH, -CN, -NH₂, -NH(C₁₋₆alkyl), -N(C₁₋₆alkyl)₂, -C₁₋₆alkyl, -OC₁₋₆alkyl, halogen, -CH₂F, -CHF₂, -CF₃, -CO₂H, -CO₂C₁₋₆alkyl, -C₃₋₇cycloalkyl, phenyl, and CH₂phenyl; and alkyl, cycloalkyl, cycloheteroalkyl, aryl and heteroaryl are unsubstituted or substituted with 1, 2, 3 or 4 substituents selected from: oxo, -(CH₂)₀₋₃OH, -CN, -NH₂, -NH(C₁₋₆alkyl), -N(C₁₋₆alkyl)₂, -C₁₋₆alkyl, -OC₁₋₆alkyl, halogen, -CH₂F, -CHF₂, -CF₃, -CO₂H, -CO₂C₁₋₆alkyl, -C₃₋₇cycloalkyl, phenyl, and CH₂phenyl. In another class of this embodiment, each CH₂ is unsubstituted or substituted with 1 or 2 substituents selected from: oxo, -CH₂OH, -OH, -CN, -NH₂, -NH(C₁₋₆alkyl), -N(C₁₋₆alkyl)₂, -C₁₋₆alkyl, -OC₁₋₆alkyl, halogen, -CH₂F, -CHF₂, -CF₃, -CO₂H, -CO₂C₁₋₆alkyl, -C₃₋₇cycloalkyl, phenyl, and CH₂phenyl; and alkyl, cycloalkyl, cycloheteroalkyl, aryl and heteroaryl are unsubstituted or substituted with 1, 2 or 3 substituents selected from: oxo, -CH₂OH, -OH, -CN, -NH₂, -NH(C₁₋₆alkyl), -N(C₁₋₆alkyl)₂, -C₁₋₆alkyl, -OC₁₋₆alkyl, halogen, -CH₂F, -CHF₂, -CF₃, -CO₂H, -CO₂C₁₋₆alkyl, -C₃₋₇cycloalkyl, phenyl, and CH₂phenyl. In another class of this embodiment, each CH₂ are unsubstituted or substituted with 1 or 2 substituents selected from: oxo, -CH₂OH, -OH, -CN, -NH₂, -CH₃, -OCH₃, F, Cl, -CH₂F, -CO₂H, -CO₂C(CH₃)₃, and cyclopropyl; and alkyl, cycloalkyl, cycloheteroalkyl, aryl and heteroaryl are unsubstituted or substituted with 1, 2 or 3 substituents selected from: oxo, -CH₂OH, -OH, -CN, -NH₂, -CH₃, -OCH₃, F, Cl, -CH₂F, -CO₂H, -CO₂C(CH₃)₃, and cyclopropyl.

In another class of this embodiment, each R^a is independently selected from the group consisting of: halogen, oxo, -(CH₂)_mOH, -(CH₂)_mN(R_j)₂, -CN, -C₁₋₆alkyl, -(CH₂)_mCF₃, -OCF₃, -C(=N-OH)N(R_j)₂, -OC₁₋₆alkyl, -SC₁₋₆alkyl, -S(O)C₁₋₆alkyl, -C(O)C₁₋₆alkyl, -C(O)C₂₋₆cycloheteroalkyl, -C(O)NH₂, -C(O)N(C₁₋₆alkyl)₂, -CO₂H, -OC(O)H, -CO₂C₁₋₆alkyl, -OC(O)C₁₋₆alkyl, -(CH₂)_mC₃₋₇cycloalkyl, -C₂₋₆cycloheteroalkyl, -C₂₋₆cycloheteroalkenyl, aryl, and heteroaryl, wherein each CH₂ is unsubstituted or substituted with 1 or 2 substituents selected from: oxo, -(CH₂)₀₋₃OH, -CN, -NH₂, -NH(C₁₋₆alkyl), -N(C₁₋₆alkyl)₂, -C₁₋₆alkyl, -OC₁₋₆alkyl, halogen, -CH₂F, -CHF₂, -CF₃, -CO₂H, -CO₂C₁₋₆alkyl, -C₃₋

7cycloalkyl, phenyl, CH₂phenyl and heteroaryl, and wherein alkyl, cycloalkyl, cycloheteroalkyl, aryl and heteroaryl are unsubstituted or substituted with 1, 2, 3 or 4 substituents selected from: oxo, -(CH₂)₀₋₃OH, -CN, -NH₂, -NH(C₁₋₆alkyl), -N(C₁₋₆alkyl)₂, -C₁₋₆alkyl, -OC₁₋₆alkyl, halogen, -CH₂F, -CHF₂, -CF₃, -CO₂H, -CO₂C₁₋₆alkyl, -C₃₋₇cycloalkyl, phenyl, CH₂phenyl and heteroaryl. In a class of this embodiment, each CH₂ is unsubstituted or substituted with 1 or

2 substituents selected from: oxo, -(CH₂)₀₋₃OH, -CN, -NH₂, -NH(C₁₋₆alkyl), -N(C₁₋₆alkyl)₂, -C₁₋₆alkyl, -OC₁₋₆alkyl, halogen, -CH₂F, -CHF₂, -CF₃, -CO₂H, -CO₂C₁₋₆alkyl, -C₃₋

7cycloalkyl, phenyl, and CH₂phenyl; and alkyl, cycloalkyl, cycloheteroalkyl, aryl and heteroaryl are unsubstituted or substituted with 1, 2, 3 or 4 substituents selected from: oxo, -(CH₂)₀₋₃OH, -CN, -NH₂, -NH(C₁₋₆alkyl), -N(C₁₋₆alkyl)₂, -C₁₋₆alkyl, -OC₁₋₆alkyl, halogen, -CH₂F, -CHF₂, -CF₃, -CO₂H, -CO₂C₁₋₆alkyl, -C₃₋₇cycloalkyl, phenyl, and CH₂phenyl. In another class of this embodiment, each CH₂ is unsubstituted or substituted with 1 or 2 substituents selected from:

oxo, -CH₂OH, -OH, -CN, -NH₂, -NH(C₁₋₆alkyl), -N(C₁₋₆alkyl)₂, -C₁₋₆alkyl, -OC₁₋₆alkyl, halogen, -CH₂F, -CHF₂, -CF₃, -CO₂H, -CO₂C₁₋₆alkyl, -C₃₋₇cycloalkyl, phenyl, and

CH₂phenyl; and alkyl, cycloalkyl, cycloheteroalkyl, aryl and heteroaryl are unsubstituted or substituted with 1, 2 or 3 substituents selected from: oxo, -CH₂OH, -OH, -CN, -NH₂, -NH(C₁₋₆alkyl), -N(C₁₋₆alkyl)₂, -C₁₋₆alkyl, -OC₁₋₆alkyl, halogen, -CH₂F, -CHF₂, -CF₃, -CO₂H, -CO₂C₁₋₆alkyl, -C₃₋₇cycloalkyl, phenyl, and CH₂phenyl. In another class of this embodiment, each CH₂ is unsubstituted or substituted with 1 or 2 substituents selected from: oxo, -CH₂OH, -

OH, -CN, -NH₂, -NH(C₁₋₆alkyl), -N(C₁₋₆alkyl)₂, -C₁₋₆alkyl, -OC₁₋₆alkyl, halogen, -CH₂F, -CHF₂, -CF₃, -CO₂H, -CO₂C₁₋₆alkyl, and -C₃₋₇cycloalkyl; and alkyl, cycloalkyl, cycloheteroalkyl, aryl and heteroaryl are unsubstituted or substituted with 1, 2 or 3 substituents selected from: oxo, -CH₂OH, -OH, -CN, -NH₂, -NH(C₁₋₆alkyl), -N(C₁₋₆alkyl)₂, -C₁₋₆alkyl, -OC₁₋₆alkyl, halogen, -CH₂F, -CHF₂, -CF₃, -CO₂H, -CO₂C₁₋₆alkyl, and -C₃₋₇cycloalkyl. In

another class of this embodiment, each CH₂ is unsubstituted or substituted with 1 or 2 substituents selected from: oxo, -CH₂OH, -OH, -CN, -NH₂, -CH₃, -OCH₃, F, Cl, -CH₂F, -CO₂H, -CO₂C(CH₃)₃, and cyclopropyl; and alkyl, cycloalkyl, cycloheteroalkyl, aryl and heteroaryl are unsubstituted or substituted with 1, 2 or 3 substituents selected from: oxo, -CH₂OH, -OH, -CN, -NH₂, -CH₃, -OCH₃, F, Cl, -CH₂F, -CO₂H, -CO₂C(CH₃)₃, and

cyclopropyl.

In another class of this embodiment, each R^a is independently selected from the group consisting of: F, Cl, oxo, -OH, -CH₂OH, -(CH₂)₂OH, -CH₂NH₂, -N(CH₃)₂, -CH₂N(CH₃)₂, -CN, methyl, ethyl, isopropyl, -CF₃, -CH₂CF₃, -OCF₃, -C(=N-OH)NH₂, -OCH₃, -SCH₃, -S(O)CH₃, -C(O)CH₃, -C(O)piperidine, -C(O)NH₂, -C(O)N(CH₃)₂, -CO₂H, -OC(O)H, -CO₂CH₃, -CO₂C(CH₃)₃, -OC(O)CH₃, -CH₂-cyclopropyl, cyclopropyl, cyclopentyl, cyclohexyl, -morpholine, pyrrolidine, piperazine, [1,6]-dihydropyridine, phenyl, pyrazole, pyridine, pyrimidine, isoxazole, imidazole, oxazole, triazole, tetrazole, oxadiazole, thiazole, thiadiazole,

and benzoxazole, wherein each CH₂ is unsubstituted or substituted with 1 or 2 substituents selected from: oxo, -(CH₂)₀₋₃OH, -CN, -NH₂, -NH(C₁₋₆alkyl), -N(C₁₋₆alkyl)₂, -C₁₋₆alkyl, -OC₁₋₆alkyl, halogen, -CH₂F, -CHF₂, -CF₃, -CO₂H, -CO₂C₁₋₆alkyl, -C₃₋₇cycloalkyl, phenyl, CH₂phenyl and heteroaryl; and wherein alkyl, cycloalkyl, cycloheteroalkyl, aryl and heteroaryl are unsubstituted or substituted with 1, 2, 3 or 4 substituents selected from: oxo, -(CH₂)₀₋₃OH, -CN, -NH₂, -NH(C₁₋₆alkyl), -N(C₁₋₆alkyl)₂, -C₁₋₆alkyl, -OC₁₋₆alkyl, halogen, -CH₂F, -CHF₂, -CF₃, -CO₂H, -CO₂C₁₋₆alkyl, -C₃₋₇cycloalkyl, phenyl, CH₂phenyl and heteroaryl. In a class of this embodiment, each CH₂ is unsubstituted or substituted with 1 or 2 substituents selected from: oxo, -(CH₂)₀₋₃OH, -CN, -NH₂, -NH(C₁₋₆alkyl), -N(C₁₋₆alkyl)₂, -C₁₋₆alkyl, -OC₁₋₆alkyl, halogen, -CH₂F, -CHF₂, -CF₃, -CO₂H, -CO₂C₁₋₆alkyl, -C₃₋₇cycloalkyl, phenyl, and CH₂phenyl; and alkyl, cycloalkyl, cycloheteroalkyl, aryl and heteroaryl are unsubstituted or substituted with 1, 2, 3 or 4 substituents selected from: oxo, -(CH₂)₀₋₃OH, -CN, -NH₂, -NH(C₁₋₆alkyl), -N(C₁₋₆alkyl)₂, -C₁₋₆alkyl, -OC₁₋₆alkyl, halogen, -CH₂F, -CHF₂, -CF₃, -CO₂H, -CO₂C₁₋₆alkyl, -C₃₋₇cycloalkyl, phenyl, and CH₂phenyl. In a class of this embodiment, each CH₂ is unsubstituted or substituted with 1 or 2 substituents selected from: oxo, -(CH₂)₀₋₃OH, -CN, -NH₂, -NH(C₁₋₆alkyl), -N(C₁₋₆alkyl)₂, -C₁₋₆alkyl, -OC₁₋₆alkyl, halogen, -CH₂F, -CHF₂, -CF₃, -CO₂H, -CO₂C₁₋₆alkyl, -C₃₋₇cycloalkyl, phenyl, and CH₂phenyl; and alkyl, cycloalkyl, cycloheteroalkyl, aryl and heteroaryl are unsubstituted or substituted with 1, 2, 3 or 4 substituents selected from: oxo, -(CH₂)₀₋₃OH, -CN, -NH₂, -NH(C₁₋₆alkyl), -N(C₁₋₆alkyl)₂, -C₁₋₆alkyl, -OC₁₋₆alkyl, halogen, -CH₂F, -CHF₂, -CF₃, -CO₂H, -CO₂C₁₋₆alkyl, -C₃₋₇cycloalkyl, phenyl, and CH₂phenyl. In another class of this embodiment, each CH₂ is unsubstituted or substituted with 1 or 2 substituents selected from: oxo, -CH₂OH, -OH, -CN, -NH₂, -NH(C₁₋₆alkyl), -N(C₁₋₆alkyl)₂, -C₁₋₆alkyl, -OC₁₋₆alkyl, halogen, -CH₂F, -CHF₂, -CF₃, -CO₂H, -CO₂C₁₋₆alkyl, -C₃₋₇cycloalkyl, phenyl, and CH₂phenyl; and alkyl, cycloalkyl, cycloheteroalkyl, aryl and heteroaryl are unsubstituted or substituted with 1, 2 or 3 substituents selected from: oxo, -CH₂OH, -OH, -CN, -NH₂, -NH(C₁₋₆alkyl), -N(C₁₋₆alkyl)₂, -C₁₋₆alkyl, -OC₁₋₆alkyl, halogen, -CH₂F, -CHF₂, -CF₃, -CO₂H, -CO₂C₁₋₆alkyl, -C₃₋₇cycloalkyl, phenyl, and CH₂phenyl. In another class of this embodiment, CH₂ is unsubstituted or substituted with 1 or 2 substituents selected from: oxo, -CH₂OH, -OH, -CN, -NH₂, -CH₃, -OCH₃, F, Cl, -CH₂F, -CO₂H, -CO₂C(CH₃)₃, and cyclopropyl; and alkyl, cycloalkyl, cycloheteroalkyl, aryl and heteroaryl are unsubstituted or substituted with 1, 2 or 3 substituents selected from: oxo, -CH₂OH, -OH, -CN, -NH₂, -CH₃, -OCH₃, F, Cl, -CH₂F, -CO₂H, -CO₂C(CH₃)₃, and cyclopropyl.

In another embodiment of the present invention, each R^b is independently selected from: hydrogen, -C₁₋₆alkyl, -C₃₋₆cycloalkyl, -C₃₋₆cycloalkenyl, halogen, -OH, -NO₂, -NH₂, -OC₁₋₆alkyl, -(CH₂)_qCO₂H, -(CH₂)_qCO₂C₁₋₆alkyl, -CF₃, -CN, -SO₂C₁₋₆alkyl, and -(CH₂)_qCON(R^c)₂, wherein each CH₂ and alkyl carbon is unsubstituted or substituted with 1, 2 or 3 halogens.

In another embodiment of the present invention, each R^b is independently selected from: hydrogen, -C₁₋₆alkyl, halogen, -OH, -NO₂, -NH₂, -OC₁₋₆alkyl, -(CH₂)_qCO₂H, -

(CH₂)_qCO₂C₁₋₆alkyl, -CF₃, -CN, -SO₂C₁₋₆alkyl, and -(CH₂)_qCON(R^e)₂, wherein each CH₂

and alkyl carbon is unsubstituted or substituted with 1, 2 or 3 halogens. In a class of this

5 embodiment, each R^b is independently selected from: hydrogen, -C₁₋₆alkyl, halogen, -OH, -

OC₁₋₆alkyl, -(CH₂)_qCO₂H, -(CH₂)_qCO₂C₁₋₆alkyl, and -CN, wherein each CH₂ and alkyl

carbon is unsubstituted or substituted with 1, 2 or 3 halogens. In another class of this

embodiment, each R^b is independently selected from: -C₁₋₆alkyl, halogen, -OH, -OC₁₋₆alkyl, -

(CH₂)_qCO₂H, -(CH₂)_qCO₂C₁₋₆alkyl, and -CN, wherein each CH₂ and alkyl carbon is

10 unsubstituted or substituted with 1, 2 or 3 halogens. In a subclass of this class, each R^b is

independently selected from: -CH₃, -CH₂CH₃, chloro, fluoro, -OH, -OCH₃, -CO₂H, -

CH₂CO₂H, -CO₂CH₃, -CH₂CO₂CH₂CH₃, and -CN, wherein each CH₂ and alkyl carbon is

unsubstituted or substituted with 1, 2 or 3 halogens. In another subclass of this class, each R^b is

independently selected from: -CH₃, -CH₂CH₃, chloro, fluoro, -OH, -OCH₃, -CO₂H, -

15 CH₂CO₂H, -CO₂CH₃, and -CN, wherein each CH₂ and alkyl carbon is unsubstituted or

substituted with 1, 2 or 3 halogens.

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

halogen, oxo, -(CH₂)_rOH, -(CH₂)_rN(R^e)₂, -(CH₂)_rCN, -C₁₋₆alkyl, -CF₃, -C₁₋₆alkyl-OH, -

OCH₂OC₁₋₆alkyl, -(CH₂)_rOC₁₋₆alkyl, -OCH₂aryl, -(CH₂)_rSC₁₋₆alkyl, -(CH₂)_rC(O)R^f, -

20 (CH₂)_rC(O)N(R^e)₂, -(CH₂)_rCO₂H, -(CH₂)_rCO₂R^f, -(CH₂)_rC₃₋₇cycloalkyl, -(CH₂)_rC₂₋

6cycloheteroalkyl, -(CH₂)_raryl, and -(CH₂)_rheteroaryl, wherein CH₂ is unsubstituted or

substituted with 1 or 2 substituents selected from: oxo, -OH, -CN, -N(R^h)₂, -C₁₋₆alkyl, -OC₁₋

6alkyl, halogen, -CH₂F, -CHF₂, -CF₃, -CO₂H, -CO₂C₁₋₆alkyl, -C₃₋₇cycloalkyl and heteroaryl,

and wherein alkyl, cycloalkyl, cycloheteroalkyl, aryl and heteroaryl are unsubstituted or

25 substituted with 1, 2, 3 or 4 substituents selected from: oxo, -OH, -CN, -N(R^h)₂, -C₁₋₆alkyl, -

OC₁₋₆alkyl, halogen, -CH₂F, -CHF₂, -CF₃, -CO₂H, -CO₂C₁₋₆alkyl, -C₃₋₇cycloalkyl and

heteroaryl. In a class of this embodiment, R^c is selected from: oxo, -(CH₂)_rCO₂H, and -

(CH₂)_rCO₂C₁₋₆alkyl, wherein CH₂ is unsubstituted or substituted with 1 or 2 substituents

selected from: oxo, -OH, -CN, -N(R^h)₂, -C₁₋₆alkyl, -OC₁₋₆alkyl, halogen, -CH₂F, -CHF₂, -

30 CF₃, -CO₂H, -CO₂C₁₋₆alkyl, -C₃₋₇cycloalkyl and heteroaryl, and wherein alkyl is unsubstituted

or substituted with 1, 2, 3 or 4 substituents selected from: oxo, -OH, -CN, -N(R^h)₂, -C₁₋₆alkyl, -

OC₁₋₆alkyl, halogen, -CH₂F, -CHF₂, -CF₃, -CO₂H, -CO₂C₁₋₆alkyl, -C₃₋₇cycloalkyl and

heteroaryl. In a subclass of this class, R^c is selected from: oxo, -(CH₂)_rCO₂H, and -

(CH₂)_rCO₂C₁₋₆alkyl, wherein CH₂ is unsubstituted or substituted with 1 or 2 substituents

35 selected from: oxo, -OH, -CN, -N(R^h)₂, -C₁₋₆alkyl, -OC₁₋₆alkyl, halogen, -CH₂F, -CHF₂, -

CF₃, -CO₂H, -CO₂C₁₋₆alkyl, and -C₃₋₇cycloalkyl. In another subclass of this class, R^c is

selected from: oxo, -(CH₂)_rCO₂H, and -(CH₂)_rCO₂C₁₋₆alkyl. In another subclass of this class,

R^c is selected from: oxo, -CH₂CO₂H, and -CH₂CO₂CH₃, wherein CH₂ is unsubstituted or substituted with 1 or 2 substituents selected from: oxo, -OH, -CN, -N(R^h)₂, -C₁-6alkyl, -OC₁-6alkyl, halogen, -CH₂F, -CHF₂, -CF₃, -CO₂H, -CO₂C₁-6alkyl, -C₃-7cycloalkyl and heteroaryl. In another subclass of this class, R^c is selected from: -CH₂CO₂H, and -CH₂CO₂CH₃, wherein

5 CH₂ is unsubstituted or substituted with 1 or 2 substituents selected from: oxo, -OH, -CN, -N(R^h)₂, -C₁-6alkyl, -OC₁-6alkyl, halogen, -CH₂F, -CHF₂, -CF₃, -CO₂H, -CO₂C₁-6alkyl, and -C₃-7cycloalkyl. In another subclass of this class, R^c is selected from: oxo, -CH₂CO₂H, and -CH₂CO₂CH₃.

10 In another class of this embodiment, each R^c is independently selected from: -CH₂CO₂H, and -CH₂CO₂CH₃, wherein CH₂ is unsubstituted or substituted with 1 or 2 substituents selected from: oxo, -OH, -CN, -N(R^h)₂, -C₁-6alkyl, -OC₁-6alkyl, halogen, -CH₂F, -CHF₂, -CF₃, -CO₂H, -CO₂C₁-6alkyl, -C₃-7cycloalkyl and heteroaryl. In a subclass of this class, each R^c is independently selected from: -CH₂CO₂H, and -CH₂CO₂CH₃.

15 In another embodiment of the present invention, each R^d is independently selected from the group consisting of: hydrogen, -NH₂, -NH(C₁-6alkyl), -N(C₁-6alkyl)₂, -C₁-6alkyl, -C₁-6alkyl-OH, -(CH₂)_rC₃-7cycloalkyl, -(CH₂)_rC₂-6cycloheteroalkyl, -(CH₂)_raryl, and -(CH₂)_rheteroaryl, wherein each CH₂ is unsubstituted or substituted with 1 or 2 substituents selected from -OH, -NH₂, -C₁-6alkyl, -OC₁-6alkyl, halogen, -CO₂H, and -CO₂C₁-6alkyl, and wherein alkyl, cycloalkyl, cycloheteroalkyl, aryl and heteroaryl are unsubstituted or substituted

20 with 1, 2, 3 or 4 substituents selected from -OH, -NH₂, -C₁-6alkyl, -OC₁-6alkyl, halogen, -CO₂H, and -CO₂C₁-6alkyl. In a class of this embodiment, each R^d is independently selected from the group consisting of: hydrogen, -NH₂, -NH(C₁-6alkyl), -N(C₁-6alkyl)₂, -C₁-6alkyl, -C₁-6alkyl-OH, wherein alkyl is unsubstituted or substituted with 1, 2, 3 or 4 substituents selected from -OH, -NH₂, -C₁-6alkyl, -OC₁-6alkyl, halogen, -CO₂H, and -CO₂C₁-6alkyl. In

25 another class of this embodiment, each R^d is independently selected from the group consisting of: -NH₂, -NH(C₁-6alkyl), -N(C₁-6alkyl)₂, wherein alkyl is unsubstituted or substituted with 1, 2 or 3 substituents selected from -OH, -NH₂, -C₁-6alkyl, -OC₁-6alkyl, halogen, -CO₂H, and -CO₂C₁-6alkyl. In another class of this embodiment, each R^d is independently selected from the group consisting of: hydrogen, -C₁-6alkyl, -C₁-6alkyl-OH, wherein alkyl is unsubstituted or

30 substituted with 1, 2 or 3 substituents selected from -OH, -NH₂, -C₁-6alkyl, -OC₁-6alkyl, halogen, -CO₂H, and -CO₂C₁-6alkyl.

In another embodiment of the present invention, each R^e, R^g and R^h is independently selected from: hydrogen, and C₁-6alkyl, wherein alkyl is unsubstituted or substituted with 1, 2, 3 or 4 substituents selected from: -OH, oxo, halogen, C₁-6alkyl, -OC₁-6alkyl, -NH₂, -NH(C₁-6alkyl), and -N(C₁-6alkyl)₂. In a class of this embodiment, each R^e, R^g and R^h is independently

35 selected from: hydrogen, and C₁-6alkyl. In another class of this embodiment, each R^e is independently selected from: hydrogen, and C₁-6alkyl, wherein alkyl is unsubstituted or

substituted with 1, 2, 3 or 4 substituents selected from: -OH, oxo, halogen, C₁-6alkyl, -OC₁-6alkyl, -NH₂, -NH(C₁-6alkyl), and -N(C₁-6alkyl)₂. In a class of this embodiment, each R^e is independently selected from: hydrogen, and C₁-6alkyl. In another class of this embodiment, each R^g is independently selected from: hydrogen, and C₁-6alkyl, wherein alkyl is unsubstituted or substituted with 1, 2, 3 or 4 substituents selected from: -OH, oxo, halogen, C₁-6alkyl, -OC₁-6alkyl, -NH₂, -NH(C₁-6alkyl), and -N(C₁-6alkyl)₂. In a class of this embodiment, each R^g is independently selected from: hydrogen, and C₁-6alkyl. In another class of this embodiment, each R^h is independently selected from: hydrogen, and C₁-6alkyl, wherein alkyl is unsubstituted or substituted with 1, 2, 3 or 4 substituents selected from: -OH, oxo, halogen, C₁-6alkyl, -OC₁-6alkyl, -NH₂, -NH(C₁-6alkyl), and -N(C₁-6alkyl)₂. In a class of this embodiment, each R^h is independently selected from: hydrogen, and C₁-6alkyl.

In another embodiment of the present invention, each R^j is independently selected from: hydrogen, C₁-6alkyl, C₃-6cycloalkyl, -C(O)Rⁱ, and -SO₂Rⁱ, wherein alkyl and cycloalkyl are unsubstituted or substituted with 1, 2, 3 or 4 substituents selected from: -OH, oxo, halogen, C₁-6alkyl, -OC₁-6alkyl, -NH₂, -NH(C₁-6alkyl), and -N(C₁-6alkyl)₂. In a class of this embodiment, each R^j is independently selected from: hydrogen, -C₁-6alkyl, -C(O)Rⁱ, and -SO₂Rⁱ, wherein alkyl is unsubstituted or substituted with 1, 2, 3 or 4 substituents selected from: -OH, oxo, halogen, C₁-6alkyl, -OC₁-6alkyl, -NH₂, -NH(C₁-6alkyl), and -N(C₁-6alkyl)₂. In another class of this embodiment, each R^j is independently selected from: hydrogen, and C₁-6alkyl, wherein alkyl is unsubstituted or substituted with 1, 2, 3 or 4 substituents selected from: -OH, oxo, halogen, C₁-6alkyl, -OC₁-6alkyl, -NH₂, -NH(C₁-6alkyl), and -N(C₁-6alkyl)₂. In another class of this embodiment, each R^j is independently selected from: hydrogen and C₁-6alkyl.

In another embodiment of the present invention, each R^f and Rⁱ is independently selected from: C₁-6alkyl, C₄-7cycloalkyl, C₄-7cycloalkenyl, C₃-7cycloheteroalkyl, C₃-7cycloheteroalkenyl, aryl, and 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, -NH₂, -C₁-6alkyl, -OC₁-6alkyl, halogen, -CH₂F, -CHF₂, -CF₃, -CO₂H, -CO₂C₁-6alkyl, -C₃-7cycloalkyl, and heteroaryl. In a class of this embodiment, each R^f and Rⁱ is independently selected from: C₁-6alkyl, C₄-7cycloalkyl, C₄-7cycloalkenyl, C₃-7cycloheteroalkyl, C₃-7cycloheteroalkenyl, aryl, and 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, -NH₂, -C₁-6alkyl, -OC₁-6alkyl, halogen, -CH₂F, -CHF₂, -CF₃, -CO₂H, -CO₂C₁-6alkyl, and -C₃-7cycloalkyl.

In a class of this embodiment, each R^f is independently selected from: C₁-6alkyl, C₄-7cycloalkyl, C₄-7cycloalkenyl, C₃-7cycloheteroalkyl, C₃-7cycloheteroalkenyl, aryl, and 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, -NH₂, -C₁₋₆alkyl, -OC₁₋₆alkyl, halogen, -CH₂F, -CHF₂, -CF₃, -CO₂H, -CO₂C₁₋₆alkyl, -C₃₋₇cycloalkyl, and heteroaryl. In a subclass of this class, each R^f is independently selected from: C₁₋₆alkyl, C₄₋₇cycloalkyl, C₄₋₇cycloalkenyl, C₃₋₇cycloheteroalkyl, C₃₋

5 7cycloheteroalkenyl, aryl, and 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, -NH₂, -C₁₋₆alkyl, -OC₁₋₆alkyl, halogen, -CH₂F, -CHF₂, -CF₃, -CO₂H, -CO₂C₁₋₆alkyl, and -C₃₋₇cycloalkyl.

In another subclass of this class, each R^f is independently selected from: C₁₋₆alkyl, and
 10 C₃₋₇cycloheteroalkyl, wherein alkyl, and cycloheteroalkyl are unsubstituted or substituted with 1, 2, 3 or 4 substituents selected from: oxo, -OH, -CN, -NH₂, -C₁₋₆alkyl, -OC₁₋₆alkyl, halogen, -CH₂F, -CHF₂, -CF₃, -CO₂H, -CO₂C₁₋₆alkyl, and -C₃₋₇cycloalkyl. In a subclass of this subclass, each R^f is independently selected from: C₁₋₆alkyl, and piperidine, wherein alkyl, and
 15 piperidine are unsubstituted or substituted with 1, 2, 3 or 4 substituents selected from: oxo, -OH, -CN, -NH₂, -C₁₋₆alkyl, -OC₁₋₆alkyl, halogen, -CH₂F, -CHF₂, -CF₃, -CO₂H, -CO₂C₁₋₆alkyl, and -C₃₋₇cycloalkyl. In another subclass of this subclass, each R^f is independently selected from: CH₃, and piperidine.

In another class of this embodiment, Rⁱ is independently selected from: C₁₋₆alkyl, C₄₋
 7cycloalkyl, C₄₋₇cycloalkenyl, C₃₋₇cycloheteroalkyl, C₃₋₇cycloheteroalkenyl, aryl, and
 20 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, -NH₂, -C₁₋₆alkyl, -OC₁₋₆alkyl, halogen, -CH₂F, -CHF₂, -CF₃, -CO₂H, -CO₂C₁₋₆alkyl, -C₃₋₇cycloalkyl, and heteroaryl. In a subclass of this class, Rⁱ is independently selected from: C₁₋₆alkyl, and aryl, wherein alkyl and aryl are unsubstituted or substituted with 1, 2, or 3
 25 substituents selected from: oxo, -OH, -CN, -NH₂, -C₁₋₆alkyl, -OC₁₋₆alkyl, halogen, -CH₂F, -CHF₂, -CF₃, -CO₂H, -CO₂C₁₋₆alkyl, and -C₃₋₇cycloalkyl. In a subclass of this subclass, Rⁱ is independently selected from: C₁₋₆alkyl, and phenyl. wherein alkyl and phenyl are unsubstituted or substituted with 1, 2, or 3 substituents selected from: oxo, -OH, -CN, -NH₂, -C₁₋₆alkyl, -OC₁₋₆alkyl, halogen, -CH₂F, -CHF₂, -CF₃, -CO₂H, -CO₂C₁₋₆alkyl, and -C₃₋₇cycloalkyl.

30 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
 35 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.

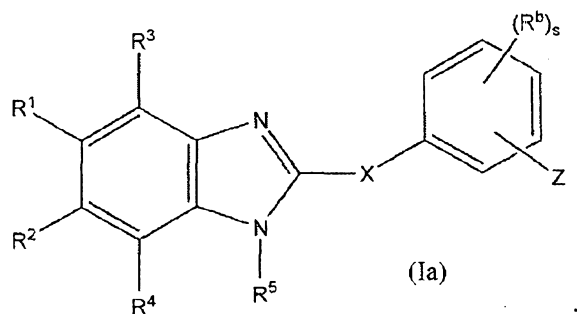
In another embodiment of the present invention, p is 0, 1, 2 or 3. In a class of this embodiment, p is 1, 2 or 3. In another class of this embodiment, p is 0, 1 or 2. In another class of this embodiment, p is 0 or 2. In another class of this embodiment, p is 0. In another class of this embodiment, p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

5 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.

10 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.

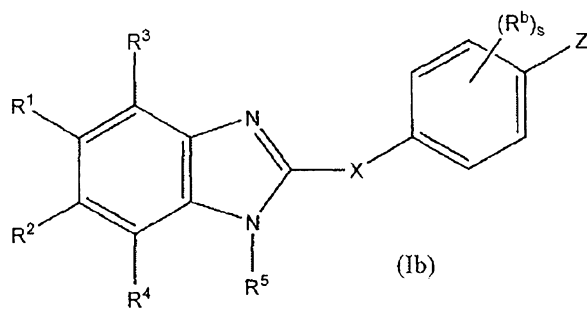
In another embodiment of the present invention, the invention relates to compounds of structural formula Ia:



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or a pharmaceutically acceptable salt thereof.

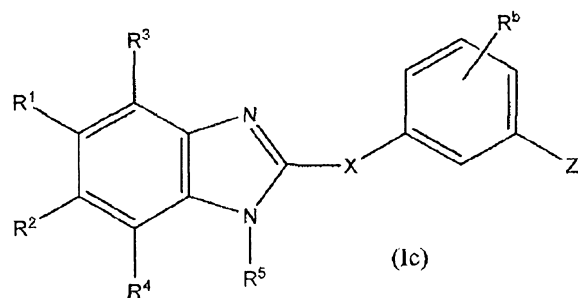
In another embodiment of the present invention, the invention relates to compounds of structural formula Ib:



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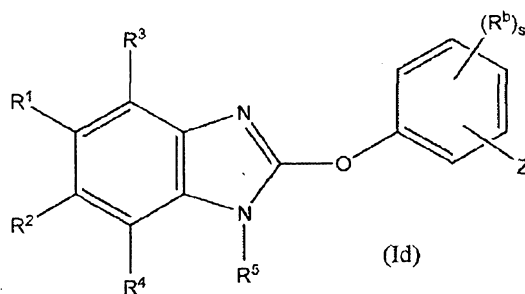
or a pharmaceutically acceptable salt thereof.

In another embodiment of the present invention, the invention relates to compounds of structural formula 1c:



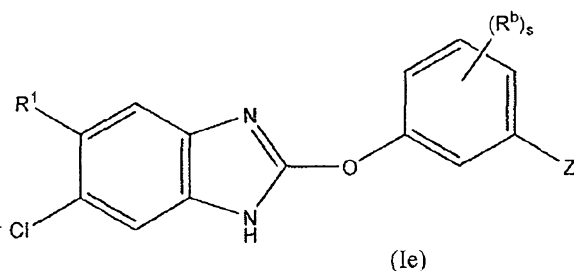
or a pharmaceutically acceptable salt thereof.

5 In another embodiment of the present invention, the invention relates to compounds of structural formula 1d:



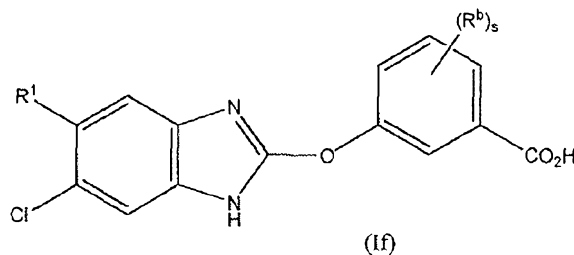
or a pharmaceutically acceptable salt thereof.

10 In another embodiment of the present invention, the invention relates to compounds of structural formula 1e:



or a pharmaceutically acceptable salt thereof.

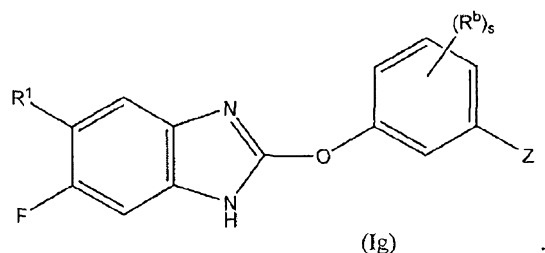
In another embodiment of the present invention, the invention relates to compounds of structural formula 1f:



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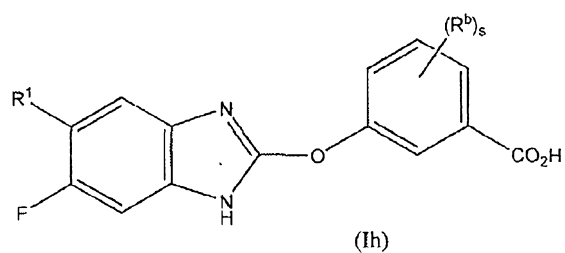
or a pharmaceutically acceptable salt thereof.

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



or a pharmaceutically acceptable salt thereof.

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



or a pharmaceutically acceptable salt thereof.

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

In one class of the embodiments of the compounds of structural formulas Ia through Ih of the present invention: R¹ is selected from: biphenyl, aryl, heteroaryl, and -C₂alkynyl-aryl, wherein each phenyl, aryl and heteroaryl is unsubstituted or substituted with 1, 2, 3 or 4 substituents independently selected from R^a; R² is halogen; R³ is hydrogen or halogen; R⁴ is hydrogen; R⁵ is hydrogen; X is -O-; Y is phenyl, unsubstituted or substituted with 1 or 2 substituents selected from R^b; Z is -CO₂H; each R^a is independently selected from the group consisting of: halogen, -(CH₂)_mOH, -C₁-6alkyl, -OC₁-6alkyl, -CO₂H, -C₃-7cycloalkyl, -C₂-6cycloheteroalkyl, and aryl, wherein each CH₂ is unsubstituted or substituted with 1 or 2 substituents selected from: oxo, -(CH₂)₀₋₃OH, -CN, -NH₂, -NH(C₁-6alkyl), -N(C₁-6alkyl)₂, -C₁-6alkyl, -OC₁-6alkyl, halogen, -CH₂F, -CHF₂, -CF₃, -CO₂H, and -CO₂C₁-6alkyl, and wherein alkyl, cycloalkyl, cycloheteroalkyl, and aryl are unsubstituted or substituted with 1, 2, 3 or 4 substituents selected from: oxo, -(CH₂)₀₋₃OH, -CN, -NH₂, -NH(C₁-6alkyl), -N(C₁-6alkyl)₂, -C₁-6alkyl, -OC₁-6alkyl, halogen, -CH₂F, -CHF₂, -CF₃, -CO₂H, and -CO₂C₁-6alkyl; each R^b is selected from hydrogen and -C₁-6alkyl, unsubstituted or substituted with 1 or 2 halogens; and s is 0, 1 or 2. In a subclass of this class, R¹ is selected from: biphenyl, aryl, heteroaryl, and -C₂alkynyl-aryl, wherein each phenyl, aryl and heteroaryl is unsubstituted or substituted with 1, 2, 3 or 4 substituents independently selected from R^a. In another subclass of this class, R¹ is selected from: biphenyl, phenyl, indole, and -C₂alkynyl-phenyl, wherein each

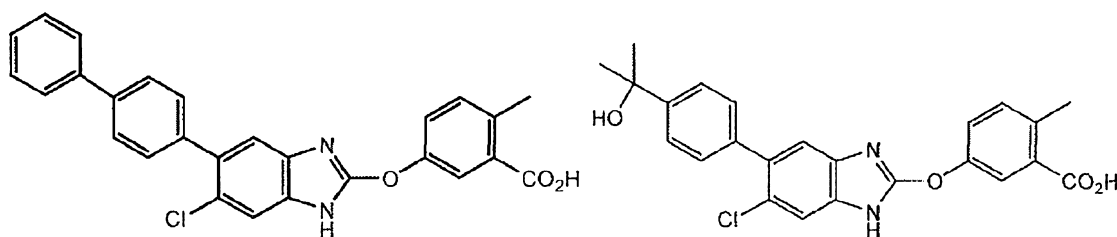
phenyl and indole is unsubstituted or substituted with 1, 2, 3 or 4 substituents independently selected from R^a . In another subclass of this class, R^2 is chlorine or fluorine. In another subclass of this class, R^3 is hydrogen or fluoro. In another subclass of this class, R^a is unsubstituted or substituted with substituents selected from: $-\text{CH}_2\text{OH}$ and $-\text{OH}$. In another

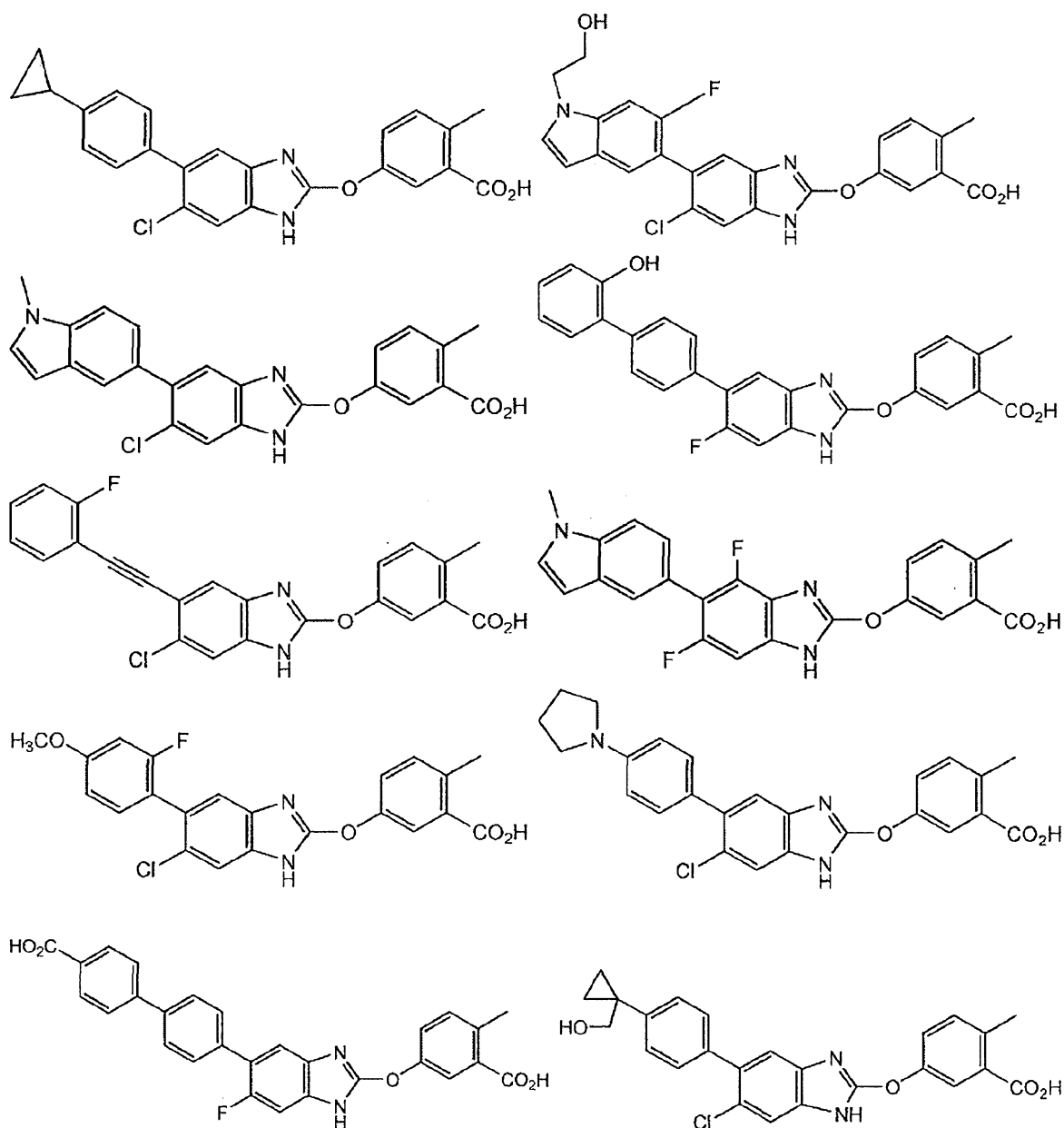
- 5 subclass of this class, each R^a is independently selected from the group consisting of: fluoro, $-\text{OH}$, $-(\text{CH}_2)_2\text{OH}$, $-\text{C}(\text{CH}_3)_2\text{OH}$, $-\text{CH}_3$, $-\text{OCH}_3$, $-\text{CO}_2\text{H}$, cyclopropyl, pyrrolidine, and phenyl, wherein each CH_2 is unsubstituted or substituted with 1 or 2 substituents selected from: oxo, $-(\text{CH}_2)_0-3\text{OH}$, $-\text{CN}$, $-\text{NH}_2$, $-\text{NH}(\text{C}_1-6\text{alkyl})$, $-\text{N}(\text{C}_1-6\text{alkyl})_2$, $-\text{C}_1-6\text{alkyl}$, $-\text{OC}_1-6\text{alkyl}$, halogen, $-\text{CH}_2\text{F}$, $-\text{CHF}_2$, $-\text{CF}_3$, $-\text{CO}_2\text{H}$, and $-\text{CO}_2\text{C}_1-6\text{alkyl}$, and wherein alkyl, cycloalkyl, cycloheteroalkyl, and phenyl are unsubstituted or substituted with 1, 2, 3 or 4 substituents selected from: oxo, $-(\text{CH}_2)_0-3\text{OH}$, $-\text{CN}$, $-\text{NH}_2$, $-\text{NH}(\text{C}_1-6\text{alkyl})$, $-\text{N}(\text{C}_1-6\text{alkyl})_2$, $-\text{C}_1-6\text{alkyl}$, $-\text{OC}_1-6\text{alkyl}$, halogen, $-\text{CH}_2\text{F}$, $-\text{CHF}_2$, $-\text{CF}_3$, $-\text{CO}_2\text{H}$, and $-\text{CO}_2\text{C}_1-6\text{alkyl}$. In a subclass of this class, R^a is unsubstituted or substituted with substituents selected from: $-\text{CH}_2\text{OH}$ and $-\text{OH}$. In another subclass of this class, R^b is selected from hydrogen and $-\text{CH}_3$. In another subclass of this class, R^b is hydrogen. In another subclass of this class, R^b is $-\text{CH}_3$. In another subclass of this class, s is 1. In another subclass of this class, s is 1 or 2. In another subclass of this class, s is 2.

In another class of the embodiments of the compounds of structural formulas Ia through Ih of the present invention: R^1 is selected from: biphenyl, phenyl, indole, and $-\text{C}_2\text{alkynyl}$ -

- 20 phenyl, wherein each phenyl and indole is unsubstituted or substituted with 1, 2, 3 or 4 substituents independently selected from R^a ; R^2 is chlorine or fluorine; R^3 is hydrogen or fluoro; R^4 and R^5 are hydrogen; X is $-\text{O}-$; Y is phenyl, unsubstituted or substituted with 1 substituent selected from R^b ; Z is $-\text{CO}_2\text{H}$; each R^a is independently selected from the group consisting of: fluoro, $-\text{OH}$, $-(\text{CH}_2)_2\text{OH}$, $-\text{C}(\text{CH}_3)_2\text{OH}$, $-\text{CH}_3$, $-\text{OCH}_3$, $-\text{CO}_2\text{H}$, cyclopropyl, pyrrolidine, and phenyl, wherein each CH_2 is unsubstituted or substituted with 1 or 2 substituents selected from: $-\text{CH}_2\text{OH}$ and $-\text{OH}$, and wherein alkyl, cycloalkyl, cycloheteroalkyl, and phenyl are unsubstituted or substituted with 1, 2, 3 or 4 substituents selected from: $-\text{CH}_2\text{OH}$ and $-\text{OH}$; each R^b is $-\text{CH}_3$; and s is 1.

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





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. 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.

“Cycloalkyl” means mono- or bicyclic 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.

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

“Cycloheteroalkyl” means nonaromatic, mono- or bicyclic 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. Examples of cycloheteroalkyl include tetrahydrofuranyl, azetidiny, perhydroazepiny, 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 imidazolidine.

“Cycloheteroalkenyl” means nonaromatic mono- or bicyclic 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.

“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 class of this embodiment, aryl is phenyl. In another class of this embodiment, aryl is naphthalene.

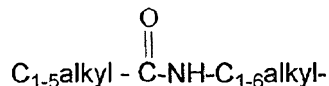
"Heteroaryl" means a monocyclic, bicyclic or tricyclic ring system containing 5-14 carbon atoms and containing 1, 2, 3, 4 or 5 heteroatoms selected from N, NH, O and S wherein at least one of the heteroatom containing rings is aromatic. Heteroaryl thus includes ring systems in which an aromatic heteroatom 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, benzopyrazole, 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.

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

When any variable (e.g., R¹, 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 C₁₋₅ alkylcarbonylamino C₁₋₆ 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. R¹, R², 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 substituent. 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.

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-ethylmorpholine, 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, 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, pantoate, 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 comprises 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 ($\alpha 1$, $\alpha 2$, $\beta 1$ and $\beta 2$) and three genes encoding isoforms of the γ subunit ($\gamma 1$, $\gamma 2$ and $\gamma 3$) leading to 12 possible heterotrimeric combinations. The $\alpha 2$ isoform is predominately found in skeletal and cardiac muscle AMPK; both the $\alpha 1$ and $\alpha 2$ isoforms are found in hepatic AMPK; while in pancreatic islet β -cells the $\alpha 1$ 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 responsive to the activation of AMP-activated protein kinase, including but not limited to: 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 are also useful for the treatment of cancer, hypoxia and glucocorticoid-induced apoptosis.

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: (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; and (11) hypertension.

Also, the compounds of Formula I may be used for the manufacture of a medicament for treating one or more of the above diseases.

One embodiment of the uses of the compounds is directed to 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 may also be used for manufacturing a medicament for use in the treatment of one or more of the above diseases.

The compounds are expected to 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 reducing the risks of adverse sequelae associated with metabolic syndrome, and in reducing the risk of developing atherosclerosis, delaying the onset of atherosclerosis, and/or 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, so that they may be useful in treating type 1 diabetes or 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 include, but are not limited to: 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 plasma triglycerides; 10) a decrease in free fatty acids; 11) a decrease in hepatic glucose output; 12) an improvement in insulin action; 13) a decrease in blood pressure; 14) an improvement in insulin sensitivity; 15) a suppression of hepatic glucose output; 15) an inhibition of de novo lipogenesis; 16) stimulation of muscle glucose uptake; 17) modulation of insulin secretion by pancreatic β cells; and 16) a decrease in body weight.

The compounds generally 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 a method 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 having formula I. The compound may be used alone or advantageously may be administered with a cholesterol biosynthesis inhibitor, particularly an HMG-CoA reductase inhibitor such as lovastatin, simvastatin, rosuvastatin, pravastatin, fluvastatin, atorvastatin, rivastatin, itavastatin, or ZD-4522.

5 The compound 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 torcetrapib and those described in published applications WO2005/100298, WO2006/014413, and WO2006/014357), niacin and niacin receptor agonists, 10 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 relates to methods and medicaments for the treatment, control, 15 or prevention of Type 2 diabetes by administering the compounds and pharmaceutical compositions of the present invention. The present invention also relates to methods and medicaments for the treatment, control, or prevention of Type 2 diabetes by administering the compounds of the present invention in combination with a therapeutically effective amount of another agent known to be useful to treat the condition. The present invention also relates to 20 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 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.

25 The present invention also relates to methods and medicaments for the treatment, control, or prevention of obesity by administering the compounds and pharmaceutical compositions of the present invention. The present invention also relates to methods and medicaments for the treatment, control, or prevention of obesity by administering the compounds of the present invention in combination with a therapeutically effective amount of another agent known to be 30 useful to treat the condition. The present invention also relates to 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 methods and medicaments for the treatment and prevention of obesity in overweight subject by administering the compounds and pharmaceutical compositions of the 35 present invention alone, or in combination. The compounds are also useful for the treatment of obesity related disorders, or eating disorders associated with excessive food intake, and complications associated therewith, including left ventricular hypertrophy, as well as treating or

preventing obesity in other mammalian species, including canines and felines.

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

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

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

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

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

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 are 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 are especially effective for treating Type 2 diabetes. The compositions of the present invention are also 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 ≥ 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 sensitivity. Another outcome of treatment may be enhancing glucose tolerance in a subject with glucose intolerance.

5 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.

10 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.

15 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.

20 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.

25 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 (≥ 140 mmHg/ ≥ 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 dyslipidemia 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/m². An “obese subject” is an otherwise healthy subject with a Body Mass Index (BMI) greater than or equal to 30 kg/m² or a subject with at least one co-morbidity with a BMI greater than or equal to 27 kg/m². 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/m² to less than 30 kg/m² or a subject with at least one co-morbidity with a BMI of 25 kg/m² to less than 27 kg/m².

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/m². 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/m². In Asia-Pacific, a “subject at risk of obesity” is a subject with a BMI of greater than 23 kg/m² to less than 25 kg/m².

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, lumbodysnia, 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 arrhythmias, 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 the present invention are also useful for reducing the risk of secondary outcomes of obesity, such as reducing the risk of left ventricular hypertrophy.

The compounds of formula I are also 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.

Left ventricular hypertrophy (LVH) is identified based on left ventricular mass index (LVMI) and relative wall thickness (RWT). Left ventricular mass index is defined as left ventricular mass in grams divided by body surface area in meters². Relative wall thickness is defined as $2 \times \text{posterior wall thickness} / \text{left ventricular end diastolic diameter}$. Normal LVMI values are typically 85 and normal RWT approximately 0.36. A male subject with LVH has a LVMI greater than 131 g/m²; a female subject with LVH has a LVMI greater than 100 g/m². A subject with an elevated LVMI value is a male subject with a LVMI between 85 g/m² and 131 g/m², or a female subject with a LVMI between 85 g/m² and 100 g/m².

Treatment of cardiac hypertrophy, or left ventricular hypertrophy, refers to the administration of the combinations of the present invention to a subject with cardiac hypertrophy or left ventricular hypertrophy. Prevention of cardiac hypertrophy, or left ventricular hypertrophy, refers to the administration of the combinations of the present invention to decrease or maintain the LVMI in a subject with an elevated LVMI value or to prevent the increase of LVMI in a subject with a normal LVMI value.

One outcome of treatment of cardiac hypertrophy or left ventricular hypertrophy may be a decrease in ventricular mass. Another outcome of treatment of cardiac hypertrophy or left ventricular hypertrophy may be a decrease in the rate of increase of ventricular mass. Another outcome of treatment of cardiac hypertrophy or left ventricular hypertrophy may be a decrease in ventricular wall thickness. Another outcome of treatment of cardiac hypertrophy or left ventricular hypertrophy may be the decrease in the rate of increase in ventricular wall thickness.

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.

5 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,

10 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

15 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

20 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

25 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.

30 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

35 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
 5 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
 10 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
 15 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:

<u>Injectable Suspension (I.M.)</u>	<u>mg/mL</u>	<u>Tablet</u>	<u>mg/tablet</u>
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

<u>Capsule</u>	<u>mg/capsule</u>	<u>Aerosol</u>	<u>Per canister</u>
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 are useful. Such other drugs may be administered, by a route and in an amount commonly used therefor, contemporaneously or sequentially with a compound of
 35 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
5 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,
10 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 therefore 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
15 be, for example, in the form of a twin pack.

It will be appreciated that for the 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 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 treat that disorder, such that together they give effective relief.
25

The present invention also provides a 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.
30

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) PPAR γ 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
5 PPAR gamma modulators) such as T131 (Amgen), FK614 (Fujisawa), netoglitazone, and metaglidase; (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,
10 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; glisohamide; 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
15 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 secretagogues such as linoglitazone, 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
20 midaglitazone; isaglitazone; deriglitazone; idazoxan; eazoxan; 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)-NH₂ exenatide/Exendin-4, Exenatide LAR, Linagliptin, AVE0010, CJC 1131, BIM51077, CS 872, THO318, BAY-694326, GP010, ALBUGON (GLP-1
25 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 farglitazone (GW-2570/GI-262579), and the like; (13) PPAR α/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
30 (Eisai), LY510929 (Lilly), AK109 (Asahi), DRF2655 (Dr. Reddy), DRF8351 (Dr. Reddy), MC3002 (Maxcore), TY51501 (Toa Eiyo), farglitazone, naveglitazone, muraglitazone, peliglitazone, tesaglitazone (GALIDA), reglitazone (JT-501), chiglitazone, 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
35 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)-1*H*-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 promoters 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, ATI-802, E3080, and the like; (26) carnitine palmitoyl transferase inhibitors such as ST 1327, and ST 1326, and the like; (27) Fructose 1,6-bisphosphatase 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-phosphate 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; and (40) insulin secretagogues;

(b) anti-dyslipidemic agents such as (1) bile acid sequestrants such as, cholestyramine, colestevem, 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 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) PPAR α 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 sequestrants such as colestevlam (WELCHOL/ CHOLESTAGEL), colestipol, cholestyramine, and dialkylaminoalkyl derivatives of a cross-linked dextran, (16) PPAR δ 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, eplerenone, and the like; (2) beta-adrenergic blockers such as
5 acebutolol, atenolol, betaxolol, bevantolol, bisoprolol, bopindolol, carteolol, carvedilol, celiprolol, esmolol, indenolol, metoprolol, 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, lemdidipine, lercanidipine,
10 nicardipine, nifedipine, nilvadipine, nimodipine, 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; perindopril; quanipril; spirapril; tenocapril; trandolapril, and zofenopril, and the like; (5) neutral endopeptidase inhibitors such as
15 omapatrilat, cadoxatril and ccadotril, 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 nicotinic acid or salt thereof, and the like; (8) angiotensin II receptor antagonists such as candesartan, eprosartan, irbesartan, losartan, prazosartan, tasosartan, telmisartan, valsartan, and EXP-3137, FI6828K, and
20 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
25 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/Norepinephrine uptake
30 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
35 (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 6,509,367; 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, 5 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 10 WO 02/08250, WO 05/012331, and the like; (5) H3 (histamine H3) antagonist/inverse agonists, such as thioperamide, 3-(1*H*-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-(1*H*-imidazol-4-yl)propanol]carbamates (Kiec-Kononowicz, K. et al., Pharmazie, 55:349-55 (2000)), piperidine-containing histamine H3-receptor antagonists 15 (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 20 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 (GlaxoSmithkline), 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 25 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 30 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 35 (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 5 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 10 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; 15 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 20 (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 25 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), 30 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 35 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, 5 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 sibutramine (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 10 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) β 3 (beta adrenergic receptor 3) agonists, such as rafebergren/AD9677/TAK677 (Dainippon/ Takeda), CL-316,243, SB 418790, BRL- 15 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, 20 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 25 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-naphthalenyl)-1-propenyl]benzoic acid (TTNPB), and retinoic acid; and those disclosed in WO 99/00123; (35) acyl-estrogens, such as oleoyl-estrone, 30 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) 11 β 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- 35 1,2,4-triazole, 3-adamantany-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 Technologies), 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 neutrotropic 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, amphetamine, amphetamine, benzphetamine, chlorphentermine, clobenzorex, cloforex, clominorex, clortermine, cyclexedrine, dexfenfluramine, dextroamphetamine, diethylpropion, diphenmethoxidine, *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, bupropion, 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-[(1*S*)-1-(3,5-difluorophenyl)-2-hydroxy-2-methylpropyl]azetidin-1-yl}methyl)benzonitrile, 3-((*S*)-(4-chlorophenyl){3-[(1*S*)-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-((1*S*)-1-{1-[(*S*)-(3-cyanophenyl)(4-cyanophenyl)methyl]azetidin-3-yl}-2-fluoro-2-methylpropyl)-5-fluorobenzonitrile, 3-[(*S*)-(4-chlorophenyl)(3-[(1*S*)-2-fluoro-1-[3-fluoro-5-(4*H*-1,2,4-triazol-4-yl)phenyl]-2-methylpropyl]azetidin-1-yl)methyl]benzonitrile, and 5-((4-chlorophenyl){3-[(1*S*)-1-(3,5-difluorophenyl)-2-fluoro-2-methylpropyl]azetidin-1-

yl)methyl]thiophene-3-carbonitrile, and pharmaceutically 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-(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-[(1*S*)-1-(3,5-difluorophenyl)-2-fluoro-2-methylpropyl] azetidin-1-yl}methyl)phenyl]-1,3,4-oxadiazol-2(3*H*)-one, 5-[3-((*S*)-(4-chlorophenyl){3-[(1*S*)-1-(3,5-difluorophenyl)-2-fluoro-2-methylpropyl]azetidin-1-yl}methyl)phenyl]-1,3,4-oxadiazol-2(3*H*)-one, 4-{(*S*)-{3-[(1*S*)-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(3*H*),4'-piperidine]-1'-carboxamide, 3-oxo-N-(7-trifluoromethylpyrido[3,2-*b*]pyridin-2-yl)spiro-[isobenzofuran-1(3*H*),4'-piperidine]-1'-carboxamide, N-[5-(3-fluorophenyl)-2-pyrimidinyl]-3-oxospiro-
 10 [isobenzofuran-1(3*H*),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(3*H*),1'-cyclohexane]-4'-carboxamide,
 15 trans-N-[5-(3-fluorophenyl)-2-pyrimidinyl]-3-oxospiro[5-azaisobenzofuran-1(3*H*),1'-cyclohexane]-4'-carboxamide, trans-N-[5-(2-fluorophenyl)-2-pyrimidinyl]-3-oxospiro[5-azaisobenzofuran-1(3*H*),1'-cyclohexane]-4'-carboxamide, trans-N-[1-(3,5-difluorophenyl)-4-imidazolyl]-3-oxospiro[7-azaisobenzofuran-1(3*H*),1'-cyclohexane]-4'-carboxamide, trans-3-oxo-N-(1-phenyl-4-pyrazolyl)spiro[4-azaisobenzofuran-1(3*H*),1'-cyclohexane]-4'-carboxamide,
 20 trans-N-[1-(2-fluorophenyl)-3-pyrazolyl]-3-oxospiro[6-azaisobenzofuran-1(3*H*),1'-cyclohexane]-4'-carboxamide, trans-3-oxo-N-(1-phenyl-3-pyrazolyl)spiro[6-azaisobenzofuran-1(3*H*),1'-cyclohexane]-4'-carboxamide, trans-3-oxo-N-(2-phenyl-1,2,3-triazol-4-yl)spiro[6-azaisobenzofuran-1(3*H*),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-(1*H*-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}-2*H*-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-(1*H*-tetrazol-5-yl)spiro[chroman-2,4'-piperidin]-4-one; and 1'-[(4-ethoxy-8-ethylquinolin-2-yl)carbonyl]-6-(1*H*-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 present invention include: 1-{4-[(1-ethylazetidin-3-yl)oxy]phenyl}-4-[(4-fluorobenzyl)oxy]pyridin-2(1*H*)-one, 4-[(4-fluorobenzyl)oxy]-1-{4-[(1-isopropylazetidin-3-yl)oxy]phenyl}pyridin-2(1*H*)-one, 1-[4-(azetidin-3-yloxy)phenyl]-4-[(5-chloropyridin-2-yl)methoxy]pyridin-2(1*H*)-one, 4-[(5-chloropyridin-2-yl)methoxy]-1-{4-[(1-ethylazetidin-3-

yl)oxy]phenyl}pyridin-2(1*H*)-one, 4-[(5-chloropyridin-2-yl)methoxy]-1-{4-[(1-propylazetidin-3-yl)oxy]phenyl}pyridin-2(1*H*)-one, and 4-[(5-chloropyridin-2-yl)methoxy]-1-(4-{[(2*S*)-1-ethylazetidin-2-yl]methoxy}phenyl)pyridin-2(1*H*)-one, or a pharmaceutically acceptable salt thereof.

5 Specific DP-IV inhibitors of use in combination with a compound of the present invention are selected from 7-[(3*R*)-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-[(3*R*)-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
10 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(3*H*)-one, 3-{4-[(1-cyclobutyl-4-piperidinyl)oxy]phenyl}-2-methylpyrido[4,3-*d*]pyrimidin-4(3*H*)-one, 2-ethyl-3-(4-
15 {3-[(3*S*)-3-methylpiperidin-1-yl]propoxy}phenyl)pyrido[2,3-*d*]pyrimidin-4(3*H*)-one 2-methyl-3-(4-{3-[(3*S*)-3-methylpiperidin-1-yl]propoxy}phenyl)pyrido[4,3-*d*]pyrimidin-4(3*H*)-one, 3-{4-[(1-cyclobutyl-4-piperidinyl)oxy]phenyl}-2,5-dimethyl-4(3*H*)-quinazolinone, 3-{4-[(1-cyclobutyl-4-piperidinyl)oxy]phenyl}-2-methyl-5-trifluoromethyl-4(3*H*)-quinazolinone, 3-{4-[(1-cyclobutyl-4-piperidinyl)oxy]phenyl}-5-methoxy-2-methyl-4(3*H*)-quinazolinone, 3-{4-[(1-cyclobutylpiperidin-4-yl)oxy]phenyl}-5-fluoro-2-methyl-4(3*H*)-quinazolinone, 3-{4-[(1-cyclobutylpiperidin-4-yl)oxy]phenyl}-7-fluoro-2-methyl-4(3*H*)-quinazolinone, 3-{4-[(1-cyclobutylpiperidin-4-yl)oxy]phenyl}-6-methoxy-2-methyl-4(3*H*)-quinazolinone, 3-{4-[(1-cyclobutylpiperidin-4-yl)oxy]phenyl}-8-fluoro-2-methyl-4(3*H*)-quinazolinone,
25 3-{4-[(1-cyclopentyl-4-piperidinyl)oxy]phenyl}-2-methylpyrido[4,3-*d*]pyrimidin-4(3*H*)-one, 3-{4-[(1-cyclobutylpiperidin-4-yl)oxy]phenyl}-6-fluoro-2-methylpyrido[3,4-*d*]pyrimidin-4(3*H*)-one, 3-{4-[(1-cyclobutyl-4-piperidinyl)oxy]phenyl}-2-ethylpyrido[4,3-*d*]pyrimidin-4(3*H*)-one, 6-methoxy-2-methyl-3-{4-[3-(1-piperidinyl)propoxy]phenyl}pyrido[3,4-*d*]pyrimidin-4(3*H*)-one, 6-methoxy-2-methyl-3-{4-[3-(1-pyrrolidinyl)propoxy]phenyl}pyrido[3,4-*d*]pyrimidin-4(3*H*)-one,
30 2,5-dimethyl-3-{4-[3-(1-pyrrolidinyl)propoxy]phenyl}-4(3*H*)-quinazolinone, 2-methyl-3-{4-[3-(1-pyrrolidinyl)propoxy]phenyl}-5-trifluoromethyl-4(3*H*)-quinazolinone, 5-fluoro-2-methyl-3-{4-[3-(1-piperidinyl)propoxy]phenyl}-4(3*H*)-quinazolinone, 6-methoxy-2-methyl-3-{4-[3-(1-piperidinyl)propoxy]phenyl}-4(3*H*)-quinazolinone, 5-methoxy-2-methyl-3-(4-{3-[(3*S*)-3-methylpiperidin-1-yl]propoxy}phenyl)-4(3*H*)-quinazolinone, 7-methoxy-2-methyl-3-(4-{3-[(3*S*)-
35 3-methylpiperidin-1-yl]propoxy}phenyl)-4(3*H*)-quinazolinone, 2-methyl-3-(4-{3-[(3*S*)-3-methylpiperidin-1-yl]propoxy}phenyl)pyrido[2,3-*d*]pyrimidin-4(3*H*)-one, 5-fluoro-2-methyl-3-(4-{3-[(2*R*)-2-methylpyrrolidin-1-yl]propoxy}phenyl)-4(3*H*)-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)-1*H*-imidazol-4-yl]carbonyl}-1-piperazinyl)-1-naphthoic acid; 3-(4-{[1-(3-ethoxyphenyl)-2-(2-fluoro-4-methylphenyl)-1*H*-imidazol-4-yl]carbonyl}-1-piperazinyl)-1-naphthoic acid; 3-(4-{[1-(3-ethoxyphenyl)-2-(4-fluorophenyl)-1*H*-imidazol-4-yl]carbonyl}-1-piperazinyl)-1-naphthoic acid; 3-(4-{[1-(3-ethoxyphenyl)-2-(2,4-difluorophenyl)-1*H*-imidazol-4-yl]carbonyl}-1-piperazinyl)-1-naphthoic acid; and 3-(4-{[1-(2,3-dihydro-1,4-benzodioxin-6-yl)-2-(4-fluorophenyl)-1*H*-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) (5*S*)-1'-{[(3*R*,4*R*)-1-*tert*-butyl-3-(2,3,4-trifluorophenyl)piperidin-4-yl]carbonyl}-3-chloro-2-methyl-5-[1-methyl-1-(1-methyl-1*H*-1,2,4-triazol-5-yl)ethyl]-5*H*-spiro[furo[3,4-*b*]pyridine-7,4'-piperidine]; 2) (5*R*)-1'-{[(3*R*,4*R*)-1-*tert*-butyl-3-(2,3,4-trifluorophenyl)piperidin-4-yl]carbonyl}-3-chloro-2-methyl-5-[1-methyl-1-(1-methyl-1*H*-1,2,4-triazol-5-yl)ethyl]-5*H*-spiro[furo[3,4-*b*]pyridine-7,4'-piperidine]; 3) 2-(1'-{[(3*S*,4*R*)-1-*tert*-butyl-4-(2,4-difluorophenyl)pyrrolidin-3-yl]carbonyl}-3-chloro-2-methyl-5*H*-spiro[furo[3,4-*b*]pyridine-7,4'-piperidin]-5-yl)-2-methylpropanenitrile; 4) 1'-{[(3*S*,4*R*)-1-*tert*-butyl-4-(2,4-difluorophenyl)pyrrolidin-3-yl]carbonyl}-3-chloro-2-methyl-5-[1-methyl-1-(1-methyl-1*H*-1,2,4-triazol-5-yl)ethyl]-5*H*-spiro[furo[3,4-*b*]pyridine-7,4'-piperidine]; 5) *N*-[(3*R*,4*R*)-3-(3-chloro-2-methyl-5-[1-methyl-1-(1-methyl-1*H*-1,2,4-triazol-5-yl)ethyl]-1*H*,5*H*-spiro[furo[3,4-*b*]pyridine-7,4'-piperidin]-1-yl)carbonyl]-4-(2,4-difluorophenyl)-cyclopentyl]-*N*-methyltetrahydro-2*H*-pyran-4-amine; 6) 2-[3-chloro-1'-{[(1*R*,2*R*)-2-(2,4-difluorophenyl)-4-[methyl(tetrahydro-2*H*-pyran-4-yl)amino]-cyclopentyl}-carbonyl]-2-methyl-5*H*-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: (±)-(2*R*3*R*,2*S*3*S*)-*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-1*H*,4*H*-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.

5 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.

10 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
15 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
20 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
25 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
30 otherwise noted. Mass spectra (MS) were measured by electron-spray ion-mass spectroscopy.

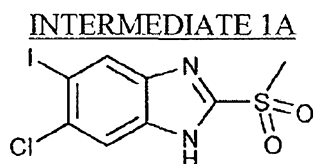
 Abbreviations used in the description of the preparation of the compounds of the present invention: AcOH is acetic acid; C is carbon; DIBAL-H is di-isobutyl aluminum hydride; DCM is dichloromethane; DME is 1,2-dimethoxyethane; DMF is dimethyl formamide; DMSO is dimethyl sulfoxide; Et₂O is diethyl ether; EtOAc is ethyl acetate; dppf is 1,1'-Bis(diphenyl-
35 phosphino)ferrocene; EtOH is ethanol; Et₃N is triethyl amine; h is hour(s); HPLC is high pressure liquid chromatography; KOAc is potassium acetate; L is liter; LC/MS is liquid chromatography/mass spectroscopy; M is molar; ml or mL is milliliter; MeCN is acetonitrile;

MeI is methyl iodide; MeOH is methanol; min is minutes; mmol is millimole(s); *m*-CPBA is meta chloro per benzoic acid; N is normal; NaOAc is sodium acetate; NBS is *N*-bromo succinamide; NIS is *N*-iodo succinamide; PPh₃ is triphenyl phosphine; wt % is weight percent; psi is pounds per square inch; Rt is retention time; Rochelles' Salt is potassium sodium tartrate; SEM is 2-(trimethylsilyl)ethoxymethyl; SEMCl is 2-(trimethylsilyl)-ethoxymethyl chloride; TBAF is tetrabutyl ammonium fluoride; TFA is trifluoro acetic acid; and THF is tetrahydrofuran.

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 = 0.03% TFA in acetonitrile; solvent B = 0.05% TFA in water; flowrate = 10 mL/min; column:

Chromolith Performance RP-18e, 100×4.6 mm; gradient program: min (%B) 0 (95), 1.6 (5), 2.6 (5), 2.7 (95), 3.0 (95). Unless specified, the ¹H NMRs were obtained in DMSO-*d*₆ at 300 or 500 MHz and spectra were recorded in units δ with CD₂HS(O)CD₃ (δ 2.504) as the reference line internal standard. 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 title compounds of general formula I.



6-chloro-5-iodo-2-(methylsulfonyl)-1H-benzimidazole

Step A 5-chloro-4-iodo-2-nitroaniline. To a solution of 5-chloro-2-nitroaniline (25 g, 145 mmol) in AcOH (250 mL) was added N-iodosuccinimide (32.6 g 145 mmol). The mixture was stirred overnight at 50 °C, cooled down to rt and filtered. The solid residue was washed with AcOH, water, saturated aqueous NaHCO₃ and water, and then dried to afford the desired product as a brown solid, which was used in the next step without further purification.

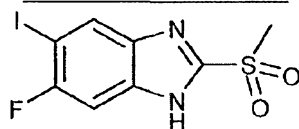
Step B 4-chloro-5-iodobenzene-1,2-diamine. To a suspension of 5-chloro-4-iodo-2-nitroaniline (36.5 g, 122 mmol) in EtOH (800 mL) and water (150 mL) was added iron powder (38 g, 673 mmol) and NH₄Cl (16 g, 306 mmol). The mixture was heated under nitrogen at 50 °C overnight. Additional iron powder (38 g, 673 mmol) and NH₄Cl (16 g, 306 mmol) were added and heating was continued for 45 h. The reaction mixture was cooled, filtered and concentrated. The residue was re-dissolved in ethyl acetate and washed with sodium bicarbonate solution. The organic phase was concentrated to afford the desired product as a gray solid, which was used in the next step without further purification.

Step C 5-chloro-6-iodo-1,3-dihydro-2H-benzimidazole-2-thione. KOH (15.7 g, 238 mmol) in water (50 mL), followed by carbon disulfide (14.4 mL, 238 mmol), was added to a solution of 4-chloro-5-iodobenzene-1,2-diamine (50 g, 198 mmol) in EtOH (300 mL). The mixture was heated at reflux for 3 h, cooled and filtered. To the filtrate was added water (300 mL) and then AcOH (25 mL) in water (50 mL). The precipitate was collected, washed with water and a small amount of EtOH and dried to afford the desired product as a brown powder, which was used in the next step without further purification.

Step D 6-chloro-5-iodo-2-(methylthio)-1H-benzimidazole. K₂CO₃ (0.22 g, 1.61 mmol), followed by iodomethane (0.1 mL, 1.61 mmol), was added to a solution of 5-chloro-6-iodo-1,3-dihydro-2H-benzimidazole-2-thione (1 g, 3.22 mmol) in acetone (20 mL) at 0°C. The reaction was stirred at rt for 1 h. Additional K₂CO₃ (1.61 mmol) and iodomethane (1.61 mmol) were added, and stirring continued at rt overnight. Volatiles were removed and the residue was partitioned between EtOAc and water. Concentration afforded the desired product as a white foam, which was used in the next step without further purification.

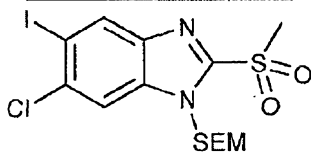
Step E 6-chloro-5-iodo-2-(methylsulfonyl)-1H-benzimidazole. *m*-Chloroperbenzoic acid (1.4 g, 6.16 mmol) was added to a suspension of 6-chloro-5-iodo-2-(methylthio)-1H-benzimidazole (1.0g, 3.08 mmol) in DCM (50 mL). The reaction stirred at rt for 10 min then washed with 10% aqueous NaHCO₃. The organic phase was concentrated. The residue was triturated with MeOH (3 mL) and filtered to afford the title compound as white powder. LC-MS: calculated for C₈H₆ClIN₂O₂S 356.57, observed *m/e* 357.30 (M + H)⁺ (R_t 1.21/2 min). NMR(CD₃OD): 8.3 (1H,s), 7.9 (1H,s), 3.3 (3H,s).

INTERMEDIATE 1B



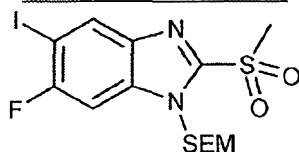
6-fluoro-5-iodo-2-(methylsulfonyl)-1H-benzimidazole. Intermediate 1B was prepared by the same procedures described for Intermediate 1A, starting with the appropriate starting material. LC-MS: calculated for C₈H₆FIN₂O₂S 340.11, observed *m/e* 341.0 (M + H)⁺ (R_t 2.45/4 min).

NMR(D₆-ACETONE): 8.22(1H, s), 7.60(1H, d), 3.45(3H, s).

INTERMEDIATE 2A

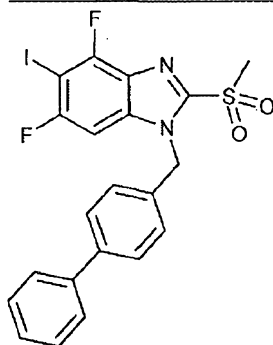
6-chloro-5-iodo-2-(methylsulfonyl)-1-([2-(trimethylsilyl)ethoxy]methyl)-1H-benzimidazole.

Et₃N (20.95 mL, 150 mmol) and 2-(trimethylsilyl)ethoxy methyl chloride (17.29 mL, 98 mmol) were added to a solution of Intermediate 1A (26.8 g, 75 mmol) in THF (200 mL). The reaction was stirred at rt for 1 h. Volatiles were removed and the residue partitioned between EtOAc and water. The organic phase was washed with 2N aqueous HCl and brine, dried (MgSO₄) and concentrated to afford the title compound as a white solid. LC-MS: calculated for C₁₄H₂₀ClN₂O₃SSi 485.97, observed m/e 428.83 (M + H)⁺ (R_t 2.30 min).

INTERMEDIATE 2B

6-fluoro-5-iodo-2-(methylsulfonyl)-1-([2-(trimethylsilyl)ethoxy]methyl)-1H-benzimidazole.

Intermediate 2B was prepared by the same procedures described for Intermediate 2A, starting with the appropriate starting material. LC-MS: calculated for C₁₄H₂₀FIN₂O₃SSi 470.37, observed m/e 413 (M-Me₃SiH + O + H)⁺ (R_t 2.25 min). NMR (CDCl₃): 8.20 (1/2H,s), 8.03(1/2H,s); 7.50(1/2H,d), 7.33(1/2H,d); 5.89(2H,s); 3.65(2H,m); 3.55(3H,s); 0.95(2H,m); - 0.98(9H,s).

INTERMEDIATE 2C

1-(biphenyl-4-ylmethyl)-4,6-difluoro-5-iodo-2-(methylsulfonyl)-1H-benzimidazole

Step A N-(biphenyl-4-ylmethyl)-3,5-difluoro-2-nitroaniline. Potassium carbonate (10.9 g, 79 mmol) was added to a solution of 1,3,5-trifluoro-2-nitrobenzene and 1-biphenyl-4-ylmethanamine in THF (200 mL). The mixture was stirred at rt for 15 h. The reaction mixture was filtered and concentrated to afford the desired product as a deep orange solid.

Step B N-(biphenyl-4-ylmethyl)-3,5-difluoro-4-iodo-2-nitroaniline. NIS (7.9 g, 35.1 mmol) was added to a solution of N-(biphenyl-4-ylmethyl)-3,5-difluoro-2-nitroaniline (10.86 g, 31.9 mmol)

in AcOH (150 mL). After heating at 70°C for 2 h, the reaction mixture was concentrated and partitioned between EtOAc and saturated aqueous NaHCO₃. The organic phase was washed with brine, dried (Na₂SO₃) and concentrated. Recrystallization from DCM/hexanes afforded the desired product as a red solid.

- 5 Step C N'-(biphenyl-4-ylmethyl)-3,5-difluoro-4-iodobenzene-1,2-diamine. A 20% solution of AcOH (6.7 mL, 117 mmol) in water was added to a suspension of iron (10.89 g, 195 mmol) in a solution of *N*-(biphenyl-4-ylmethyl)-3,5-difluoro-4-iodo-2-nitroaniline (12.12 g, 26 mmol) in EtOH (70 mL). After heating at 76 °C for 2 h, volatiles were removed. The residue was extracted with EtOAc. Combined organic extracts were filtered through Celite®, washed with aqueous
10 ammonium hydroxide and brine, dried (Na₂SO₄) and concentrated. Chromatography over silica eluting with 10-50% EtOAc/hexanes afforded the desired product as a yellow solid.

Step D 1-(biphenyl-4-ylmethyl)-4,6-difluoro-5-iodo-1,3-dihydro-2*H*-benzimidazole-2-thione. 1,1'-thiocarbonyldiimidazole (4.75 g, 26.6 mmol) was added to a solution of *N'*-(biphenyl-4-ylmethyl)-3,5-difluoro-4-iodobenzene-1,2-diamine (9.68 g, 22.19 mmol) in DMSO (30 mL).

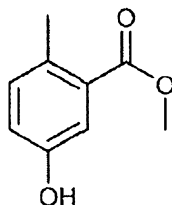
- 15 After stirring at rt for 16 h, the reaction mixture was diluted with DCM and the precipitated solid collected to afford the desired product.

Step E 1-(biphenyl-4-ylmethyl)-4,6-difluoro-5-iodo-2-(methylthio)-1*H*-benzimidazole.

- Iodomethane (2 M in methyl-*tert*-butyl ether, 22.87 mL, 45.7 mmol) was added to a solution of cesium carbonate (14.9 g, 45.7 mmol) and 1-(biphenyl-4-ylmethyl)-4,6-difluoro-5-iodo-1,3-
20 dihydro-2*H*-benzimidazole-2-thione (10.94 g, 22.87 mmol) in THF (100 mL). After stirring at rt overnight, volatiles were removed. Chromatography over silica eluting with 15-60% EtOAc/hexanes afforded the desired product as a beige solid.

- Step F 1-(biphenyl-4-ylmethyl)-4,6-difluoro-5-iodo-2-(methylsulfonyl)-1*H*-benzimidazole. *m*-CPBA (10 g, 44.6 mmol) in DCM (200 mL) was added to 1-(biphenyl-4-ylmethyl)-4,6-difluoro-
25 5-iodo-2-(methylthio)-1*H*-benzimidazole (10.98 g, 22.3 mmol). The reaction mixture was stirred at rt for 16 h. A further 3 g of *m*-CPBA was added and stirring continued for 1 h. Volatiles were removed and the residue was partitioned between EtOAc and saturated aqueous NaHCO₃. The organic phase was washed with brine, dried (Na₂SO₄) and concentrated. Chromatography over silica eluting with 15-30% EtOAc/hexanes afforded the title compound as a white solid. LC-MS:
30 calculated for C₂₁H₁₅F₂IN₂O₂S 523.99, observed *m/e* 525.00 (*M* + *H*)⁺ (*R*_t 2.15 min).

INTERMEDIATE 3



Methyl 5-hydroxy-2-methylbenzoate

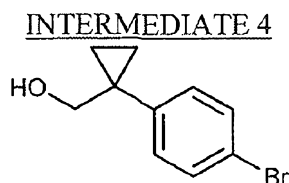
Step A Methyl 2-methyl-5-nitrobenzoate. To a solution of 2-methyl-5-nitrobenzoic acid (60 g,

331 mmol) in MeOH (400 mL) was added HCl (4 M in dioxane) (10 mL). The mixture was heated at reflux over night. Volatiles were removed and the residue was dissolved in EtOAc and washed with saturated aqueous NaHCO₃ and brine, dried (MgSO₄) and concentrated to afford the desired product as white powder.

5 Step B Methyl 5-amino-2-methylbenzoate. To a solution of methyl 2-methyl-5-nitrobenzoate (60g, 307 mmol) in MeOH (600 mL) was added Pd (10 wt% on carbon) (1.6 g). The reaction was shaken under hydrogen (30-50 psi) for 1 h, filtered through a celite pad and concentrated to afford the desired product as a red paste, which was used in the next step without purification.

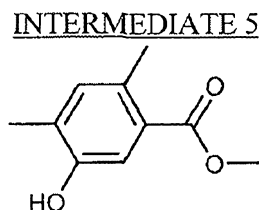
10 Step C Methyl 5-hydroxy-2-methylbenzoate. A 0°C solution of sulfuric acid (89g, 908 mmol) in water (700 mL) was added to a flask containing methyl 5-amino-2-methylbenzoate (50 g, 303 mmol) in an ice-water bath. The resulting mixture was stirred until the mixture become a cloudy solution. A solution of sodium nitrite (21 g, 303 mmol) in cold water (200 mL) was added dropwise and stirring was continued for 1 h at 0°C then at 100°C for another 1 h. The reaction was cooled and the solid collected by filtration, and rinsed with water. The resultant dark red
15 solid was re-dissolved in MeOH (500 mL). Charcoal (2 g) was added and the reaction was heated at reflux for 1 h. The mixture was filtered and concentrated. Chromatography over silica eluting with 0-50% EtOAc/hexane afforded the title compound as white solid. LC-MS: calculated for C₉H₁₀O₃ 166.17, observed m/e: no ionization (R_t 0.89/2 min). NMR (CDCl₃): 7.48 (1H,s), 7.15(1H, d); 6.95(1H,d), 6.04(1H,s); 3.95(3H,s); 2.53(3H,s).

20



[1-(4-bromophenyl)cyclopropyl]methanol. LiAlH₄ (2M in THF) (1.6 mL, 3.20 mmol) was added to a solution of 1-(4-bromophenyl)cyclopropanecarboxylic acid (480 mg, 1.991 mmol) in THF (12 ml) at 0 °C. The reaction mixture was stirred at rt for 45 min, then quenched with
25 water (3 mL) at 0 °C. The mixture was diluted with EtOAc (30 mL) and 1N aqueous potassium sodium tartrate and stirred at rt for 2 h. The organic layer was removed. Aqueous layer was extracted with EtOAc. Combined organic layers were dried (MgSO₄), filtered and concentrated to afford the title compound that was used without further purification. LC-MS calculated for C₁₀H₁₁BrO 226, No ionization. Rt : 2.85/ 5.5 min.

30

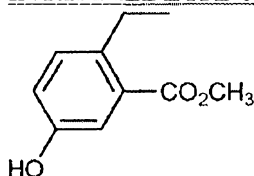


Methyl 5-hydroxy-2,4-dimethylbenzoate

Step A Methyl 5-amino-2,4-dimethylbenzoate. A flask containing methyl 2,4-dimethylbenzoate (1.48 g, 9.01 mmol) was cooled with an ice bath. A mixture of H_2SO_4 (1.5 mL, 28.1 mmol) and HNO_3 (1.5 mL, 23.5 mmol) was carefully added. After 50 min, the mixture was poured into ice and extracted with EtOAc. The organic phase was washed with water and brine, dried (Na_2SO_4) and concentrated. The residue was dissolved in 30 mL of methanol. Pd (10 wt% on C) (120 mg) was added, and the reaction was shaken under hydrogen (50 psi) for 1 h. The reaction was filtered and concentrated. Chromatography over silica eluting with 50-75% EtOAc/hexane afforded the desired product. ^1H NMR (CDCl_3) δ 7.34 (s, 1H), 6.96 (s, 1H), 4.05 (bs, 1H), 3.88 (s, 3H), 2.50 (s, 3H), 2.22 (s, 3H).

Step B Methyl 5-hydroxy-2,4-dimethylbenzoate. Methyl 5-amino-2,4-dimethylbenzoate (0.752 g, 4.20 mmol) in 5 mL water was cooled with an ice bath. H_2SO_4 (1.1 mL, 21 mmol) was added followed by a solution of sodium nitrite (0.301 g, 4.4 mmol) in 3 mL of water. The reaction was stirred in an ice bath for 30 min, and then in a 100 °C oil bath for 60 min. The reaction was cooled to rt and partitioned between EtOAc and brine. The organic phase was dried (Na_2SO_4) and concentrated to give the title compound as a yellow oil. ^1H NMR (CDCl_3) δ 7.48 (s, 1H), 7.00 (s, 1H), 5.95 (bs, 1H), 3.90 (s, 3H), 2.50 (s, 3H), 2.28 (s, 3H).

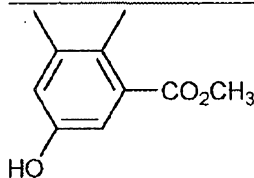
INTERMEDIATE 6



Methyl 2-ethyl-5-hydroxybenzoate. Intermediate 6 was prepared by the same procedures

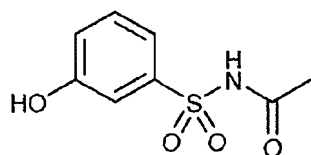
described for Intermediate 5, starting with the appropriate starting material. ^1H NMR (CDCl_3) δ 7.41 (d, 1H, $J = 2.8$ Hz), 7.15 (d, 1H, $J = 8.3$ Hz), 6.98 (dd, 1H, $J = 2.8, 8.2$ Hz), 6.3 (bs, 1H), 3.91 (s, 3H), 2.90 (q, 2H, $J = 7.3$ Hz), 1.21 (t, 1H, 7.5 Hz).

INTERMEDIATE 7



Methyl 5-hydroxy-2,3-dimethylbenzoate. Intermediate 7 was prepared by the same procedure described for Intermediate 5, starting with the appropriate starting material. ^1H NMR (CDCl_3) δ 7.12 (d, 1H, $J = 2.5$ Hz), 6.83 (d, 1H, $J = 2.5$ Hz), 5.90 (bs, 1H), 3.89 (s, 3H), 2.36 (s, 3H), 2.26 (s, 3H).

INTERMEDIATE 8

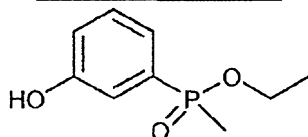


N-[(3-hydroxyphenyl)sulfonyl]acetamide

Step A N-[(3-methoxyphenyl)sulfonyl]acetamide. To a solution of 3-methoxybenzenesulphonamide (2 g, 10.68 mmol) and acetic anhydride (1.51 mL, 16.0 mmol) in acetonitrile (20 mL) were added 2 drops of concentrated sulfuric acid. The reaction was heated at 60°C for 1h, then cooled and concentrated. Water (15 mL) was added and the precipitated solid was collected and dried to afford the desired product as a white solid.

Step B N-[(3-hydroxyphenyl)sulfonyl]acetamide. To a solution of N-[(3-methoxyphenyl)sulfonyl]acetamide (0.4 g, 1.75 mmol) in DCM at 0 °C was added BBr₃ and the reaction was stirred at rt for 2 h. The reaction was quenched with pH = 4 buffer and extracted with EtOAc. The organic phase was dried (Na₂SO₄) and concentrated to afford the title compound. LC-MS: m/e 216 (M + H)⁺ (0.5 min).

INTERMEDIATE 9

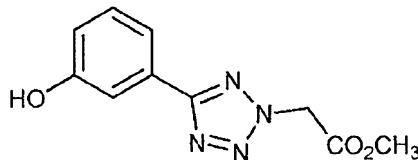


Ethyl (3-hydroxyphenyl)methylphosphinate

Step A Ethyl (3-methoxyphenyl)methylphosphinate. A mixture of 1-iodo-3-methoxybenzene (2.75 g, 11.75 mmol) and NiCl₂ (0.076 g, 0.588 mmol) was added to ethyl dimethylphosphinite (2.08 g, 15.3 mmol) at rt. The reaction mixture was gradually heated to 170 °C for 2.5 h. The reaction mixture was partitioned between with EtOAc and water. The organic phase was washed with brine, dried (Na₂SO₄), filtered and concentrated. Chromatography over silica eluting with 66-100% EtOAc/hexane afforded the desired product.

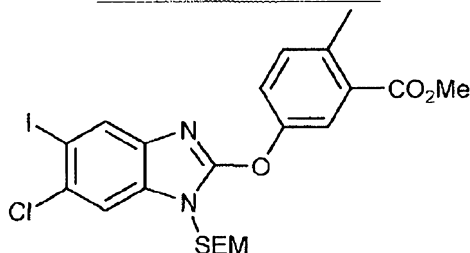
Step B Ethyl (3-hydroxyphenyl)methylphosphinate. BBr₃ (3.16 mL, 1 M solution in DCM) was added to a solution of ethyl (3-methoxyphenyl)methylphosphinate (0.169 g, 0.789 mmol) in DCM at 0°C. The reaction was stirred at rt for 15 h, then partitioned between EtOAc and saturated aqueous NaHCO₃. The organic phase was washed with brine, dried (Na₂SO₄), filtered and concentrated to give the title compound. ¹H NMR (500 MHz, CD₃OD): δ 7.35-7.40 (m, 1H), 7.19-7.26 (m, 2H), 7.05 (dd, 1H, J = 8.3, 2.6 Hz), 3.85 – 4.05 (m, 2H), 1.69 (d, 3H, J = 14.6 Hz), 1.29 (t, 3H, J = 7.1 Hz).

INTERMEDIATE 10



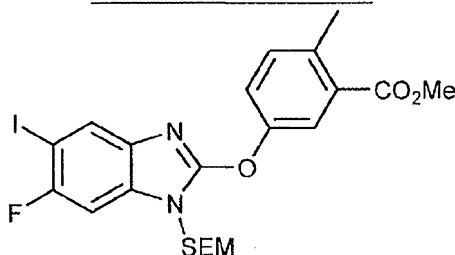
Methyl [5-(3-hydroxyphenyl)-2*H*-tetrazol-2-yl]acetate. To a solution of 3-(2*H*-tetrazol-5-yl)phenol (250.8 mg, 1.547 mmol) in MeCN (10 mL) at rt was added Et₃N (0.237 mL, 1.701 mmol) followed by methyl bromoacetate (260 mg, 1.701 mmol). The reaction was stirred at rt for 16 h. Volatiles were removed. Chromatography over silica eluting with 30-60% EtOAc/hexanes afforded the title compound as a white solid. ¹H NMR (500 MHz, CDCl₃): δ 7.75 (d, 1H, J = 7.5 Hz), 7.69 (s, 1H), 7.39 (t, 1H, J = 8.0 Hz), 7.01 (dd, 1H, J = 8.0, 2.3 Hz), 5.53 (bs, 1H), 5.50 (s, 2H), 3.86 (s, 3H).

INTERMEDIATE 11A



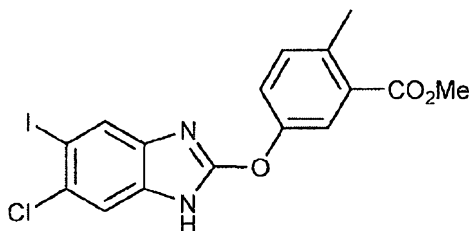
Methyl 5-[(6-chloro-5-iodo-1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-benzimidazol-2-yl)oxy]-2-methylbenzoate. K₂CO₃ (2.3 g, 16.64 mmol) was added to a solution of Intermediate 3 (1 g, 6.57 mmol) and Intermediate 2A (2.1g, 4.31 mmol) in DMF (30 mL). The reaction stirred at rt for 24 h. Volatiles were removed and the residue was acidified with 2 N aqueous HCl and extracted with EtOAc. The organics were washed with water and brine, dried (MgSO₄) and concentrated to afford the title compound as a brown solid, which was used without further purification. LC-MS: calculated for C₂₁H₂₄ClN₂O₄Si 558.02, observed m/e 558.82 (M + H)⁺ (R_t 2.26 min).

INTERMEDIATE 11B



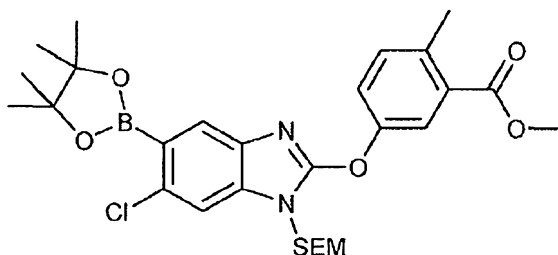
Methyl 5-[(6-fluoro-5-iodo-1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-benzimidazol-2-yl)oxy]-2-methylbenzoate. Intermediate 11B was prepared by the same procedure described for Intermediate 11A, starting with the appropriate starting material. LC-MS: calculated for C₂₁H₂₄ClN₂O₄Si 558.02, observed m/e 558.82 (M + H)⁺ (R_t 2.26 min).

INTERMEDIATE 12



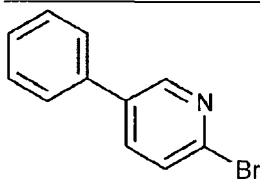
Methyl 5-[(6-chloro-5-iodo-1H-benzimidazol-2-yl)oxy]-2-methylbenzoate. Intermediate 11A (7.5g, 13.1 mmol) was dissolved in HCl (4M in dioxane) (250 mL) and stirred at rt for 65 h. The reaction mixture was concentrated and partitioned between EtOAc and saturated aqueous NaHCO₃. The organic phase was concentrated to afford the title compound as white powder. LCMS: calculated for C₁₆H₁₂ClIN₂O₃ 442.64, observed m/e 443.9 (M+H)⁺, (R_t 2.05/4 min).

INTERMEDIATE 13



Methyl 5-[(6-chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-([2-(trimethylsilyl)ethoxy)methyl]-1H-benzimidazol-2-yl)oxy]-2-methylbenzoate. A solution of Intermediate 11A (15.98 g, 27.9 mmol), bis(pinacolato)diboron (7.22 g, 28.5 mmol), KOAc (8.21 g, 84 mmol), and PdCl₂(dppf) (0.612 g, 0.837 mmol) in DMSO (100 mL) was degassed and then flushed with nitrogen. This cycle was repeated 4 times. The reaction was then heated at 80°C for 16 h. The reaction mixture was diluted with ice water and extracted with Et₂O. The combined ethereal extracts were washed with brine, dried (MgSO₄) and concentrated. Chromatography over silica eluting with 4:1 hexanes:EtOAc afforded the title compound as a reddish brown oil, which was used without further purification. LC-MS: calculated for C₂₈H₃₈BClN₂O₆Si 572.23, observed m/e 572.96 (M + H)⁺ (R_t 2.54 min). ¹H NMR (500 MHz, CDCl₃): δ 7.92 (s, 1H), 7.75 (s, 1/2H), 7.55 (s, 1/2H), 7.47(m, 1H), 7.40 (s, 1H) 7.35 (m, 1H), 5.57 (s, 1H), 5.51 (s, 1H), 3.90 (s, 3H), 3.67 (t, 2H), 2.64 (s, 3H), 1.41 (s, 6H), 1.37 (s, 6H), 0.98 (m, 2H), 0.00 (s, 9H).

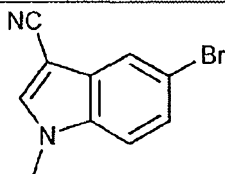
INTERMEDIATE 14



2-bromo-5-phenylpyridine. Na₂CO₃ (1.117 mL, 2.234 mmol) followed by Pd(PPh₃)₄ (51.6 mg,

0.045 mmol) were added to a solution of iodobenzene (0.1 mL, 0.894 mmol) and 2-bromopyridine-5-boronic acid (271 mg, 1.340 mmol) in DMF (4 mL). The reaction was heated at 60 °C for 4 h, cooled and concentrated. The residue was partitioned between EtOAc and water. The organic phase was washed with brine, dried (MgSO₄), and concentrated. Chromatography over silica eluting with 4:1 hexanes:EtOAc afforded the title compound as an off-white solid. LC-MS: calculated for C₁₁H₈BrN 234.09, observed m/e 236.5 (M + H)⁺ (R_t 1.72 min).

INTERMEDIATE 15

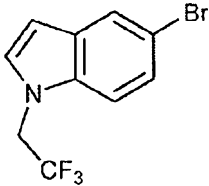
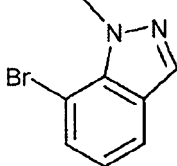
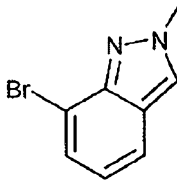
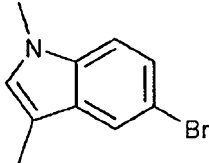
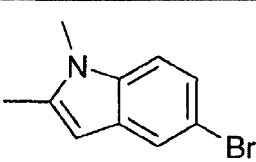
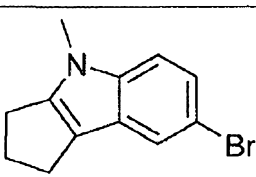
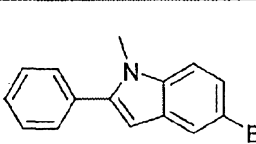
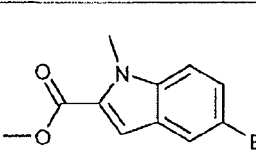
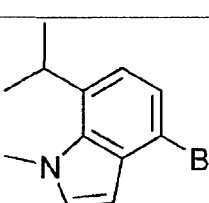


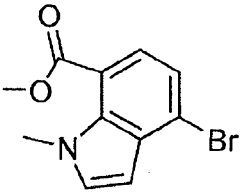
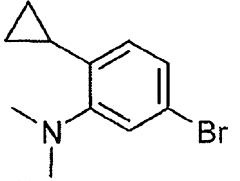
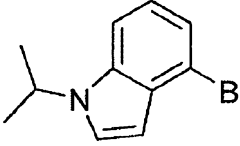
5-bromo-1-methyl-1H-indole-3-carbonitrile. To a solution of 5-bromo-1H-indole-3-carbonitrile (240 mg, 1.086 mmol) in DMF (2 mL) at 0°C was added NaH (130 mg, 3.26 mmol). After stirring at 0°C for 30 minutes, MeI (0.102 mL, 1.629 mmol) was added. Upon completion as judged by LCMS, the reaction was quenched with water. Volatiles were removed and the residue partitioned between EtAOc and water. The organic phase was washed with brine, dried (MgSO₄) and concentrated to afford the desired product as an off-white solid, which was used without further purification. LC-MS: calculated for C₁₀H₇BrN₂ 235.08, observed m/e 236.97 (M + H)⁺ (R_t 1.04/2 min).

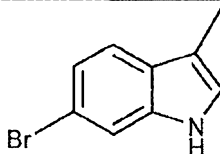
Intermediates 16-30 in Table I-1 were prepared following the procedures described for Intermediate 15 by substituting 5-bromo-1H-indole-3-carbonitrile with the appropriate amine, alcohol, acid or heterocycle from commercial sources or from among the Intermediates; and by substituting MeI with the appropriate alkylating agent from commercial sources.

Table I-1. Intermediates prepared according to the methods described in Intermediate 15.

In. No.	Name	Structure	HPLC-mass spectrum m/e
16	1-(5-bromo-1-methyl-1H-indol-3-yl)-N,N-dimethylmethanamine		223.9

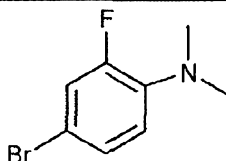
17	5-bromo-1-(2,2,2-trifluoroethyl)-1 <i>H</i> -indole		278.7
18	7-bromo-1-methyl-1 <i>H</i> -indazole		213.1
19	7-bromo-2-methyl-2 <i>H</i> -indazole		213.1
20	5-bromo-1,3-dimethyl-1 <i>H</i> -indole		224.9
21	5-bromo-1,2-dimethyl-1 <i>H</i> -indole		225.0
22	7-bromo-4-methyl-1,2,3,4-tetrahydrocyclopenta[b]indole		250.7
23	5-bromo-1-methyl-2-phenyl-1 <i>H</i> -indole		287.87
24	methyl 5-bromo-1-methyl-1 <i>H</i> -indole-2-carboxylate		270.1
25	4-bromo-7-isopropyl-1-methyl-1 <i>H</i> -indole		253.6

26	methyl 4-bromo-1-methyl-1H-indole-7-carboxylate		268.2
27	5-bromo-2-cyclopropyl-N,N-dimethylaniline		339.98
28	4-bromo-1-isopropyl-1H-indole		238.03

INTERMEDIATE 296-bromo-3-methyl-1H-indole

- 5 Step A 6-bromo-3-hydroxy-3-methyl-1,3-dihydro-2H-indol-2-one. CH_3MgBr (2 M in THF) (14.6 mL, 29.2 mmol) was added to a solution of 6-bromo-1H-indole-2,3-dione (2.2 g, 9.73 mmol) in THF (50 mL). The reaction was stirred at rt for 16 h then partitioned between saturated aqueous NH_4Cl (100 mL) and EtOAc (50 mL). The organic layer was separated, washed with brine, dried (MgSO_4) and concentrated to afford the desired compound, which was used in the
- 10 next step without further purification.

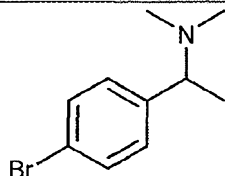
- Step B 6-bromo-3-methyl-1H-indole. A mixture of 6-bromo-3-hydroxy-3-methyl-1,3-dihydro-2H-indol-2-one (0.25 g, 1.0 mmol) and $\text{BH}_3\text{-S}(\text{CH}_3)_2$ (5.16 mL, 1.0 M, 5.16 mmol) in THF (20 mL) was heated at 60 °C. The reaction was quenched with MeOH. Volatiles were removed. Chromatography over silica eluting with 4:1 hexane:EtOAc afforded the title compound. LC-
- 15 MS: calculated for $\text{C}_9\text{H}_8\text{BrN}$ 210.07, observed m/e 211.0 ($\text{M} + \text{H}$)⁺ (R_t 1.14 min).

INTERMEDIATE 30

4-bromo-2-fluoro-N,N-dimethylaniline. To a solution of 2-fluoro-4-bromoaniline (1.0 g, 5.26 mmol) in AcOH (20 mL) at rt was added NaCNBH_3 (1.654 g, 26.3 mmol). The mixture was

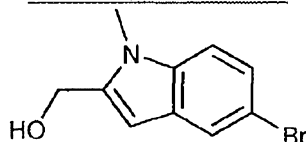
stirred at rt overnight (~17 h). The reaction was cooled in an ice bath. Water (10 mL) was added, followed by solid KOH until pH > 11. The mixture was extracted with DCM. The combined extracts were dried (MgSO₄) and concentrated to afford the title compound, which was used without further purification. LC-MS: calculated for C₈H₉BrFN 218.07, observed m/e 219.99 (M + H)⁺ (R_t 0.96 min).

INTERMEDIATE 31



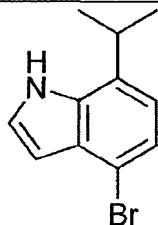
1-(4-bromophenyl)-N,N-dimethylethanamine. A solution of 1-(4-bromophenyl)ethanamine (1.65 g, 8.25 mmol), aqueous formaldehyde (1.8 mL, 37 wt% in water, 24.74 mmol), and NaOAc (2.71 g, 33.0 mmol) in MeOH (15 mL) was stirred at rt for 5 minutes. NaCNBH₃ (1.04 g, 16.5 mmol) was added, and the mixture was stirred at rt for 2 h. The reaction was partitioned between water and EtOAc. The organic phase was washed with 2 N aqueous NaOH and brine, dried (MgSO₄) and concentrated to afford the title compound, which was used without further purification.

INTERMEDIATE 32



(5-bromo-1-methyl-1H-indol-2-yl)methanol. LiAlH₄ (0.4 mL, 0.800 mmol) was added to a solution of Intermediate 24 (100 mg, 0.373 mmol) in THF (4 mL) at 0 °C. The reaction mixture was stirred at rt for 15 min and quenched with ice-water. The aqueous phase was extracted with EtOAc. The combined organics were dried (MgSO₄), filtered and concentrated to afford the title compound, which was used without further purification. LC-MS: calculated for C₁₀H₁₀BrNO 240.1, observed m/e 242.1 (M+H)⁺ Rt (3.04/4min.).

INTERMEDIATE 33



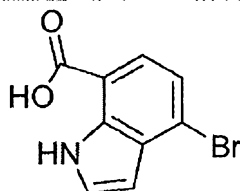
4-bromo-7-isopropyl-1H-indole

Step A 4-bromo-1-isopropyl-2-nitrobenzene. 1-Isopropyl-2-nitrobenzene (5 g, 30.3 mmol) and NBS (5.39 g, 30.3 mmol) were dissolved in TFA (150 mL) and H₂SO₄ (15 mL). The reaction was stirred at rt for 15 h, and then poured into ice water (200 mL). The organic phase was washed with brine, dried (MgSO₄), filtered and concentrated to afford the desired product, which

was used in the following step without further purification.

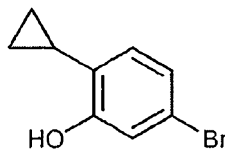
Step B 4-bromo-7-isopropyl-1H-indole. Vinyl magnesium bromide (1 M in THF) (98 mL, 98 mmol) was added to 4-bromo-1-isopropyl-2-nitrobenzene (4 g, 16.39 mmol) in THF (60 mL) at -40 °C. The reaction mixture was stirred for 1 h, then poured into saturated aqueous NH₄Cl and extracted with ether. The combined ethereal extracts were dried (MgSO₄) and concentrated. Chromatography over silica eluting with 1-20% EtOAc/ hexanes afforded the title compound. LC-MS: calculated for C₁₁H₁₂BrN 237.02, observed m/e 238.2 (M+H)⁺ Rt (1.96/4min.).

INTERMEDIATE 34



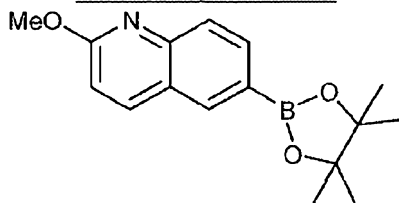
- 10 4-bromo-1H-indole-7-carboxylic acid. Intermediate 34 was prepared by the procedure of Step B of Intermediate 33, starting from the appropriate starting material.

INTERMEDIATE 35



- 15 5-bromo-2-cyclopropylphenol. An ice-cold solution of H₂SO₄ (0.23 mL, 4.31 mmol) in water (2 mL) was added to 5-bromo-2-cyclopropylaniline (300 mg, 1.42 mmol) at 0 °C. The reaction was stirred for 10 min, then sodium nitrite (98 mg, 1.415 mmol) in 2 mL cold water was added dropwise. The reaction was stirred at 0 °C for 1 h and then heated at 100 °C for 1 h. Reaction was extracted with EtOAc. Combined organic layers were washed with brine, dried (MgSO₄), filtered and concentrated to afford the title compound, which was used without further purification. LC-MS calculated for C₉H₉BrO 211.98, no ionization, (Rt: 1.57/ 4 min.).

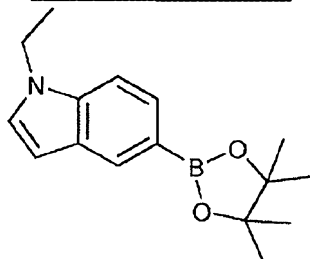
INTERMEDIATE 36



- 25 2-methoxy-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinoline. 6-bromo-2-methoxyquinoline (400 mg, 1.68 mmol), bis(pinacolato)diboron (482 mg, 1.90 mmol), PdCl₂(dppf) (41 mg, 0.050 mmol), and NaOAc (413 mg, 5.04 mmol) were dissolved in DMF (10 mL) and heated at 90 °C for 24 h. The reaction was concentrated, diluted with EtOAc and filtered. The filtrate was concentrated. Chromatography over silica eluting with 10% EtOAc/hexanes afforded the title compound as a white solid. LC-MS: calculated for

$C_{16}H_{20}BNO_3$ 285.15, observed m/e 286.2 ($M + H$)⁺ (R_t 2.06 min).

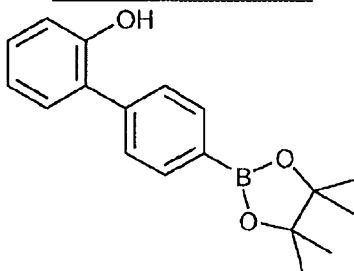
INTERMEDIATE 37



1-ethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole. To a 0 °C suspension of NaH

- 5 (43 mg, 1.81 mmol) in THF (4 mL) was added a solution of 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole (400 mg, 1.65 mmol, Aldrich) in THF (4 mL). The reaction mixture was maintained at 0 °C for 15 min, iodoethane (0.200 mL, 2.47 mmol) was added and the reaction was heated at 50 °C for 30 min. The mixture was partitioned between water and EtOAc. The aqueous layer was extracted with EtOAc and the combined organics were washed
- 10 with brine, dried (Na_2SO_4), filtered, and concentrated. Chromatography over silica eluting with 1-8% EtOAc/hexanes afforded the title compound as a white solid. LC-MS: calculated for $C_{16}H_{22}BNO_2$ 271.16, observed m/e 273.2 ($M + H$)⁺ (R_t 2.09 min).

INTERMEDIATE 38



- 15 4'-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)biphenyl-2-ol.

Step A 4'-bromobiphenyl-2-ol. Potassium phosphate (2 M in water) (5.5 mL, 10.9 mmol) and $Pd(PPh_3)_4$ (209 mg, 0.18 mmol) were added to a solution of 1-bromo-4-iodobenzene (2.05 g, 7.25 mmol), and 2-hydroxybenzeneboronic acid (1 g, 7.25 mmol) in dioxane (50 mL). The reaction was heated at 100°C for 1 h. Volatiles were removed and the residue was purified by

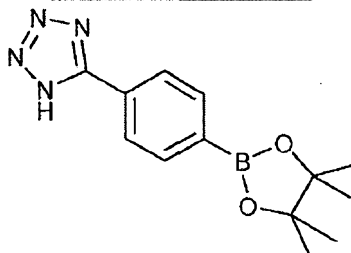
20 chromatography over silica eluting with 0-50% EtOAc/hexane to afford the desired product as a light yellow oil.

Step B 4'-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)biphenyl-2-ol. Potassium acetate (366 mg, 3.73 mmol) and dichloro [1,1'-bis (diphenylphosphino) ferrocene] palladium II DCM adduct (25.4 mg, 31 μ mol) were added to a solution of 4'-bromobiphenyl-2-ol (310mg, 1.24 mmol), and bis(pinacolato)diboron (348 mg, 1.37 mmol) in DME (3 mL). The reaction was heated at 150°C

25 under microwave irradiation for 10 min. Reaction mixture was filtered through a pad of celite and purified by chromatography over silica eluting with 0-50% EtOAc/hexane to furnish the title

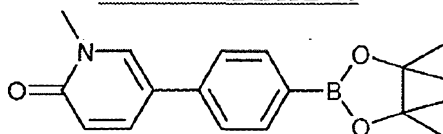
compound as a white solid.

INTERMEDIATE 39



- 5 5-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1H-tetrazole. To a solution of 4-cyanophenylboronic acid (220 mg, 1.497 mmol) in DME (1.5 mL) was added pinacol (186 mg, 1.574 mmol) and MgSO_4 (660 mg, 5.48 mmol). The mixture was stirred at room temperature for 18 h and then filtered, rinsing with DME (1 mL). To the filtrate was added azidotrimethylsilane (0.4 mL, 3.01 mmol) and dibutyltin oxide (37 mg, 0.149 mmol). The reaction was heated at 150°C under microwave irradiation for 15 min. The reaction mixture was concentrated.
- 10 Chromatography over silica eluting with 50:50 EtOAc:hexanes afforded the title compound as a white solid. LC-MS: calculated for $\text{C}_{13}\text{H}_{17}\text{BN}_4\text{O}_2$ 272.14, observed m/e 273.3 ($\text{M}+\text{H}$) $^+$ Rt (1.61/4 min.).

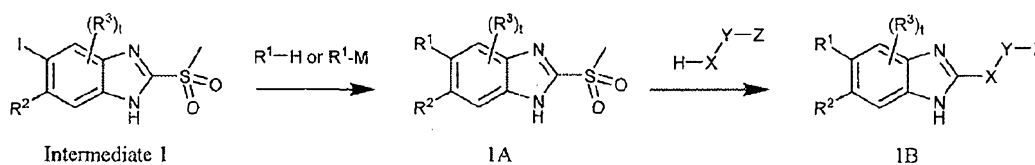
INTERMEDIATE 40



- 15 1-methyl-5-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]pyridin-2(1H)-one. To a solution of 5-Bromo-1-methylpyridine-2-(1H)-one (250 mg, 1.330 mmol) in dioxane (16 mL) was added $\text{Pd}(\text{PPh}_3)_4$ (100 mg, 0.087 mmol), 1,4-benzenediboronic acid dipinacol ester (1.23 g, 3.73 mmol) and 1 M aqueous K_2CO_3 (4.8 mL). The reaction mixture was heated at 120°C for 30 minutes, cooled and partitioned between EtOAc and water. The aqueous phase was extracted
- 20 with EtOAc. The combined organics were washed with brine, dried (MgSO_4), filtered and concentrated. Chromatography over silica eluting with 20-50% EtOAc/hexanes afforded the title compound. LC-MS calculated for $\text{C}_{18}\text{H}_{22}\text{BN}_3\text{O}_3$ 311.17, observed m/e 312.5 ($\text{M}+\text{H}$) $^+$ (Rt: 1.75 / 4 min).

SCHEME 1

25

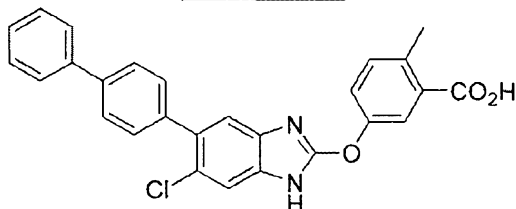


In Scheme 1, Intermediate 1 is reacted with a boronic acid, boronate ester or stannane

(R¹-M) in the presence of palladium tetrakis(triphenylphosphine) to afford compound 1A.

Alternatively, Intermediate 1 is reacted with an acetylene (R¹-H) in the presence of copper (I) iodide and bis(triphenylphosphine)palladium (II) chloride to afford compound 1A. Subsequent reaction of compound 1A with H-X-Y-Z (where X-H is an alcohol, thiol or amine) and, where appropriate, hydrolysis of ester Z affords the 2-substituted benzimidazole 1B.

EXAMPLE 1

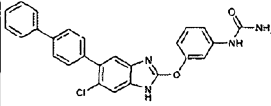
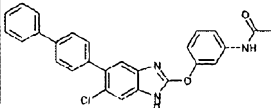
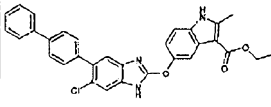
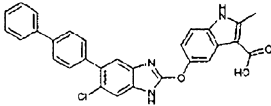
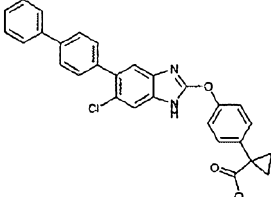
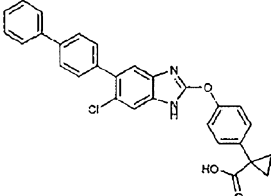


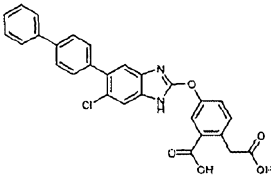
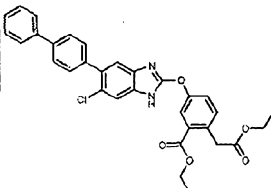
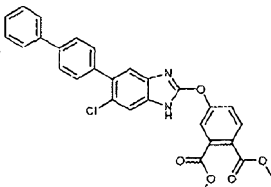
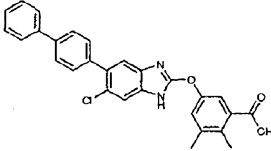
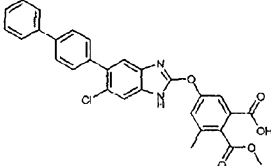
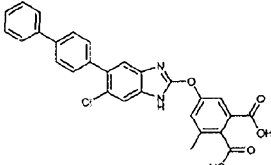
5-[(5-biphenyl-4-yl-6-chloro-1H-benzimidazol-2-yl)oxy]-2-methylbenzoic acid

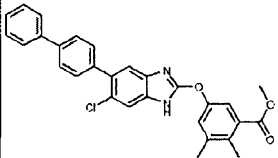
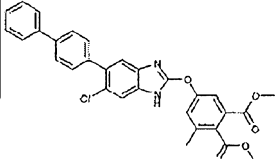
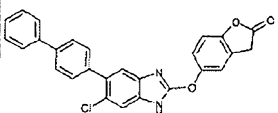
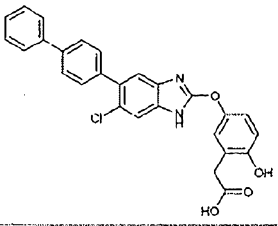
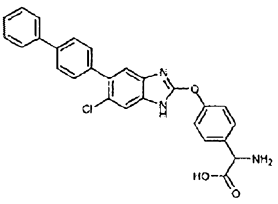
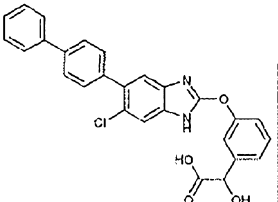
- 10 Step A 5-biphenyl-4-yl-6-chloro-2-(methylsulfonyl)-1H-benzimidazole. To a solution of potassium phosphate, tribasic (2 M solution in water) (63 mL, 126 mmol), Pd(PPh₃)₄ (2 g, 1.7 mmol), 4-biphenylboronic acid (12.5 g, 63.1 mmol) and Intermediate 1A (15 g, 42.1 mmol) in dioxane (300 mL) was heated at 100°C for 5 h. The aqueous phase was removed and the organic phase was concentrated, diluted with EtOAc and DCM, filtered and concentrated to afford the
- 15 desired product as a white solid, which was used in the next step without further purification.
- Step B Methyl 5-[(5-biphenyl-4-yl-6-chloro-1H-benzimidazol-2-yl)oxy]-2-methylbenzoate. A solution of 5-biphenyl-4-yl-6-chloro-2-(methylsulfonyl)-1H-benzimidazole (6.08 g, 36.6 mmol) and Intermediate 5 (7 g, 18.28 mmol) in DCM (100 mL) was concentrated. The resultant solid was placed under nitrogen in a sealed vessel and heated at 130°C for 3 h, then cooled and
- 20 extracted with EtOAc and water. The mixture was filtered and the organic phase was concentrated. Chromatography over silica eluting with 40% EtOAc/hexane afforded the desired product as a white foam.
- Step C 5-[(5-biphenyl-4-yl-6-chloro-1H-benzimidazol-2-yl)oxy]-2-methylbenzoic acid. To a solution of methyl 5-[(5-biphenyl-4-yl-6-chloro-1H-benzimidazol-2-yl)oxy]-2-methylbenzoate
- 25 (11 g, 23.46 mmol) in MeOH/water (1:1) (250 mL) was added NaOH (5 M in water) (23.46 mL, 117 mmol). The mixture was heated at 70°C for 1 h. The mixture was then cooled, diluted with water and acidified with 2 M aqueous HCl. The precipitated white solid was filtered and dried to afford the title compound as a white powder. LCMS: calculated for C₂₇H₁₉ClN₂O₃ 454.90, observed m/e 455.5 (M+H)⁺ (Rt 2.27/4min). ¹H NMR (500 MHz, CD₃OD): δ 7.98-7.35(m, 14H), 2.62 (s, 3H).
- 30

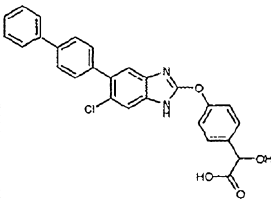
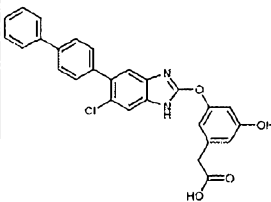
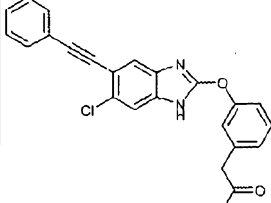
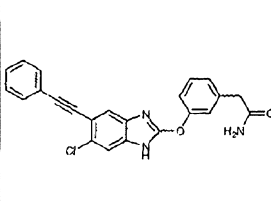
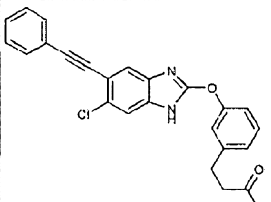
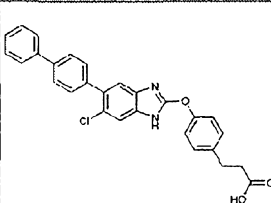
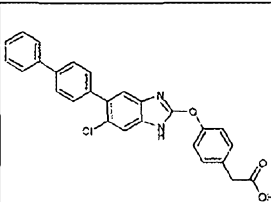
Examples 2-65 in Table 1 were prepared following the procedures described in Example 1 by substituting the appropriate boronic acid, boronate ester, stannane or acetylene from the Intermediates, or from commercial sources; and by substituting the appropriate phenols from the Intermediates, or from commercial sources.

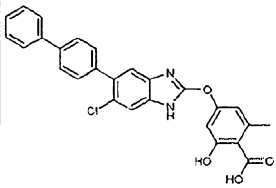
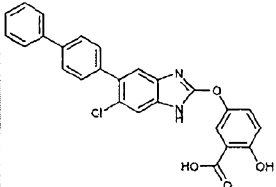
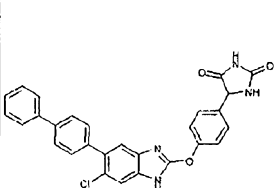
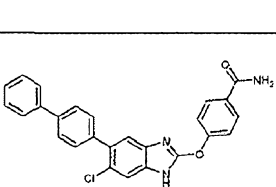
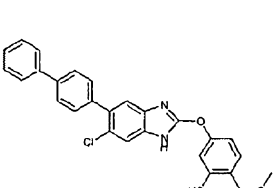
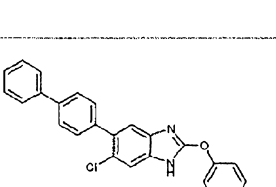
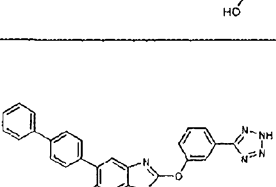
Table 1. Compounds prepared according to the methods described in Example 1 and Scheme 1.

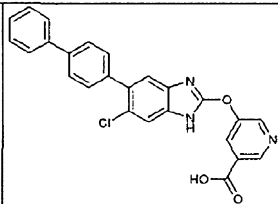
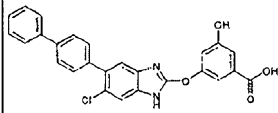
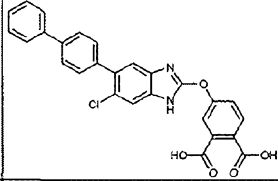
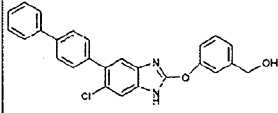
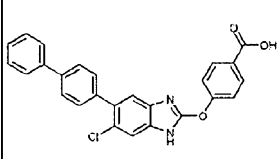
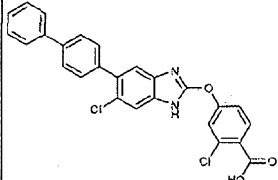
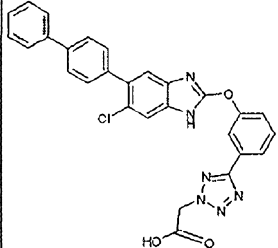
Ex. No.	Name	Structure	HPLC-mass spectrum m/e
2	[3-(5-Biphenyl-4-yl-6-chloro-1H-benzimidazol-2-yloxy)-phenyl]-urea		455
3	N-[3-(5-Biphenyl-4-yl-6-chloro-1H-benzimidazol-2-yloxy)-phenyl]-acetamide		454
4	5-(5-Biphenyl-4-yl-6-chloro-1H-benzimidazol-2-yloxy)-2-methyl-1H-indole-3-carboxylic acid ethyl ester		522
5	5-(5-Biphenyl-4-yl-6-chloro-1H-benzimidazol-2-yloxy)-2-methyl-1H-indole-3-carboxylic acid		494
6	1-[4-(5-Biphenyl-4-yl-6-chloro-1H-benzimidazol-2-yloxy)-phenyl]-cyclopropanecarboxylic acid methyl ester		495
7	1-[4-(5-Biphenyl-4-yl-6-chloro-1H-benzimidazol-2-yloxy)-phenyl]-cyclopropanecarboxylic acid		481

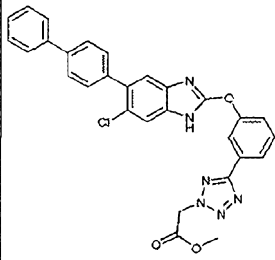
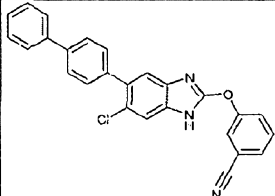
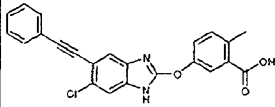
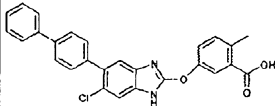
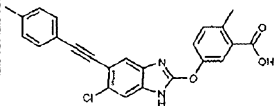
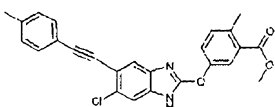
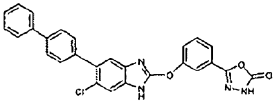
	cyclopropanecarboxylic acid		
8	5-(5-Biphenyl-4-yl-6-chloro-1H-benzimidazol-2-yloxy)-2-carboxymethylbenzoic acid		499
9	5-(5-Biphenyl-4-yl-6-chloro-1H-benzimidazol-2-yloxy)-2-ethoxycarbonylmethylbenzoic acid ethyl ester		555
10	4-(5-Biphenyl-4-yl-6-chloro-1H-benzimidazol-2-yloxy)-phthalic acid dimethyl ester		513
11	5-(5-Biphenyl-4-yl-6-chloro-1H-benzimidazol-2-yloxy)-2,3-dimethylbenzoic acid		469
12	5-(5-Biphenyl-4-yl-6-chloro-1H-benzimidazol-2-yloxy)-3-methylphthalic acid 2-methyl ester		499
13	5-(5-Biphenyl-4-yl-6-chloro-1H-benzimidazol-2-yloxy)-3-methyl-		513

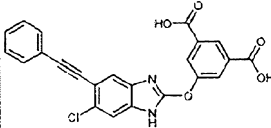
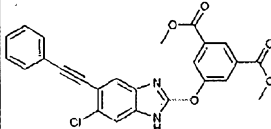
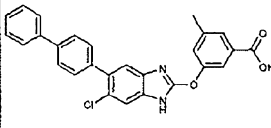
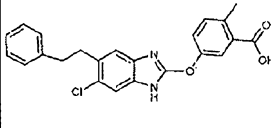
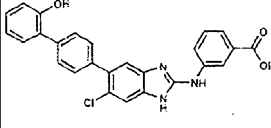
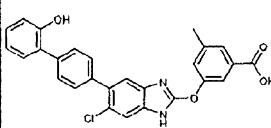
	phthalic acid		
14	5-(5-Biphenyl-4-yl-6-chloro-1H-benzoimidazol-2-yloxy)-2,3-dimethylbenzoic acid methyl ester		483
15	5-(5-Biphenyl-4-yl-6-chloro-1H-benzoimidazol-2-yloxy)-3-methylphthalic acid dimethyl ester		527
16	5-(5-Biphenyl-4-yl-6-chloro-1H-benzoimidazol-2-yloxy)-3H-benzofuran-2-one		453
17	[5-(5-Biphenyl-4-yl-6-chloro-1H-benzoimidazol-2-yloxy)-2-hydroxyphenyl]-acetic acid		471
18	Amino-[4-(5-biphenyl-4-yl-6-chloro-1H-benzoimidazol-2-yloxy)-phenyl]-acetic acid		470
19	[3-(5-Biphenyl-4-yl-6-chloro-1H-benzoimidazol-2-yloxy)-phenyl]-hydroxy-acetic acid		471

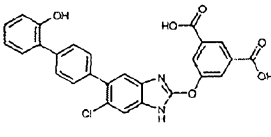
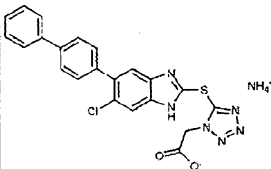
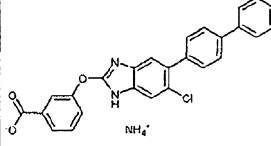
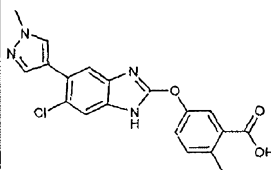
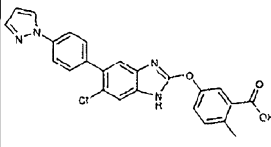
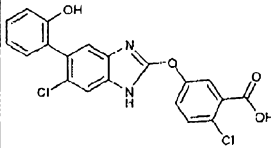
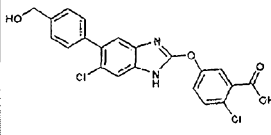
20	[4-(5-Biphenyl-4-yl-6-chloro-1H-benzimidazol-2-yloxy)-phenyl]-hydroxy-acetic acid		471
21	[3-(5-Biphenyl-4-yl-6-chloro-1H-benzimidazol-2-yloxy)-5-hydroxy-phenyl]-acetic acid		471
22	[3-(6-Chloro-5-phenylethynyl-1H-benzimidazol-2-yloxy)-phenyl]-acetic acid		403
23	2-[3-(6-Chloro-5-phenylethynyl-1H-benzimidazol-2-yloxy)-phenyl]-acetamide		402
24	3-[3-(6-Chloro-5-phenylethynyl-1H-benzimidazol-2-yloxy)-phenyl]-propionic acid		417
25	3-[4-(5-Biphenyl-4-yl-6-chloro-1H-benzimidazol-2-yloxy)-phenyl]-propionic acid		469
26	[4-(5-Biphenyl-4-yl-6-chloro-1H-benzimidazol-2-yloxy)-phenyl]-acetic acid		455

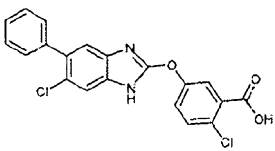
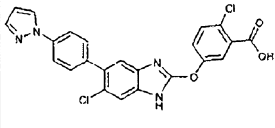
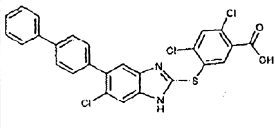
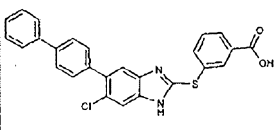
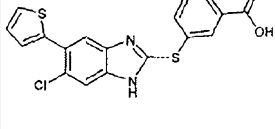
27	4-(5-Biphenyl-4-yl-6-chloro-1H-benzoimidazol-2-yloxy)-2-hydroxy-6-methyl-benzoic acid		471
28	5-(5-Biphenyl-4-yl-6-chloro-1H-benzoimidazol-2-yloxy)-2-hydroxy-benzoic acid		457
29	5-[4-(5-Biphenyl-4-yl-6-chloro-1H-benzoimidazol-2-yloxy)-phenyl]-imidazolidine-2,4-dione		495
30	4-(5-Biphenyl-4-yl-6-chloro-1H-benzoimidazol-2-yloxy)-benzamide		440
31	4-(5-Biphenyl-4-yl-6-chloro-1H-benzoimidazol-2-yloxy)-2-hydroxy-benzoic acid methyl ester		471
32	4-(5-Biphenyl-4-yl-6-chloro-1H-benzoimidazol-2-yloxy)-2-hydroxy-benzoic acid		457
33	5-Biphenyl-4-yl-6-chloro-2-[3-(2H-tetrazol-5-yl)-phenoxy]-1H-benzoimidazole		465

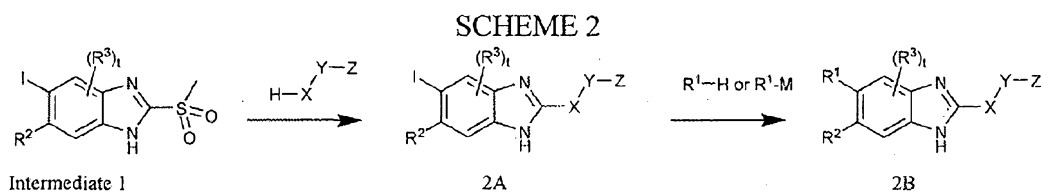
34	5-(5-Biphenyl-4-yl-6-chloro-1H-benzimidazol-2-yloxy)-nicotinic acid		442
35	3-(5-Biphenyl-4-yl-6-chloro-1H-benzimidazol-2-yloxy)-5-hydroxybenzoic acid		457
36	4-(5-Biphenyl-4-yl-6-chloro-1H-benzimidazol-2-yloxy)-phthalic acid		485
37	[3-(5-Biphenyl-4-yl-6-chloro-1H-benzimidazol-2-yloxy)-phenyl]-methanol		427
38	4-(5-Biphenyl-4-yl-6-chloro-1H-benzimidazol-2-yloxy)-benzoic acid		441
39	4-(5-Biphenyl-4-yl-6-chloro-1H-benzimidazol-2-yloxy)-2-chlorobenzoic acid		476
40	{5-[3-(5-Biphenyl-4-yl-6-chloro-1H-benzimidazol-2-yloxy)-phenyl]-tetrazol-2-yl}-acetic acid		523

41	{5-[3-(5-Biphenyl-4-yl-6-chloro-1H-benzoimidazol-2-yloxy)-phenyl]-tetrazol-2-yl}-acetic acid methyl ester		537
42	3-(5-Biphenyl-4-yl-6-chloro-1H-benzoimidazol-2-yloxy)-benzonitrile		422
43	5-(6-Chloro-5-phenylethynyl-1H-benzoimidazol-2-yloxy)-2-methylbenzoic acid		403
44	5-(5-Biphenyl-4-yl-6-chloro-1H-benzoimidazol-2-yloxy)-2-methylbenzoic acid		455
45	5-(6-Chloro-5-p-tolyethynyl-1H-benzoimidazol-2-yloxy)-2-methylbenzoic acid		417.36
46	5-(6-Chloro-5-p-tolyethynyl-1H-benzoimidazol-2-yloxy)-2-methylbenzoic acid methyl ester		421.24
47	5-[3-(5-Biphenyl-4-yl-6-chloro-1H-benzoimidazol-2-yloxy)-phenyl]-3H-[1,3,4]oxadiazol-2-		480.88

	one		
48	5-(6-Chloro-5-phenylethynyl-1H-benzimidazol-2-yloxy)-isophthalic acid		433.17
49	5-(6-Chloro-5-phenylethynyl-1H-benzimidazol-2-yloxy)-isophthalic acid dimethyl ester		461.7
50	3-(5-Biphenyl-4-yl-6-chloro-1H-benzimidazol-2-yloxy)-5-methylbenzoic acid		455.51
51	5-(6-Chloro-5-phenethyl-1H-benzimidazol-2-yloxy)-2-methylbenzoic acid		407.71
52	3-[6-Chloro-5-(2'-hydroxy-biphenyl-4-yl)-1H-benzimidazol-2-ylamino]-benzoic acid		456.93
53	3-[6-Chloro-5-(2'-hydroxy-biphenyl-4-yl)-1H-benzimidazol-2-yloxy]-5-methylbenzoic acid		471

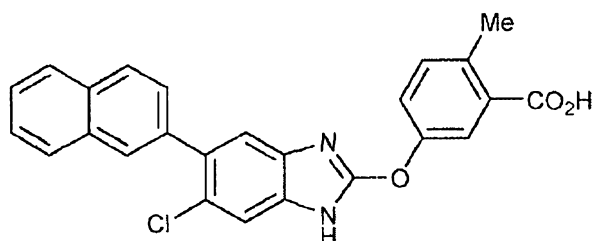
54	5-[6-Chloro-5-(2'-hydroxy-biphenyl-4-yl)-1H-benzimidazol-2-yloxy]-isophthalic acid		501
55	[5-(5-biphenyl-4-yl-6-chloro-1H-benzimidazol-2-ylsulfanyl)-tetrazol-1-yl]-acid, ammonium salt		462.9
56	3-(5-biphenyl-4-yl-6-chloro-1H-benzimidazol-2-yloxy)-benzoic acid, ammonium salt		441.34
57	5-[6-Chloro-5-(1-methyl-1H-pyrazol-4-yl)-1H-benzimidazol-2-yloxy]-2-methylbenzoic acid		383.4
58	5-[6-Chloro-5-(4-pyrazol-1-yl-phenyl)-1H-benzimidazol-2-yloxy]-2-methylbenzoic acid		445.5
59	2-Chloro-5-[6-chloro-5-(2-hydroxy-phenyl)-1H-benzimidazol-2-yloxy]-benzoic acid		416.1
60	2-Chloro-5-[6-chloro-5-(4-hydroxymethyl-phenyl)-1H-benzimidazol-2-yloxy]-benzoic acid		530.3

61	2-Chloro-5-(6-chloro-5-phenyl-1H-benzimidazol-2-yloxy)-benzoic acid		399.1
62	2-Chloro-5-[6-chloro-5-(4-pyrazol-1-yl-phenyl)-1H-benzimidazol-2-yloxy]-benzoic acid		465.2
63	5-[(5-biphenyl-4-yl-6-chloro-1H-benzimidazol-2-yl)thio]-2,4-dichloroben		524.9
64	3-[(5-biphenyl-4-yl-6-chloro-1H-benzimidazol-2-yl)thio]benzoic acid		457.1
65	3-{[6-chloro-5-(2-thienyl)-1H-benzimidazol-2-yl]thio}benzoic acid		388.0



In Scheme 2, Intermediate 1 is reacted with H-X-Y-Z (where X-H is an alcohol, thiol or amine) to afford the 2-substituted benzimidazole 2A. Subsequent reaction of 2A with a boronic acid, boronate ester or stannane (R^1 -M) in the presence of palladium tetrakis(triphenylphosphine) and, where appropriate, hydrolysis of ester Z affords the benzimidazole 2B. Alternatively, reaction of 2A with an acetylene (R^1 -H) in the presence of copper (I) iodide and bis(triphenylphosphine)palladium(II) chloride and, where appropriate, hydrolysis of ester Z affords the benzimidazole 2B.

EXAMPLE 66

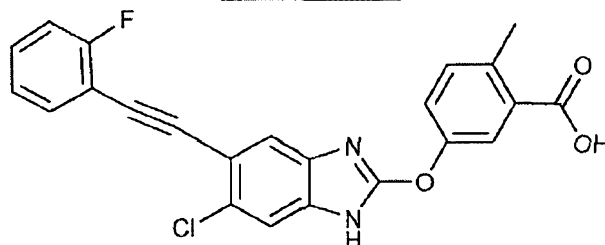


5-([6-chloro-5-(2-naphthyl)-1H-benzimidazol-2-yl]oxy)-2-methylbenzoic acid

Step A Methyl 5-([6-chloro-5-(2-naphthyl)-1H-benzimidazol-2-yl]oxy)-2-methylbenzoate. A microwave vial was charged with Intermediate 12 (95 mg, 0.215 mmol), 2-naphthyleneboronic acid pinacol ester (79 mg, 0.311 mmol), Pd(PPh₃)₄ (37 mg, 0.032 mmol), DMF (2.1 mL), and 1 M aqueous K₂CO₃ (0.64 mL). The reaction was heated at 150°C under microwave irradiation for 8 min. The reaction was partitioned between water and EtOAc. The aqueous phase was extracted with EtOAc. The combined organics were washed with brine, dried (Na₂SO₄), filtered and concentrated. Chromatography over silica eluting with 30% EtOAc/hexanes afforded the desired product as a yellow-orange oil.

Step B 5-([6-chloro-5-(2-naphthyl)-1H-benzimidazol-2-yl]oxy)-2-methylbenzoic acid. To a solution of methyl 5-([6-chloro-5-(2-naphthyl)-1H-benzimidazol-2-yl]oxy)-2-methylbenzoate in MeOH (3 mL) was added NaOH (2.5 M in water) (0.5 mL, 1 mmol). The mixture was heated at 50 °C and monitored by LC-MS. When the reaction was complete, it was partitioned between EtOAc and 2 M aqueous HCl. The aqueous phase was extracted with EtOAc. The combined organics were washed with brine, dried (MgSO₄), filtered, and concentrated. Purification by reverse phase HPLC eluting with MeCN:H₂O afforded the title compound as a white solid. LC-MS: calculated for C₂₅H₁₇ClN₂O₃ 428.87, observed m/e 429.5 (M + H)⁺ (R_t 2.19 min). ¹H NMR (500 MHz, CD₃OD): δ 7.92-7.84 (m, 5H), 7.58-7.54 (m, 1H), 7.53 (s, 1H), 7.52-7.48 (m, 2H), 7.46-7.39 (m, 3H), 2.62 (s, 3H).

EXAMPLE 67



5-([6-chloro-5-[(2-fluorophenyl)ethynyl]-1H-benzimidazol-2-yl]oxy)-2-methylbenzoic acid

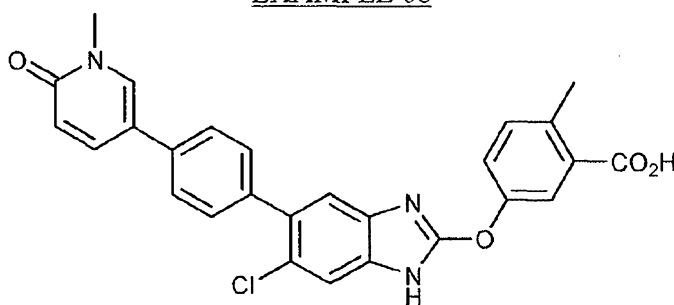
Step A Methyl 5-([6-chloro-5-[(2-fluorophenyl)ethynyl]-1H-benzimidazol-2-yl]oxy)-2-methylbenzoate. A mixture of Intermediate 12 (930mg, 2.1 mmol), 1-ethynyl-2-fluorobenzene (278 mg, 2.3 mmol), ammonia (3mL, 21mmol), copper(I) iodide (40 mg, 0.2 mmol) and bis(triphenylphosphine)palladium(II) chloride (147 mg, 0.2 mmol) in 10 mL DMF was heated under nitrogen at 140°C for 1 hour. Volatiles were removed. The residue was redissolved in

EtOAc and washed with NaHCO₃. Chromatography over silica afforded the desired product as a light yellow solid.

Step B 5-({6-chloro-5-[(2-fluorophenyl)ethynyl]-1*H*-benzimidazol-2-yl}oxy)-2-methylbenzoic acid. A solution of methyl 5-({6-chloro-5-[(2-fluorophenyl)ethynyl]-1*H*-benzimidazol-2-

yl}oxy)-2-methylbenzoate (910 mg, 2.1 mmol) and 4.2 mL 5 M aqueous NaOH in 15 mL MeOH and 15 mL water was heated at 70°C for 30 min. Volatiles were removed. The residue was dissolved in water (30 mL), and acidified with 2 N aqueous HCl, the precipitated solid was filtered (rinsing with water) and dried to afford the desired product as a white solid. LC/MS: calculated for C₂₃H₁₄ClFN₂O₃ 420, observed m/e 421 (M+H)⁺ (2.1/4min). ¹H NMR (500MHz, CD₃OD): δ7.88-7.16(9H, m), 2.61(3H, s).

EXAMPLE 68



5-({6-chloro-5-[4-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl]-1*H*-benzimidazol-2-yl}oxy)-2-methylbenzoic acid

Step A Methyl 5-({6-chloro-5-[4-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl]-1*H*-benzimidazol-2-yl}oxy)-2-methylbenzoate. Intermediate 12 (140 mg, 0.316 mmol), Intermediate 40 (118 mg, 0.38 mmol) and Pd(PPh₃)₄ (29 mg, 0.025mmol) were dissolved in DMF (1.4 mL). K₂CO₃ (1M in water) (0.95 mL, 0.950 mmol) was added, and the reaction was microwaved at 120 °C for 25 minutes. The reaction mixture was concentrated and partitioned between EtOAc (50mL) and water (50mL). The aqueous phase was extracted with EtOAc. The combined organics were washed with brine, dried (MgSO₄), filtered and concentrated. Purification by MS directed HPLC eluting with 20-80% acetonitrile:water afforded the product.

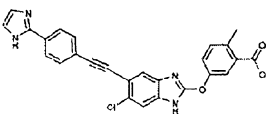
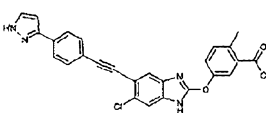
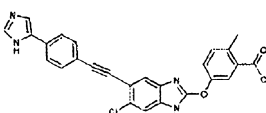
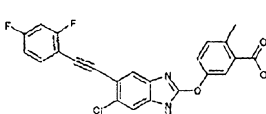
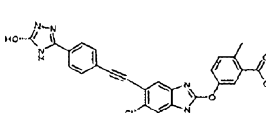
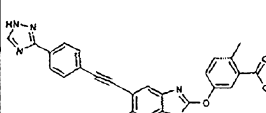
Step B 5-({6-chloro-5-[4-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl]-1*H*-benzimidazol-2-yl}oxy)-2-methylbenzoic acid. Methyl 5-({6-chloro-5-[4-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl]-1*H*-benzimidazol-2-yl}oxy)-2-methylbenzoate (43 mg, 0.086 mmol) was dissolved in MeOH (1.7 mL). Then 2.5 M aqueous NaOH (0.5 mL, 1.250 mmol) was added, and the reaction was stirred at 50 °C for 2 h. The reaction mixture was concentrated, and then partitioned between EtOAc and water. The aqueous phase was acidified to pH=1 with 2 N aqueous HCl and extracted with EtOAc. The combined organic extracts were dried (MgSO₄), filtered and concentrated to give the desired product as an off-white solid. LC-MS: calculated for C₂₇H₂₀ClN₃O₄ 485.11, observed m/e 486.25 (M+H)⁺ (R_t: 1.85min). ¹H NMR (500 MHz,

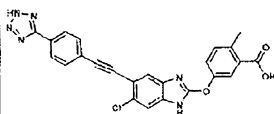
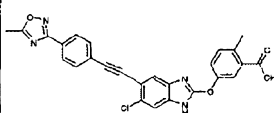
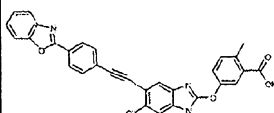
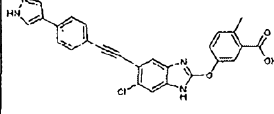
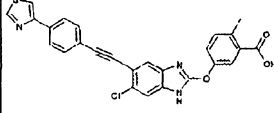
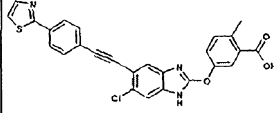
C₂D₆OS): δ 8.20 (s, 1H), 7.90 (d, 1H), 7.80 (s, 1H), 7.65 (d, 2H), 7.55 (s, 1H), 7.45-7.50 (m, 3H), 7.41 (d, 1H), 7.35 (s, 1H), 6.5 (d, 1H), 3.5 (s, 3H), 2.55 (s, 3H).

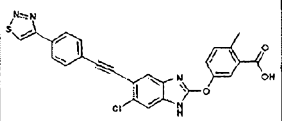
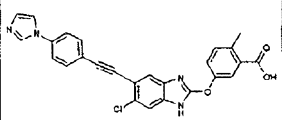
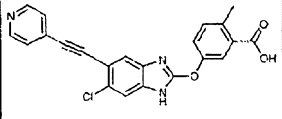
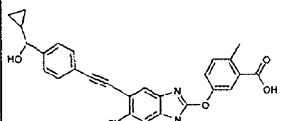
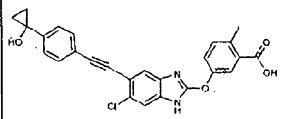
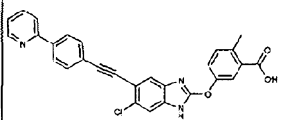
Examples 69-181 in Table 2 were prepared following the procedures described in Examples 66-68 by substituting the appropriate boronic acid, boronate ester, stannane or acetylene from the Intermediates, or from commercial sources; and by substituting the appropriate phenols from the Intermediates, or from commercial sources.

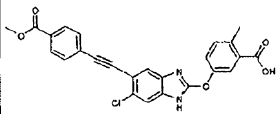
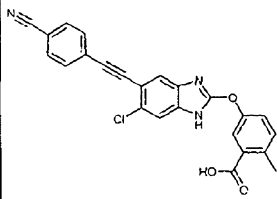
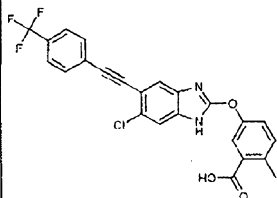
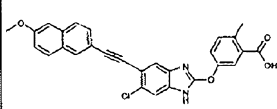
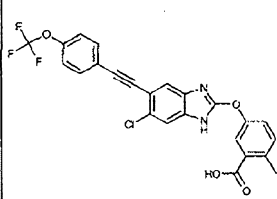
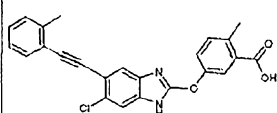
Table 2. Compounds prepared according to the methods described in Examples 66-68 and Scheme 2.

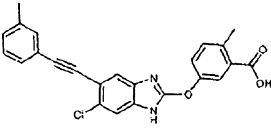
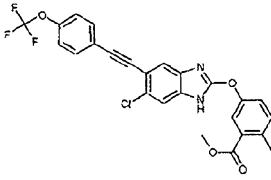
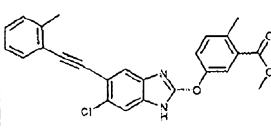
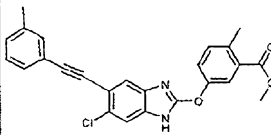
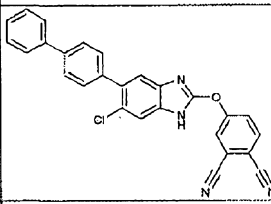
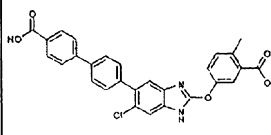
Ex. No.	Name	Structure	HPLC-mass spectrum <i>m/e</i>
69	5-{6-Chloro-5-[4-(2-hydroxy-ethyl)-phenylethynyl]-1 <i>H</i> -benzoimidazol-2-yloxy}-2-methyl-benzoic acid		448.06
70	5-[6-Chloro-5-(4-pyridin-3-yl-phenylethynyl)-1 <i>H</i> -benzoimidazol-2-yloxy]-2-methyl-benzoic acid		480.69
71	5-[6-Chloro-5-(4-pyrazol-1-yl-phenylethynyl)-1 <i>H</i> -benzoimidazol-2-yloxy]-2-methyl-benzoic acid		469.76
72	5-[5-(4-Aminomethyl-phenylethynyl)-6-chloro-1 <i>H</i> -benzoimidazol-2-yloxy]-2-methyl-benzoic acid		863.08 dimer

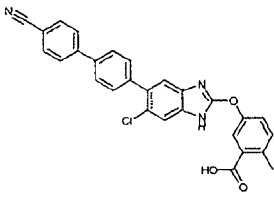
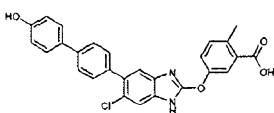
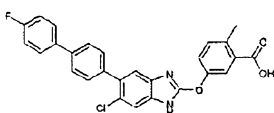
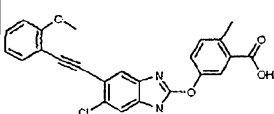
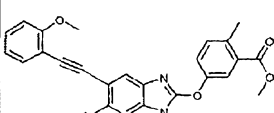
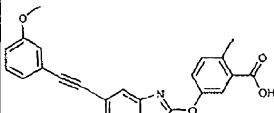
73	5-{6-Chloro-5-[4-(1 <i>H</i> -imidazol-2-yl)-phenylethynyl]-1 <i>H</i> -benzoimidazol-2-yloxy}-2-methylbenzoic acid		469.7
74	5-{6-Chloro-5-[4-(1 <i>H</i> -pyrazol-3-yl)-phenylethynyl]-1 <i>H</i> -benzoimidazol-2-yloxy}-2-methylbenzoic acid		469.07
75	5-{6-Chloro-5-[4-(3 <i>H</i> -imidazol-4-yl)-phenylethynyl]-1 <i>H</i> -benzoimidazol-2-yloxy}-2-methylbenzoic acid		469.02
76	5-[6-Chloro-5-(2,4-difluorophenylethynyl)-1 <i>H</i> -benzoimidazol-2-yloxy]-2-methylbenzoic acid		439.81
77	5-{6-Chloro-5-[4-(5-hydroxy-4 <i>H</i> -[1,2,4]triazol-3-yl)-phenylethynyl]-1 <i>H</i> -benzoimidazol-2-yloxy}-2-methylbenzoic acid		485.9
78	5-{6-Chloro-5-[4-(1 <i>H</i> -[1,2,4]triazol-3-yl)-phenylethynyl]-1 <i>H</i> -benzoimidazol-2-yloxy}-2-methylbenzoic acid		

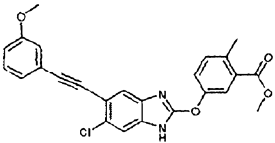
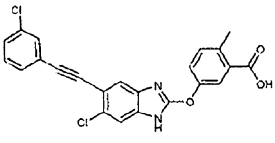
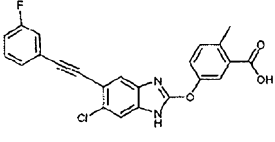
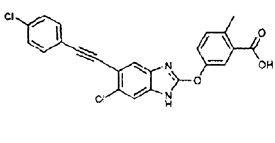
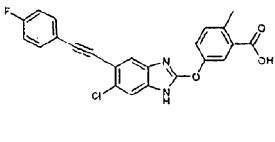
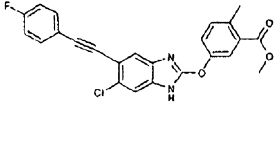
79	5-{6-Chloro-5-[4-(2H-tetrazol-5-yl)-phenylethynyl]-1H-benzoimidazol-2-yloxy}-2-methylbenzoic acid		471.98
80	5-{6-Chloro-5-[4-(5-methyl-[1,2,4]oxadiazol-3-yl)-phenylethynyl]-1H-benzoimidazol-2-yloxy}-2-methylbenzoic acid		486.44
81	5-[5-(4-Benzooxazol-2-yl-phenylethynyl)-6-chloro-1H-benzoimidazol-2-yloxy]-2-methylbenzoic acid		521.26
82	5-{6-Chloro-5-[4-(1H-pyrazol-4-yl)-phenylethynyl]-1H-benzoimidazol-2-yloxy}-2-methylbenzoic acid		469.69
83	5-[6-Chloro-5-(4-thiazol-4-yl-phenylethynyl)-1H-benzoimidazol-2-yloxy]-2-methylbenzoic acid		486.97
84	5-[6-Chloro-5-(4-thiazol-2-yl-phenylethynyl)-1H-benzoimidazol-2-yloxy]-2-methylbenzoic acid		487.26

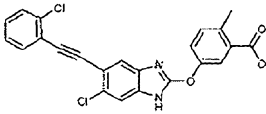
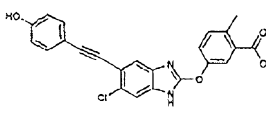
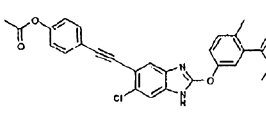
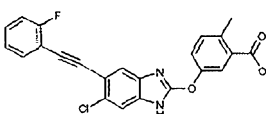
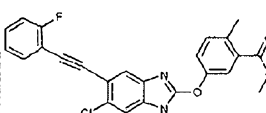
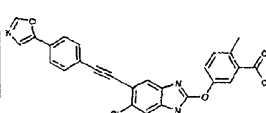
85	5-[6-Chloro-5-(4-[1,2,3]thiadiazol-4-yl-phenylethynyl)-1 <i>H</i> -benzoimidazol-2-yloxy]-2-methylbenzoic acid		487.6
86	5-[6-Chloro-5-(4-imidazol-1-yl-phenylethynyl)-1 <i>H</i> -benzoimidazol-2-yloxy]-2-methylbenzoic acid		469.61
87	5-(6-Chloro-5-pyridin-4-ylethynyl)-1 <i>H</i> -benzoimidazol-2-yloxy)-2-methylbenzoic acid		404.74
88	5-{6-Chloro-5-[4-(cyclopropyl-hydroxymethyl)-phenylethynyl]-1 <i>H</i> -benzoimidazol-2-yloxy}-2-methylbenzoic acid		473.7
89	5-{6-Chloro-5-[4-(1-hydroxy-cyclopropyl)-phenylethynyl]-1 <i>H</i> -benzoimidazol-2-yloxy}-2-methylbenzoic acid		459.79
90	5-[6-Chloro-5-(4-pyridin-2-yl-phenylethynyl)-1 <i>H</i> -benzoimidazol-2-yloxy]-2-methylbenzoic acid		480.66

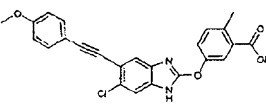
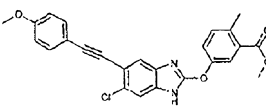
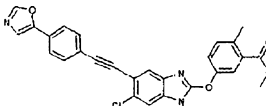
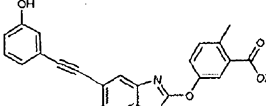
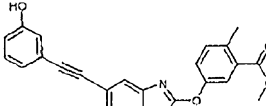
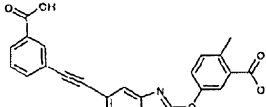
91	5-[6-Chloro-5-(4-methoxycarbonyl-phenylethynyl)-1 <i>H</i> -benzoimidazol-2-yloxy]-2-methylbenzoic acid		460.34
92	5-[6-Chloro-5-(4-cyano-phenylethynyl)-1 <i>H</i> -benzoimidazol-2-yloxy]-2-methylbenzoic acid		428.31
93	5-[6-Chloro-5-(4-trifluoromethyl-phenylethynyl)-1 <i>H</i> -benzoimidazol-2-yloxy]-2-methylbenzoic acid		471.32
94	5-[6-Chloro-5-(6-methoxy-naphthalen-2-ylethynyl)-1 <i>H</i> -benzoimidazol-2-yloxy]-2-methylbenzoic acid		483.37
95	5-[6-Chloro-5-(4-trifluoromethoxy-phenylethynyl)-1 <i>H</i> -benzoimidazol-2-yloxy]-2-methylbenzoic acid		487.4
96	5-(6-Chloro-5- <i>o</i> -tolylethynyl)-1 <i>H</i> -benzoimidazol-2-yloxy)-2-methylbenzoic acid		417.47

97	5-(6-Chloro-5- <i>m</i> -tolylethynyl-1 <i>H</i> -benzoimidazol-2-yloxy)-2-methylbenzoic acid		417.46
98	5-[6-Chloro-5-(4-trifluoromethoxyphenylethynyl)-1 <i>H</i> -benzoimidazol-2-yloxy]-2-methylbenzoic acid methyl ester		501.38
99	5-(6-Chloro-5- <i>o</i> -tolylethynyl-1 <i>H</i> -benzoimidazol-2-yloxy)-2-methylbenzoic acid methyl ester		431.42
100	5-(6-Chloro-5- <i>m</i> -tolylethynyl-1 <i>H</i> -benzoimidazol-2-yloxy)-2-methylbenzoic acid methyl ester		431.43
101	4-(5-Biphenyl-4-yl-6-chloro-1 <i>H</i> -benzoimidazol-2-yloxy)-phthalonitrile		447.55
102	4'-[2-(3-Carboxy-4-methyl-phenoxy)-6-chloro-1 <i>H</i> -benzoimidazol-5-yl]-biphenyl-4-carboxylic acid		498.31

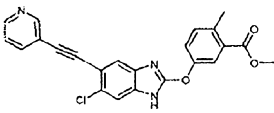
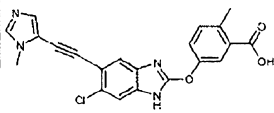
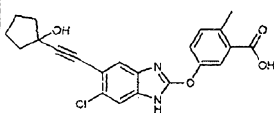
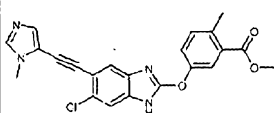
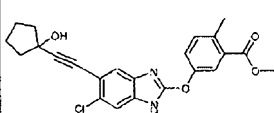
103	5-[6-Chloro-5-(4'-cyano-biphenyl-4-yl)-1 <i>H</i> -benzoimidazol-2-yloxy]-2-methylbenzoic acid		480.32
104	5-[6-Chloro-5-(4'-hydroxy-biphenyl-4-yl)-1 <i>H</i> -benzoimidazol-2-yloxy]-2-methylbenzoic acid		471.09
105	5-[6-Chloro-5-(4'-fluoro-biphenyl-4-yl)-1 <i>H</i> -benzoimidazol-2-yloxy]-2-methylbenzoic acid		473.27
106	5-[6-Chloro-5-(2-methoxyphenylethynyl)-1 <i>H</i> -benzoimidazol-2-yloxy]-2-methylbenzoic acid		433.27
107	5-[6-Chloro-5-(2-methoxyphenylethynyl)-1 <i>H</i> -benzoimidazol-2-yloxy]-2-methylbenzoic acid methyl ester		447.23
108	5-[6-Chloro-5-(3-methoxyphenylethynyl)-1 <i>H</i> -benzoimidazol-2-yloxy]-2-methylbenzoic acid		433.21

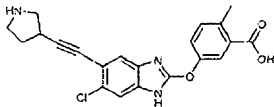
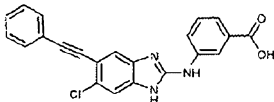
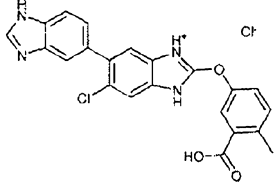
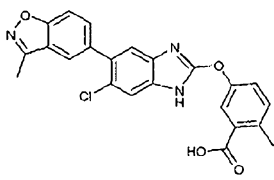
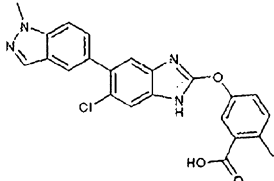
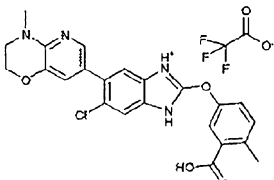
109	5-[6-Chloro-5-(3-methoxy-phenylethynyl)-1 <i>H</i> -benzimidazol-2-yloxy]-2-methylbenzoic acid methyl ester		447.25
110	5-[6-Chloro-5-(3-chloro-phenylethynyl)-1 <i>H</i> -benzimidazol-2-yloxy]-2-methylbenzoic acid		437.13
111	5-[6-Chloro-5-(3-fluoro-phenylethynyl)-1 <i>H</i> -benzimidazol-2-yloxy]-2-methylbenzoic acid		421.09
112	5-[6-Chloro-5-(4-chloro-phenylethynyl)-1 <i>H</i> -benzimidazol-2-yloxy]-2-methylbenzoic acid		437
113	5-[6-Chloro-5-(4-fluoro-phenylethynyl)-1 <i>H</i> -benzimidazol-2-yloxy]-2-methylbenzoic acid		421.08
114	5-[6-Chloro-5-(4-fluoro-phenylethynyl)-1 <i>H</i> -benzimidazol-2-yloxy]-2-methylbenzoic acid methyl ester		435.1

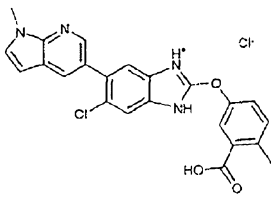
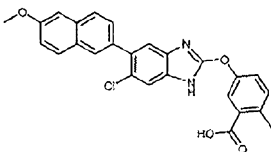
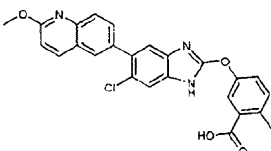
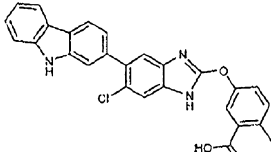
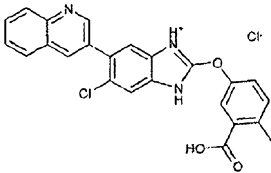
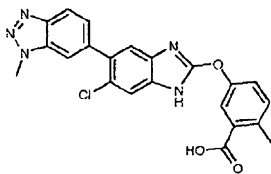
115	5-[6-Chloro-5-(2-chloro-phenylethynyl)-1 <i>H</i> -benzimidazol-2-yloxy]-2-methylbenzoic acid		437.08
116	5-[6-Chloro-5-(4-hydroxy-phenylethynyl)-1 <i>H</i> -benzimidazol-2-yloxy]-2-methylbenzoic acid		419.21
117	5-[5-(4-Acetoxy-phenylethynyl)-6-chloro-1 <i>H</i> -benzimidazol-2-yloxy]-2-methylbenzoic acid methyl ester		475.38
118	5-[6-Chloro-5-(2-fluoro-phenylethynyl)-1 <i>H</i> -benzimidazol-2-yloxy]-2-methylbenzoic acid		421
119	5-[6-Chloro-5-(2-fluoro-phenylethynyl)-1 <i>H</i> -benzimidazol-2-yloxy]-2-methylbenzoic acid methyl ester		435.03
120	5-[6-Chloro-5-(4-oxazol-5-yl-phenylethynyl)-1 <i>H</i> -benzimidazol-2-yloxy]-2-methylbenzoic acid		470.05

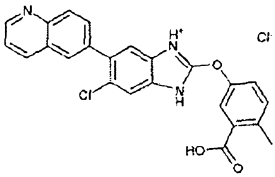
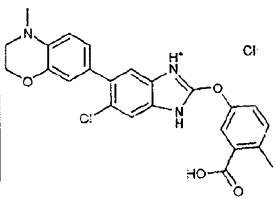
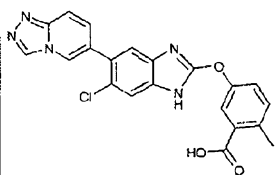
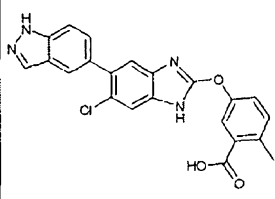
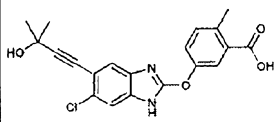
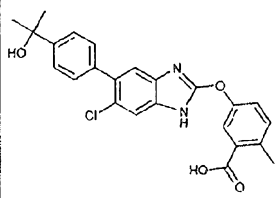
121	5-[6-Chloro-5-(4-methoxy-phenylethynyl)-1 <i>H</i> -benzoimidazol-2-yl]oxy]-2-methylbenzoic acid		433.09
122	5-[6-Chloro-5-(4-methoxy-phenylethynyl)-1 <i>H</i> -benzoimidazol-2-yl]oxy]-2-methylbenzoic acid methyl ester		447.16
123	5-[6-Chloro-5-(4-oxazol-5-yl-phenylethynyl)-1 <i>H</i> -benzoimidazol-2-yl]oxy]-2-methylbenzoic acid methyl ester		483
124	5-[6-Chloro-5-(3-hydroxy-phenylethynyl)-1 <i>H</i> -benzoimidazol-2-yl]oxy]-2-methylbenzoic acid		417.93
125	5-[6-Chloro-5-(3-hydroxy-phenylethynyl)-1 <i>H</i> -benzoimidazol-2-yl]oxy]-2-methylbenzoic acid methyl ester		431.93
126	5-[5-(3-Carboxy-phenylethynyl)-6-chloro-1 <i>H</i> -benzoimidazol-2-yl]oxy]-2-methylbenzoic acid		445.98

	loxy]-2-methylbenzoic acid		
127	5-({5-[(4-carboxy-2-methoxyphenyl)ethynyl]-6-chloro-1H-benzimidazol-2-yl}oxy)-2-methylbenzoic acid		476.88
128	5-[6-Chloro-5-(6-oxo-1,6-dihydro-pyridin-3-ylethynyl)-1H-benzimidazol-2-yl]oxy]-2-methylbenzoic acid		419.14
129	5-[6-Chloro-5-(6-methoxy-pyridin-3-ylethynyl)-1H-benzimidazol-2-yl]oxy]-2-methylbenzoic acid		433.12
130	5-[6-Chloro-5-(2-hydroxy-cyclopentylethynyl)-1H-benzimidazol-2-yl]oxy]-2-methylbenzoic acid		411.23
131	5-(6-Chloro-5-pyridin-3-ylethynyl-1H-benzimidazol-2-yl]oxy)-2-methylbenzoic acid		404.38
132	5-[6-Chloro-5-(6-methyl-pyridin-3-ylethynyl)-1H-benzimidazol-2-yl]oxy]-2-methylbenzoic acid		417.32

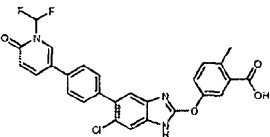
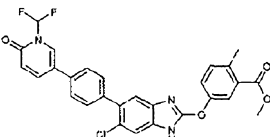
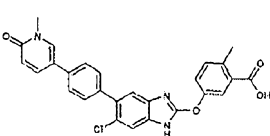
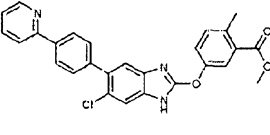
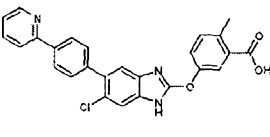
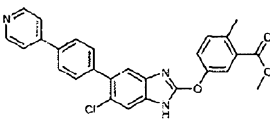
	loxy]-2-methyl- benzoic acid		
133	5-(6-Chloro-5-pyridin- 3-ylethynyl)-1 <i>H</i> - benzimidazol-2- loxy]-2-methyl- benzoic acid methyl ester		417.2
134	5-[6-Chloro-5-(3- methyl-3 <i>H</i> -imidazol- 4-ylethynyl)-1 <i>H</i> - benzimidazol-2- loxy]-2-methyl- benzoic acid		408.42
135	5-[6-Chloro-5-(1- hydroxy- cyclopentylethynyl)- 1 <i>H</i> -benzimidazol-2- loxy]-2-methyl- benzoic acid		411.97
136	5-[6-Chloro-5-(3- methyl-3 <i>H</i> -imidazol- 4-ylethynyl)-1 <i>H</i> - benzimidazol-2- loxy]-2-methyl- benzoic acid methyl ester		421.2
137	5-[6-Chloro-5-(1- hydroxy- cyclopentylethynyl)- 1 <i>H</i> -benzimidazol-2- loxy]-2-methyl- benzoic acid methyl ester		424.56

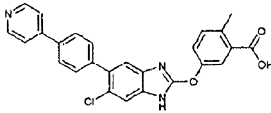
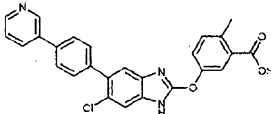
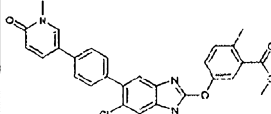
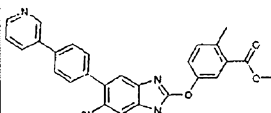
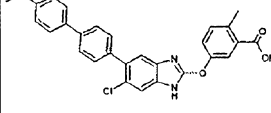
138	5-(6-Chloro-5-pyrrolidin-3-ylethynyl-1 <i>H</i> -benzoimidazol-2-yloxy)-2-methylbenzoic acid		396.21
139	3-(6-Chloro-5-phenylethynyl-1 <i>H</i> -benzoimidazol-2-ylamino)-benzoic acid		388.08
140	2-(3-Carboxy-4-methyl-phenoxy)-6-chloro-1 <i>H</i> ,1' <i>H</i> -[5,5']bibenzoimidazolyl-3-ium; chloride		419.6
141	5-[6-Chloro-5-(3-methylbenzo[<i>d</i>]isoxazol-5-yl)-1 <i>H</i> -benzoimidazol-2-yloxy]-2-methylbenzoic acid		434.3
142	5-[6-Chloro-5-(1-methyl-1 <i>H</i> -indazol-5-yl)-1 <i>H</i> -benzoimidazol-2-yloxy]-2-methylbenzoic acid		433.1
143	2-(3-carboxy-4-methylphenoxy)-6-chloro-5-(4-methyl-3,4-dihydro-2 <i>H</i> -pyrido[3,2- <i>b</i>][1,4]oxazin-7-yl)-1 <i>H</i> -3,1-benzimidazol-3-ium trifluoroacetate		451.3

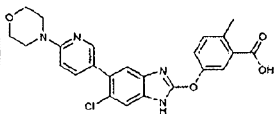
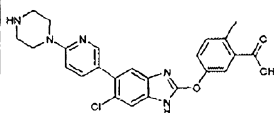
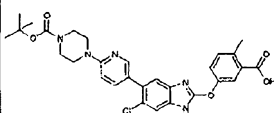
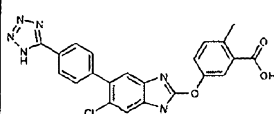
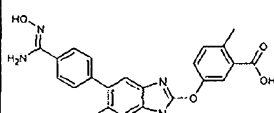
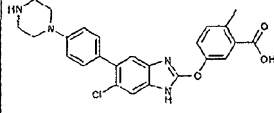
144	2-(3-carboxy-4-methylphenoxy)-6-chloro-5-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-3,1-benzimidazol-3-ium chloride		433.4
145	5-[6-Chloro-5-(6-methoxy-naphthalen-2-yl)-1H-benzoimidazol-2-yloxy]-2-methylbenzoic acid		459.2
146	5-[6-Chloro-5-(2-methoxy-quinolin-6-yl)-1H-benzoimidazol-2-yloxy]-2-methylbenzoic acid		460.1
147	5-[5-(9H-Carbazol-2-yl)-6-chloro-1H-benzoimidazol-2-yloxy]-2-methylbenzoic acid		468.3
148	2-(3-carboxy-4-methylphenoxy)-6-chloro-5-quinolin-3-yl-1H-3,1-benzimidazol-3-ium chloride		429.3
149	5-[6-Chloro-5-(3-methyl-3H-benzotriazol-5-yl)-1H-benzoimidazol-2-yloxy]-2-methylbenzoic acid		434.6

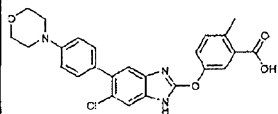
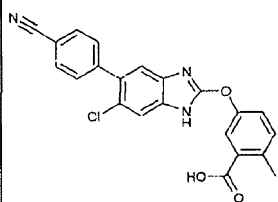
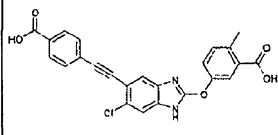
150	2-(3-carboxy-4-methylphenoxy)-6-chloro-5-quinolin-6-yl-1 <i>H</i> -3,1-benzimidazol-3-ium chloride		429.6
151	2-(3-carboxy-4-methylphenoxy)-6-chloro-5-(4-methyl-3,4-dihydro-2 <i>H</i> -1,4-benzoxazin-7-yl)-1 <i>H</i> -3,1-benzimidazol-3-ium chloride		
152	5-(6-Chloro-5-[1,2,4]triazolo[4,3- <i>a</i>]pyridin-6-yl)-1 <i>H</i> -benzoimidazol-2-yloxy)-2-methylbenzoic acid		420.9
153	5-[6-Chloro-5-(1 <i>H</i> -indazol-5-yl)-1 <i>H</i> -benzoimidazol-2-yloxy]-2-methylbenzoic acid		418.9
154	5-[6-Chloro-5-(3-hydroxy-3-methyl-but-1-ynyl)-1 <i>H</i> -benzoimidazol-2-yloxy]-2-methylbenzoic acid		386.4
155	5-{6-Chloro-5-[4-(1-hydroxy-1-methyl-ethyl)-phenyl]-1 <i>H</i> -benzoimidazol-2-yloxy}-2-methylbenzoic acid		437.4

156	5-{6-Chloro-5-[4-(1-hydroxy-ethyl)-phenyl]-1 <i>H</i> -benzoimidazol-2-yl-oxy}-2-methyl-benzoic acid		423.8
157	5-[5-(4-Acetyl-phenyl)-6-chloro-1 <i>H</i> -benzoimidazol-2-yl-oxy]-2-methyl-benzoic acid		421.5
158	2-(3-carboxy-4-methylphenoxy)-6-chloro-5-(1-pyrimidin-2-yl-1,2,3,6-tetrahydropyridin-4-yl)-1 <i>H</i> -3,1-benzimidazol-3-ium trifluoroacetate		461.7
159	5-[6-Chloro-5-(1-isobutyl-1 <i>H</i> -pyrazol-4-yl)-1 <i>H</i> -benzoimidazol-2-yl-oxy]-2-methyl-benzoic acid		425.7
160	5-[6-Chloro-5-(1 <i>H</i> -pyrazol-4-yl)-1 <i>H</i> -benzoimidazol-2-yl-oxy]-2-methyl-benzoic acid		369.0
161	5-{6-Chloro-5-[4-(1-oxy-pyridin-3-yl)-phenyl]-1 <i>H</i> -benzoimidazol-2-yl-oxy}-2-methyl-benzoic acid		

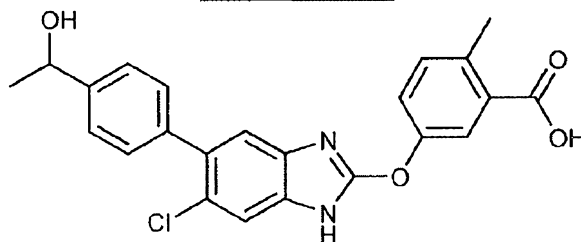
162	5-{6-Chloro-5-[4-(1-difluoromethyl-6-oxo-1,6-dihydro-pyridin-3-yl)-phenyl]-1 <i>H</i> -benzoimidazol-2-yloxy}-2-methyl-benzoic acid		522.3
163	5-{6-Chloro-5-[4-(1-difluoromethyl-6-oxo-1,6-dihydro-pyridin-3-yl)-phenyl]-1 <i>H</i> -benzoimidazol-2-yloxy}-2-methyl-benzoic acid methyl ester		536.4
164	5-{6-Chloro-5-[4-(1-methyl-6-oxo-1,6-dihydro-pyridin-3-yl)-phenyl]-1 <i>H</i> -benzoimidazol-2-yloxy}-2-methyl-benzoic acid		486.25
165	5-[6-Chloro-5-(4-pyridin-2-yl-phenyl)-1 <i>H</i> -benzoimidazol-2-yloxy]-2-methyl-benzoic acid methyl ester		470.17
166	5-[6-Chloro-5-(4-pyridin-2-yl-phenyl)-1 <i>H</i> -benzoimidazol-2-yloxy]-2-methyl-benzoic acid		456.14
167	5-[6-Chloro-5-(4-pyridin-4-yl-phenyl)-1 <i>H</i> -benzoimidazol-2-yloxy]-2-methyl-		470.19

	benzoic acid methyl ester		
168	5-[6-Chloro-5-(4-pyridin-4-yl-phenyl)-1 <i>H</i> -benzoimidazol-2-yl-oxy]-2-methyl-benzoic acid		456.17
169	5-[6-Chloro-5-(4-pyridin-3-yl-phenyl)-1 <i>H</i> -benzoimidazol-2-yl-oxy]-2-methyl-benzoic acid		456.5
170	5-{6-Chloro-5-[4-(1-methyl-6-oxo-1,6-dihydro-pyridin-3-yl)-phenyl]-1 <i>H</i> -benzoimidazol-2-yl-oxy}-2-methyl-benzoic acid methyl ester		500.4
171	5-[6-Chloro-5-(4-pyridin-3-yl-phenyl)-1 <i>H</i> -benzoimidazol-2-yl-oxy]-2-methyl-benzoic acid methyl ester		470.21
172	5-[6-Chloro-5-(4'-methoxy-biphenyl-4-yl)-1 <i>H</i> -benzoimidazol-2-yl-oxy]-2-methyl-benzoic acid		484.96

173	5-[6-Chloro-5-(6-morpholin-4-yl-pyridin-3-yl)-1 <i>H</i> -benzoimidazol-2-yloxy]-2-methylbenzoic acid		465.9
174	5-[6-Chloro-5-(6-piperazin-1-yl-pyridin-3-yl)-1 <i>H</i> -benzoimidazol-2-yloxy]-2-methylbenzoic acid		464.1
175	4-{5-[2-(3-Carboxy-4-methyl-phenoxy)-6-chloro-1 <i>H</i> -benzoimidazol-5-yl]-pyridin-2-yl}-piperazine-1-carboxylic acid <i>tert</i> -butyl ester		564.1
176	5-{6-Chloro-5-[4-(1 <i>H</i> -tetrazol-5-yl)-phenyl]-1 <i>H</i> -benzoimidazol-2-yloxy}-2-methylbenzoic acid		
177	5-{6-Chloro-5-[4-(<i>N</i> -hydroxycarbamimidoyl)-phenyl]-1 <i>H</i> -benzoimidazol-2-yloxy}-2-methylbenzoic acid		
178	5-[6-Chloro-5-(4-piperazin-1-yl-phenyl)-1 <i>H</i> -benzoimidazol-2-yloxy]-2-methylbenzoic acid		463.4

179	5-[6-Chloro-5-(4-morpholin-4-yl-phenyl)-1 <i>H</i> -benzimidazol-2-yloxy]-2-methylbenzoic acid		464.3
180	5-[6-Chloro-5-(4-cyano-phenyl)-1 <i>H</i> -benzimidazol-2-yloxy]-2-methylbenzoic acid		404.0
181	5-[5-(4-Carboxyphenylethynyl)-6-chloro-1 <i>H</i> -benzimidazol-2-yloxy]-2-methylbenzoic acid		

EXAMPLE 182



5-({6-chloro-5-[4-(1-hydroxyethyl)phenyl]-1*H*-benzimidazol-2-yl}oxy)-2-methylbenzoic acid

- 5 Step A Methyl 5-([5-(4-acetylphenyl)-6-chloro-1*H*-benzimidazol-2-yl]oxy)-2-methylbenzoate.
A microwave vial was charged with Intermediate 12 (176 mg, 0.398 mmol), 1-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]ethanone (147 mg, 0.596 mmol), Pd(PPh₃)₄ (23 mg, 0.020 mmol), dioxane (2 mL), and 1 M aqueous K₂CO₃ (1.2 mL). The reaction was sealed and microwaved at 120 °C for 25 min. An additional 40 mg of Pd(PPh₃)₄ was added and the reaction
10 was microwaved for another 30 min. The reaction was extracted with EtOAc. The combined organic extracts were dried (Na₂SO₄), filtered, and concentrated. Chromatography over silica eluting with 40% EtOAc/hexanes afforded the desired compound.

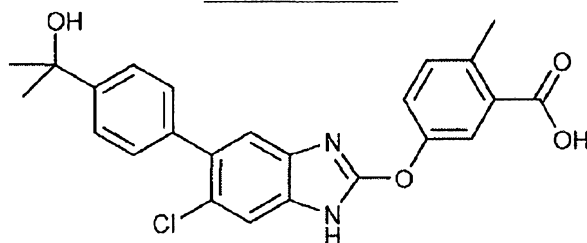
- Step B Methyl 5-({6-chloro-5-[4-(1-hydroxyethyl)phenyl]-1*H*-benzimidazol-2-yl}oxy)-2-methylbenzoate. To a 0 °C solution of methyl 5-([5-(4-acetylphenyl)-6-chloro-1*H*-
15 benzimidazol-2-yl]oxy)-2-methylbenzoate (50 mg, 0.115 mmol) in MeOH (2 mL) was added NaBH₄ (6.5 mg, 0.172 mmol). The mixture was warmed to rt and stirred for 15 min. Water (5-6

drops) was added and the mixture was concentrated. The residue was partitioned between Et₂O and water. The aqueous phase was extracted with Et₂O. The combined ethereal extracts were washed with brine, dried (MgSO₄), filtered, and concentrated to afford the desired product, which was used in the next step without further purification.

- 5 Step C 5-({6-chloro-5-[4-(1-hydroxyethyl)phenyl]-1H-benzimidazol-2-yl}oxy)-2-methylbenzoic acid. 2.5 M NaOH (0.2 mL, 0.500 mmol) was added to a solution of methyl 5-({6-chloro-5-[4-(1-hydroxyethyl)phenyl]-1H-benzimidazol-2-yl}oxy)-2-methylbenzoate in MeOH (2.5 mL). Additional 2.5 M NaOH (0.250 mL, 0.625 mmol) was added and the reaction was stirred at rt overnight. The reaction mixture was diluted with Et₂O (50 mL) and washed with 10 mL of 1 M aqueous HCl. The aqueous phase was extracted with Et₂O. The combined organics were washed with brine, dried (MgSO₄), filtered, and concentrated to afford the desired product. LC-MS: calculated for C₂₃H₁₉ClN₂O₄ 422.86, observed m/e 423.8 (M+H)⁺ (R_t: 1.74 min). ¹H NMR (500 MHz, CD₃OD): δ 7.85 (d, 1H), 7.47 (s, 1H), 7.44-7.36 (m, 6H), 7.30 (s, 1H), 4.87 (m, 1H), 2.61 (s, 3H), 1.48 (d, 3H).

15

EXAMPLE 183

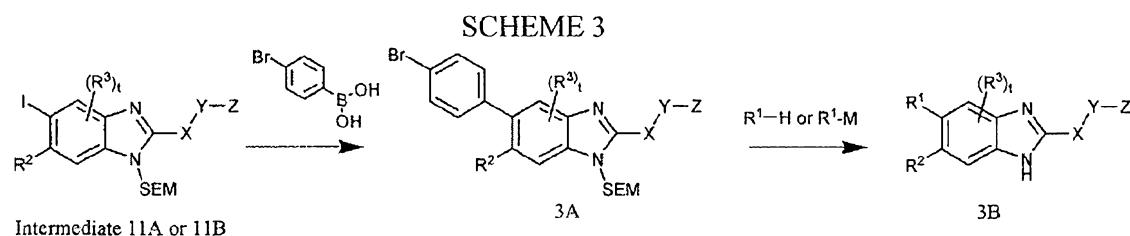


5-({6-chloro-5-[4-(1-hydroxy-1-methylethyl)phenyl]-1H-benzimidazol-2-yl}oxy)-2-methylbenzoic acid

- Step A 5-({[5-(4-acetylphenyl)-6-chloro-1H-benzimidazol-2-yl]oxy}-2-methylbenzoic acid. Methyl 5-({[5-(4-acetylphenyl)-6-chloro-1H-benzimidazol-2-yl]oxy}-2-methylbenzoate (174 mg, 0.4 mmol, from Example 182 Step A) was dissolved in 5 mL MeOH and treated with 1.0 mL of 2.5 N NaOH. The mixture was heated to 45 °C for 4 h. Ether (50 mL) was added. The resulting layers were separated and the organic layer was washed with 1 M aqueous HCl (10 mL). The aqueous phase was extracted with Et₂O. The combined organic layers were washed with brine, dried (Na₂SO₄), filtered and concentrated. Purification by reverse phase HPLC eluting with MeCN:H₂O afforded the desired product.
- Step B 5-({6-chloro-5-[4-(1-hydroxy-1-methylethyl)phenyl]-1H-benzimidazol-2-yl}oxy)-2-methylbenzoic acid. To a 0 °C suspension of 5-({[5-(4-acetylphenyl)-6-chloro-1H-benzimidazol-2-yl]oxy}-2-methylbenzoic acid (52 mg, 0.124 mmol) and CeCl₃ (244 mg, 0.988 mmol) in THF (4 mL) was added MeMgBr (1.4 M in THF) (0.618 mL, 0.865 mmol) dropwise via syringe. The reaction was stirred at rt for 30 min, diluted with Et₂O (50 mL) and washed with 1 M HCl (10 mL). The aqueous phase was extracted with Et₂O. The combined organics were washed with H₂O and brine, dried (Na₂SO₄), filtered and concentrated. Purification by reverse phase HPLC

eluting with MeCN:H₂O afforded the desired product as an off-white solid. LC-MS: calculated for C₂₄H₂₁ClN₂O₄ 436.89, observed m/e 437.2 (M+H)⁺ (R_t: 1.81 min). ¹H NMR (500 MHz, CD₃OD): δ 7.89 (d, 1H), 7.54 (d, 2H), 7.49 (s, 1H), 7.47-7.39 (m, 2H), 7.37 (m, 2H), 7.32 (s, 1H), 2.62 (s, 3H), 1.57 (s, 6H).

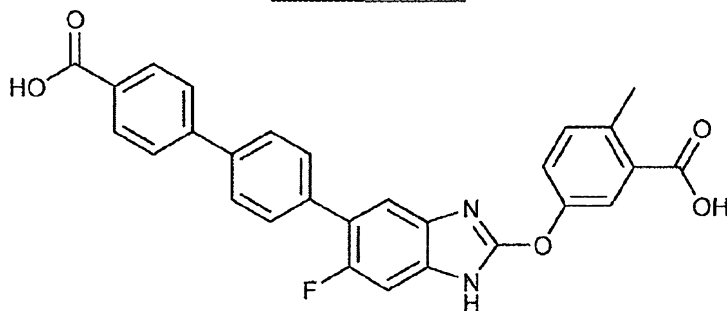
5



In Scheme 3, Intermediate 11A or 11B is reacted with *para*-bromophenylboronic acid in the presence of palladium tetrakis(triphenyl)phosphine to afford the phenyl-substituted benzimidazole 3A. Subsequent reaction of 3A with a boronic acid, boronate ester or stannane (R¹-M) in the presence of palladium tetrakis(triphenyl)phosphine and, where appropriate, hydrolysis of ester Z affords the benzimidazole 3B. Alternatively, reaction of 3A with an acetylene (R¹-H) in the presence of copper (I) iodide and bis(triphenylphosphine)palladium (II) chloride and, where appropriate, hydrolysis of ester Z, affords the benzimidazole 3B.

15

EXAMPLE 184



4'-[2-(3-carboxy-4-methylphenoxy)-6-fluoro-1H-benzimidazol-5-yl]biphenyl-4-carboxylic acid

Step A Methyl 5-[(5-(4-bromophenyl)-6-fluoro-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-benzimidazol-2-yl)oxy]-2-methylbenzoate. Potassium phosphate, tribasic (2 M solution in water) (9.5 mL, 19 mmol) and Pd(PPh₃)₄ (0.7 g, 0.6 mmol) were added to a solution of 4-bromophenylboronic acid (1.4 g, 7 mmol) and Intermediate 11B (3.5 g, 6.3 mmol) in dioxane (100 mL). The reaction was heated at 110°C for 1 h. The aqueous phase was removed and the organic phase was concentrated. Chromatography over silica eluting with 20% EtOAc/hexane afforded the desired product as white solid.

25

Step B Ethyl, 4'-(6-fluoro-2-[3-(methoxycarbonyl)-4-methylphenoxy]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-benzimidazol-5-yl)biphenyl-4-carboxylate. Potassium phosphate, tribasic (2 M solution in water) (3.2 mL, 6.3 mmol) and Pd(PPh₃)₄ (0.12 g, 0.1 mmol) were added to a

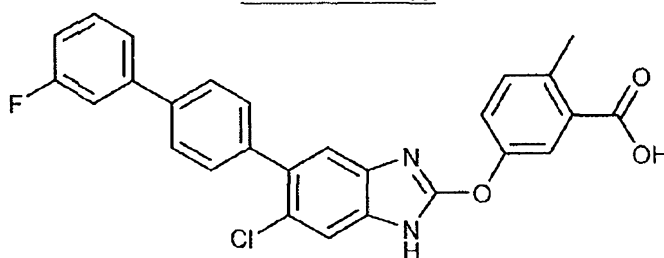
solution of [4-(ethoxycarbonyl)phenyl]boronic acid (0.5 g, 2.5 mmol) and methyl 5-[(5-(4-bromophenyl)-6-fluoro-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-benzimidazol-2-yl)oxy]-2-methylbenzoate (1.23 g, 2.1 mmol) in dioxane (100 mL). The reaction was heated at 110°C for 2 h. The aqueous phase was removed and the organic phase was concentrated. Chromatography over silica eluting with 10% EtOAc/hexane afforded the desired product as white solid.

Step C Ethyl, 4'-{6-fluoro-2-[3-(methoxycarbonyl)-4-methylphenoxy]-1H-benzimidazol-5-yl}biphenyl-4-carboxylate. Ethyl, 4'-(6-fluoro-2-[3-(methoxycarbonyl)-4-methylphenoxy]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-benzimidazol-5-yl)biphenyl-4-carboxylate (0.94 g, 1.44 mmol) was dissolved in 4 M HCl in dioxane (10 mL) and stirred at room temperature for 2 days.

Volatiles were removed and the residue was extracted with ethyl acetate and washed with saturated aqueous NaHCO₃, dried (Na₂SO₄) and concentrated. Chromatography over silica eluting with 40% EtOAc/hexane afforded the desired product as white solid.

Step D 4'-[2-(3-carboxy-4-methylphenoxy)-6-fluoro-1H-benzimidazol-5-yl]biphenyl-4-carboxylic acid. 5 M aqueous NaOH (3 mL) was added to a solution of ethyl, 4'-{6-fluoro-2-[3-(methoxycarbonyl)-4-methylphenoxy]-1H-benzimidazol-5-yl}biphenyl-4-carboxylate (750 mg, 1.43 mmol) in MeOH (30 mL). The solution was diluted with water until cloudy and heated at 70°C for 20 min. Volatiles were removed and the residue was dissolved in 20 mL water and acidified with 2 N aqueous HCl. The precipitated white solid was filtered and dried to afford the title compound as a white solid. LC-MS: calculated for C₂₈H₁₉FN₂O₅ 482.46, observed m/e 483.11 (M + H)⁺ (R_t 1.91/4.0 min). ¹H NMR (500 MHz, CD₃OD): δ 8.18-7.25 (m, 13H), 2.62 (s, 3H).

EXAMPLE 185



5-{[6-chloro-5-(3'-fluorobiphenyl-4-yl)-1H-benzimidazol-2-yl]oxy}-2-methylbenzoic acid

Step A Methyl 5-{[5-(4-bromophenyl)-6-chloro-1H-benzimidazol-2-yl]oxy}-2-methylbenzoate. K₂CO₃ (1 M in water) (17 mL, 17.60 mmol) was added to a solution of Intermediate 12 (2 g, 4.52 mmol), *para*-bromophenylboronic acid (1.9 g, 9.49 mmol) and Pd(PPh₃)₄ (470 mg, 0.407 mmol) in dioxane (65 mL). The reaction was microwaved at 120 °C for 40 minutes. Volatiles were removed. The residue was partitioned between EtOAc (100 mL), and water (100 mL). The aqueous phase was extracted with EtOAc (3 x 70 mL). Combined organics were washed with brine, dried (MgSO₄), filtered and concentrated. Chromatography over silica eluting with 30% EtOAc / hexanes afforded the desired product.

Step B Methyl 5-{[6-chloro-5-(3'-fluorobiphenyl-4-yl)-1H-benzimidazol-2-yl]oxy}-2-

methylbenzoate. K_2CO_3 (1 M in water) (0.16 mL, 0.162 mmol) was added to a solution of methyl 5-{[5-(4-bromophenyl)-6-chloro-1*H*-benzimidazol-2-yl]oxy}-2-methylbenzoate (25.5 mg, 0.054 mmol), 3-fluorophenylboronic acid (9 mg, 0.068 mmol) and $Pd(PPh_3)_4$ (6 mg) in dioxane (1 mL). The reaction was microwaved at 150°C for 8 minutes. Volatiles were removed.

- 5 The residue was partitioned between EtOAc (50 mL), and water (50 mL). The aqueous phase was extracted with EtOAc (3 x 40 mL). Combined organics were washed with brine, dried ($MgSO_4$), filtered and concentrated. Purification by HPLC eluting with 10-90% MeCN:water afforded the desired product.

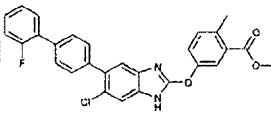
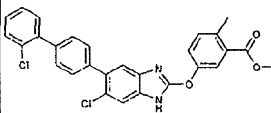
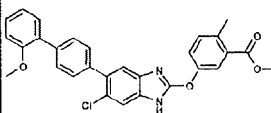
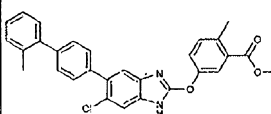
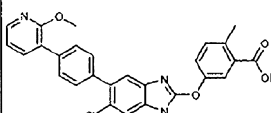
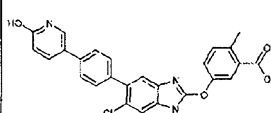
- Step C 5-{[6-chloro-5-(3'-fluorobiphenyl-4-yl)-1*H*-benzimidazol-2-yl]oxy}-2-methylbenzoic acid. NaOH (5M in water) (0.12 mL, 0.600 mmol) was added to a solution of methyl 5-{[6-chloro-5-(3'-fluorobiphenyl-4-yl)-1*H*-benzimidazol-2-yl]oxy}-2-methylbenzoate (8.5 mg, 0.017 mmol) in MeOH (1 mL). The reaction was stirred at 50 °C for 2 h. Volatiles were removed. The residue was partitioned between EtOAc and water. The aqueous phase was acidified to pH=1 with 2 N aqueous HCl and extracted with ethyl acetate (3 x 30 mL). Combined organics were dried ($MgSO_4$), filtered and concentrated to obtain the desired product. LC-MS: calculated for $C_{27}H_{18}ClFN_2O_3$ 472.10, observed m/e 473.2 ($M+H$)⁺ (R_t : 2.28min). 1H NMR (500 MHz, CD_3OD): δ 7.90 (d, 1H), 7.70 (d, 2H), 7.40-7.55 (m, 9H), 7.05 (t, 1H), 2.61 (s, 3H).
- 15

- Examples 186-205 in Table 3 were prepared following the procedures described in Examples 184-185 by substituting the appropriate boronic acid, boronate ester, stannane or acetylene from the Intermediates, or from commercial sources.
- 20

Table 3. Compounds prepared according to the methods described in Examples 184-185 and Scheme 3.

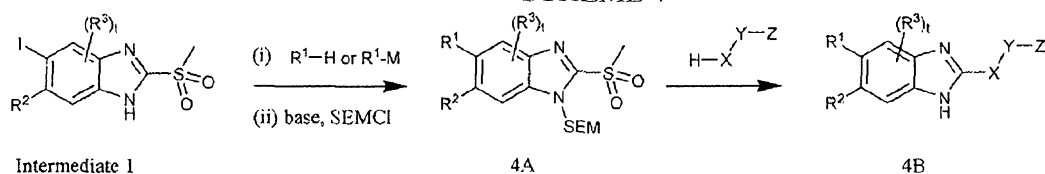
Ex. No.	Name	Structure	HPLC-mass spectrum m/e
186	5-{[6-chloro-5-(3'-chlorobiphenyl-4-yl)-1 <i>H</i> -benzimidazol-2-yl]oxy}-2-methylbenzoic acid		489.0
187	5-{[6-chloro-5-(3'-methoxybiphenyl-4-yl)-1 <i>H</i> -benzimidazol-2-yl]oxy}-2-methylbenzoic acid		484.0

188	5-({6-chloro-5-[4-(6-hydroxypyridin-3-yl)phenyl]-1H-benzimidazol-2-yl}oxy)-2-methylbenzoic acid		486.2
189	5-{{6-chloro-5-(3'-chlorobiphenyl-4-yl)-1H-benzimidazol-2-yl}oxy}-2-methylbenzoic acid		503.1
190	5-{{6-chloro-5-(3'-methoxybiphenyl-4-yl)-1H-benzimidazol-2-yl}oxy}-2-methylbenzoic acid		4.98
191	5-{{6-chloro-5-(2'-chlorobiphenyl-4-yl)-1H-benzimidazol-2-yl}oxy}-2-methylbenzoic acid		489.35
192	5-{{6-chloro-5-(2'-fluorobiphenyl-4-yl)-1H-benzimidazol-2-yl}oxy}-2-methylbenzoic acid		473.33
193	5-{{6-chloro-5-(2'-methylbiphenyl-4-yl)-1H-benzimidazol-2-yl}oxy}-2-methylbenzoic acid		469.31
194	5-{{6-chloro-5-(2'-methoxybiphenyl-4-yl)-1H-benzimidazol-2-yl}oxy}-2-methylbenzoic acid		485.13

195	Methyl 5-{{6-chloro-5-(2'-fluorobiphenyl-4-yl)-1H-benzimidazol-2-yl}oxy}-2-methylbenzoate		487.22
196	Methyl 5-{{6-chloro-5-(2'-chlorobiphenyl-4-yl)-1H-benzimidazol-2-yl}oxy}-2-methylbenzoate		503.17
197	Methyl 5-{{6-chloro-5-(2'-methoxybiphenyl-4-yl)-1H-benzimidazol-2-yl}oxy}-2-methylbenzoate		499.23
198	Methyl 5-{{6-chloro-5-(2'-methylbiphenyl-4-yl)-1H-benzimidazol-2-yl}oxy}-2-methylbenzoate		483.18
199	5-({6-chloro-5-[4-(2-methoxypyridin-3-yl)phenyl]-1H-benzimidazol-2-yl}oxy)-2-methylbenzoic acid		485.5
200	5-({6-chloro-5-[4-(6-hydroxypyridin-3-yl)phenyl]-1H-benzimidazol-2-yl}oxy)-2-methylbenzoic acid		473.1

201	5-({6-chloro-5-[4-(6-methoxypyridin-3-yl)phenyl]-1H-benzimidazol-2-yl}oxy)-2-methylbenzoic acid		486.5
202	5-({6-chloro-5-[4-(1H-pyrazol-4-yl)phenyl]-1H-benzimidazol-2-yl}oxy)-2-methylbenzoic acid		445.3
203	5-({6-chloro-5-[4-(3,5-dimethyl-1H-pyrazol-4-yl)phenyl]-1H-benzimidazol-2-yl}oxy)-2-methylbenzoic acid		473.0
204	5-({6-chloro-5-[4-(3,5-dimethylisoxazol-4-yl)phenyl]-1H-benzimidazol-2-yl}oxy)-2-methylbenzoic acid		474.7
205	5-{[5-(2'-aminobiphenyl-4-yl)-6-chloro-1H-benzimidazol-2-yl]oxy}-2-methylbenzoic acid		470.0

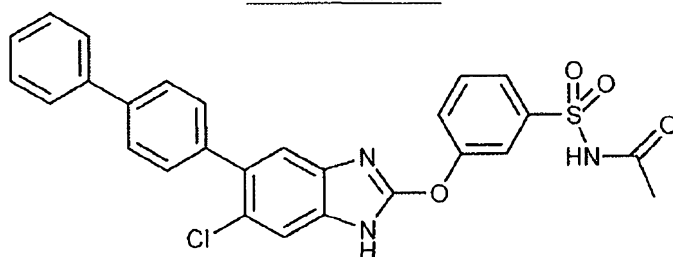
SCHEME 4



In Scheme 4, Intermediate 1 is reacted with a boronic acid, boronate ester or stannane

(R¹-M) in the presence of palladium tetrakis(triphenylphosphine) followed by reaction with SEMCl and base to afford compound 4A. Alternatively, Intermediate 1 is reacted with an acetylene (R¹-H) in the presence of copper (I) iodide and bis(triphenylphosphine)palladium (II) chloride, followed by reaction with SEMCl and base to afford compound 4A. Subsequent
 5 reaction of compound 4A with H-X-Y-Z (where X-H is an alcohol, thiol or amine), followed by removal of the SEM group and, where appropriate, hydrolysis of ester Z affords the 2-substituted benzimidazole 4B.

EXAMPLE 206



10 N-Acetyl-3-(5-biphenyl-4-yl-6-chloro-1H-benzimidazol-2-yloxy)-benzenesulfonamide

Step A 5-biphenyl-4-yl-6-chloro-2-(methylsulfonyl)-1H-benzimidazole. A mixture of 2 M aqueous K₃PO₄ (63 mL, 126 mmol), Pd(PPh₃)₄ (1.0 g, 0.865 mmol), 4-biphenylboronic acid (11.9 g, 60.1 mmol) and Intermediate 1A (15.0 g, 42.1 mmol) in dioxane (200 mL) was heated at 120 °C for 1.5 h. The aqueous layer was removed. Volatiles were removed to give a solid, which
 15 was washed with EtOAc and CH₂Cl₂ to give the title compound as a white solid.

Step B 5-biphenyl-4-yl-6-chloro-2-(methylsulfonyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-benzimidazole. SEMCl (2.28 mL, 12.87 mmol) was added to a solution of 5-biphenyl-4-yl-6-chloro-2-(methylsulfonyl)-1H-benzimidazole (3.79 g, 9.9 mmol) and Hunig's base (2.08 mL, 11.88 mmol) in THF (20 mL) at 0°C. The reaction was stirred at rt for 3 h then partitioned
 20 between EtOAc and saturated aqueous NaHCO₃, washed with brine, dried (Na₂SO₄), filtered and concentrated. Chromatography over silica eluting with 5-25% EtOAc/hexanes afforded the desired product as a white solid.

Step C N-({3-[(5-biphenyl-4-yl-6-chloro-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-benzimidazol-2-yl)oxy]phenyl}sulfonyl)acetamide. A mixture Cs₂CO₃ (193 mg, 0.59 mmol),
 25 Intermediate 8 (96 mg, 0.44 mmol) and 5-biphenyl-4-yl-6-chloro-2-(methylsulfonyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-benzimidazole (190 mg, 0.37 mmol) in DMF were heated at 42 °C for 16 h. Volatiles were removed. Chromatography over silica eluting with 6-25% EtOAc/hexanes afforded the desired product.

Step D N-Acetyl-3-(5-biphenyl-4-yl-6-chloro-1H-benzimidazol-2-yloxy)-benzenesulfonamide.

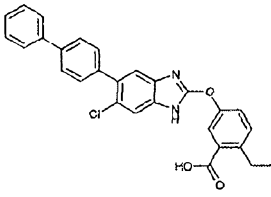
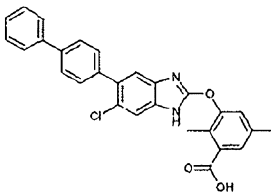
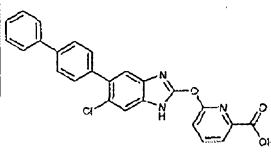
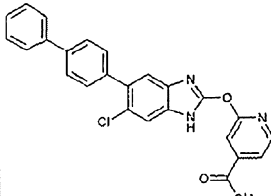
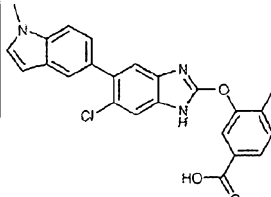
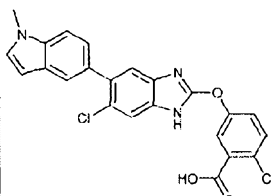
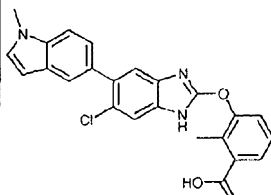
30 A solution of N-({3-[(5-biphenyl-4-yl-6-chloro-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-benzimidazol-2-yl)oxy]phenyl}sulfonyl)acetamide (38 mg, 0.059 mmol) and tetrabutylammonium fluoride (1 M in THF) (0.234 mL) in THF (3 mL) was heated at 80 °C for 2 h. Volatiles were removed and the residue was purified by reverse HPLC eluting with

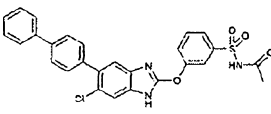
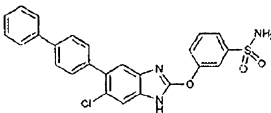
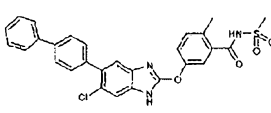
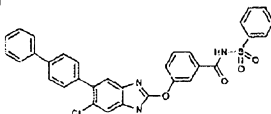
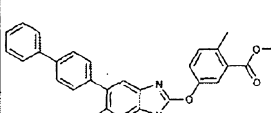
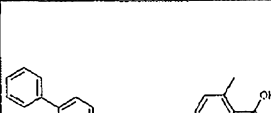
MeCN/water to give the title compound. LC-MS: calculated for $C_{27}H_{20}ClN_3O_4S$ 517.09, observed m/e 518 ($M + H$)⁺ (R_t 3.77 min).

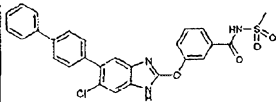
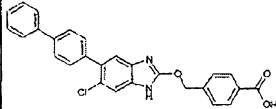
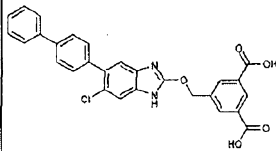
Examples 207-227 in Table 4 were prepared following the procedures described in Example 206 by substituting the appropriate boronic acid, boronate ester, stannane or acetylene from the Intermediates, or from commercial sources; and by substituting the appropriate phenols from the Intermediates, or from commercial sources.

Table 4. Compounds were prepared according to the methods described in Example 206 and Scheme 4.

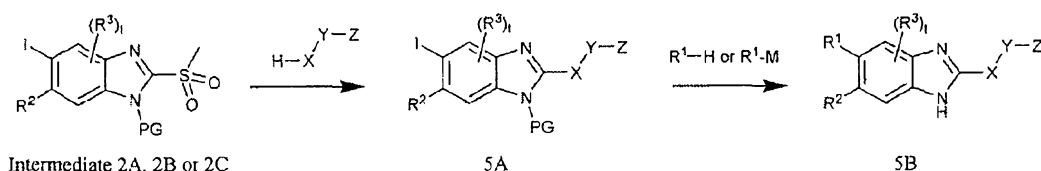
Ex. No.	Name	Structure	HPLC-mass spectrum m/e
207	5-(5-Biphenyl-4-yl-1 <i>H</i> -benzimidazol-2-yloxy)-2-methylbenzoic acid		421
208	5-(5-Biphenyl-4-yl-6-chloro-1 <i>H</i> -benzimidazol-2-yloxy)-2,4-dimethylbenzoic acid		469
209	3-(5-Biphenyl-4-yl-6-chloro-1 <i>H</i> -benzimidazol-2-yloxy)-4-fluorobenzoic acid		459
210	3-(5-Biphenyl-4-yl-6-chloro-1 <i>H</i> -benzimidazol-2-yloxy)-4-chlorobenzoic acid		476
211	3-(5-Biphenyl-4-yl-6-chloro-1 <i>H</i> -benzimidazol-2-yloxy)-4-methoxybenzoic acid		470

212	5-(5-Biphenyl-4-yl-6-chloro-1 <i>H</i> -benzimidazol-2-yloxy)-2-ethyl-benzoic acid		469
213	3-(5-Biphenyl-4-yl-6-chloro-1 <i>H</i> -benzimidazol-2-yloxy)-2,5-dimethyl-benzoic acid		469
214	6-(5-Biphenyl-4-yl-6-chloro-1 <i>H</i> -benzimidazol-2-yloxy)-pyridine-2-carboxylic acid		442
215	2-(5-Biphenyl-4-yl-6-chloro-1 <i>H</i> -benzimidazol-2-yloxy)-isonicotinic acid		442
216	3-[6-Chloro-5-(1-methyl-1 <i>H</i> -indol-5-yl)-1 <i>H</i> -benzimidazol-2-yloxy]-4-methyl-benzoic acid		433
217	2-Chloro-5-[6-chloro-5-(1-methyl-1 <i>H</i> -indol-5-yl)-1 <i>H</i> -benzimidazol-2-yloxy]-benzoic acid		453
218	3-[6-Chloro-5-(1-methyl-1 <i>H</i> -indol-5-yl)-1 <i>H</i> -benzimidazol-2-yloxy]-2-methyl-benzoic acid		432

219	N-Acetyl-3-(5-biphenyl-4-yl-6-chloro-1H-benzoimidazol-2-yloxy)-benzenesulfonamide		518
220	3-(5-Biphenyl-4-yl-6-chloro-1H-benzoimidazol-2-yloxy)-benzenesulfonamide		476
221	N-[5-(5-Biphenyl-4-yl-6-chloro-1H-benzoimidazol-2-yloxy)-2-methylbenzoyl]-methanesulfonamide		533
222	N-[3-(5-Biphenyl-4-yl-6-chloro-1H-benzoimidazol-2-yloxy)-benzoyl]-benzenesulfonamide		581
223	5-(5-Biphenyl-4-yl-6-chloro-1-methoxycarbonylmethyl-1H-benzoimidazol-2-yloxy)-2-methylbenzoic acid methyl ester		541
224	5-(5-Biphenyl-4-yl-1-carboxymethyl-6-chloro-1H-benzoimidazol-2-yloxy)-2-methylbenzoic acid		513

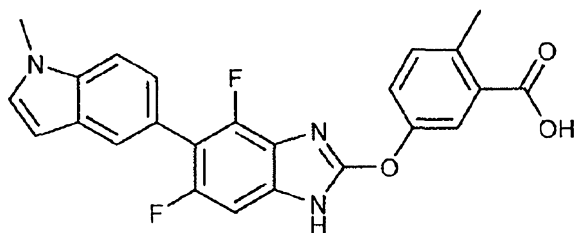
225	N-[3-(5-Biphenyl-4-yl-6-chloro-1 <i>H</i> -benzimidazol-2-yloxy)-benzoyl]-methanesulfonamide		518
226	4-(5-Biphenyl-4-yl-6-chloro-1 <i>H</i> -benzimidazol-2-yloxymethyl)-benzoic acid		455
227	5-(5-Biphenyl-4-yl-6-chloro-1 <i>H</i> -benzimidazol-2-yloxymethyl)-isophthalic acid		499

SCHEME 5



In Scheme 5, Intermediate 2A, 2B (protected with a suitable protecting group (PG) such as SEM or para-phenylbenzyl), or Intermediate 2C is reacted with H-X-Y-Z (where X-H is an alcohol, thiol or amine) to afford the 2-substituted benzimidazole 5A. Subsequent reaction of 5A with a boronic acid, boronate ester or stannane (R^1 -M) in the presence of palladium tetrakis(triphenyl)phosphine, followed by removal of the protecting group PG and, where appropriate hydrolysis of ester Z, affords the benzimidazole 5B. Alternatively, reaction of 5A with an acetylene (R^1 -H) in the presence of copper (I) iodide and bis(triphenylphosphine)-palladium (II) chloride, followed by removal of the protecting group and, where appropriate hydrolysis of ester Z, affords the benzimidazole 5B.

EXAMPLE 228



5-[4,6-Difluoro-5-(1-methyl-1*H*-indol-5-yl)-1*H*-benzoimidazol-2-yloxy]-2-methylbenzoic acid

Step A 1-Biphenyl-4-ylmethyl-4,6-difluoro-2-methanesulfonyl-5-(1-methyl-1*H*-indol-5-yl)-1*H*-benzoimidazole. A microwave vial was charged with Intermediate 2C (1550 mg, 2.9 mmol), N-methylindole-5-boronic acid (1550 mg, 8.9 mmol), PdCl₂[P(Ph-*o*-Me)₃]₂ (204 mg, 0.29 mmol), and Cs₂CO₃ (2830 mg, 8.7 mmol) in DMF (15 mL) and water (3.75 mL). The reaction was heated at 130 °C under microwave irradiation for 10 min. The reaction was partitioned between water and EtOAc. The layers were separated and the organic phase was washed with saturated ammonium chloride solution, dried (Na₂SO₄), filtered and concentrated. Chromatography over silica gel afforded the desired product as a yellow-orange oil.

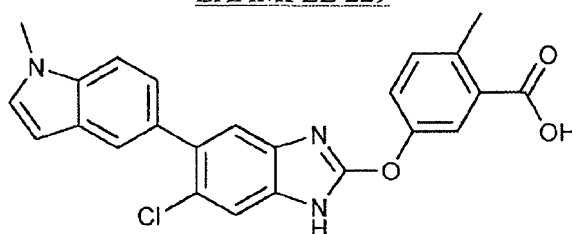
Step B 5-[1-Biphenyl-4-ylmethyl-4,6-difluoro-5-(1-methyl-1*H*-indol-5-yl)-1*H*-benzoimidazol-2-yloxy]-2-methylbenzoic acid methyl ester. A solution of 1-biphenyl-4-ylmethyl-4,6-difluoro-2-methanesulfonyl-5-(1-methyl-1*H*-indol-5-yl)-1*H*-benzoimidazole (1088 mg, 2.1 mmol), 5-hydroxy-2-methylbenzoic acid methyl ester (513 mg, 3.1 mmol) and potassium carbonate (580 mg, 4.2 mmol) in DMF (20 mL) was stirred at room temperature under nitrogen. After 18h, the reaction mixture was transferred to a microwave vial and heated under microwave at 130 °C for 10 min. The cooled reaction mixture was diluted with EtOAc and washed 3 times with saturated ammonium chloride, dried (MgSO₄), filtered, and concentrated. Chromatography over silica gel afforded the desired product as a colorless foam.

Step C 5-[4,6-Difluoro-5-(1-methyl-1*H*-indol-5-yl)-1*H*-benzoimidazol-2-yloxy]-2-methylbenzoic acid methyl ester. A solution of 5-[1-biphenyl-4-ylmethyl-4,6-difluoro-5-(1-methyl-1*H*-indol-5-yl)-1*H*-benzoimidazol-2-yloxy]-2-methylbenzoic acid methyl ester (900 mg, 1.467 mmol) and Pearlman's catalyst (20% Pd(OH)₂ on carbon) (180 mg) in EtOAc-EtOH (2:1, 7 mL) was treated with cyclohexadiene (2351 mg), and the resulting reaction mixture was heated under microwave at 130 °C for 10 min, and then at 130 °C for another 10 min. The cooled reaction mixture was filtered through a Celite pad (washed with 10% MeOH-CH₂Cl₂), and the filtrate was absorbed onto silica gel and purified by ISCO flash chromatography to give desired product as a white foam.

Step D 5-[4,6-Difluoro-5-(1-methyl-1*H*-indol-5-yl)-1*H*-benzoimidazol-2-yloxy]-2-methylbenzoic acid. A solution of 5-[4,6-difluoro-5-(1-methyl-1*H*-indol-5-yl)-1*H*-benzoimidazol-2-yloxy]-2-methylbenzoic acid methyl ester (655 mg, 1.464 mmol) in THF:MeOH:H₂O (7 mL) was treated with sodium hydroxide (1N, 3 mL) at room temperature. After 3h, another 3 mL of sodium hydroxide (1N) was added and stirred at room temperature for another 1.5h, and at 50 °C

for another 1.5h. The cooled reaction solution was concentrated on a rotavapor and the resulting aqueous solution was neutralized with 1N hydrogen chloride (6 mL), and the resulting white solid was collected through filtration (washed with water) and dried under high vacuum to give the desired product as a white solid. LC-MS: calculated for $C_{24}H_{17}F_2N_3O_3$ 434.41, observed m/e 434.6 ($M + H$)⁺ (R_t 1.52 min). ¹H NMR (300 MHz, DMSO-*d*₆): δ 7.78-7.15 (m, 8H), 6.45 (d, J = 3.3 Hz, 1H), 3.81 (s, 3H), 2.53 (s, 3H).

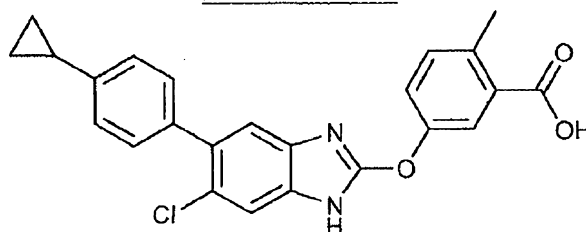
EXAMPLE 229



- 10 5-([6-chloro-5-(1-methyl-1H-indol-5-yl)-1H-benzimidazol-2-yl]oxy)-2-methylbenzoic acid
 Step A Methyl 5-([6-chloro-5-(1-methyl-1H-indol-5-yl)-1-([2-(trimethylsilyl)ethoxy]methyl)-1H-benzimidazol-2-yl]oxy)-2-methylbenzoate. A 500 mL flask was charged with Intermediate 11A (5.0 g, 8.73 mmol), 1-methylindole-5-boronic acid pinacol ester (2.92 g, 11.4 mmol), Pd(PPh₃)₄ (1.51 g, 1.31 mmol), DMF (97 mL), and 1 M aqueous K₂CO₃ (26.2 mL). The reaction
 15 was degassed with N₂ and then heated at 120 °C for 45 min. The reaction was concentrated, then partitioned between H₂O (100 mL) and EtOAc (200 mL). The aqueous phase was extracted with EtOAc (2 x 100 mL). The combined organic layers were washed with brine, dried (MgSO₄), filtered, and concentrated. Chromatography over silica eluting with 10-30% EtOAc/hexanes afforded the desired product as a yellow-orange foam.
- 20 Step B Methyl 5-([6-chloro-5-(1-methyl-1H-indol-5-yl)-1H-benzimidazol-2-yl]oxy)-2-methylbenzoate. To a solution of methyl 5-([6-chloro-5-(1-methyl-1H-indol-5-yl)-1-([2-(trimethylsilyl)ethoxy]methyl)-1H-benzimidazol-2-yl]oxy)-2-methylbenzoate (3.35 g, 5.81 mmol) in THF (60 mL) was added TBAF (1.0 M in THF) (26 mL, 26.1 mmol) dropwise via syringe. The reaction was heated at 80 °C for 45 min. TBAF (3 mL) was added and heating
 25 continued for 4 h. The reaction was cooled and diluted with EtOAc (200 mL) and saturated aqueous KHSO₄ (~pH 3). The aqueous phase was extracted with EtOAc (100 mL). The combined organic layers were washed with H₂O and brine, dried (Na₂SO₄), filtered, and concentrated. The residue was dissolved in MeOH (100 mL) and treated with 2.5 N aqueous NaOH (46 mL, 115 mmol). The reaction was heated at 45 °C for 1 h. Volatiles were removed
 30 and the residue was dissolved in H₂O (150 mL). The aqueous phase was washed with EtOAc (2 x 100 mL), acidified to pH ~ 1 with 2 N aqueous HCl and extracted with EtOAc (2 x 100 mL). The combined organics were washed with H₂O and brine, dried (Na₂SO₄), filtered, and concentrated. Trituration of the solid residue with Et₂O and filtration afforded the title compound

as an off-white solid. LC-MS: m/e 432.6 ($M + H$)⁺ (2.0 min). ¹H NMR (500 MHz, CD₃OD): δ 7.85 (d, 1H), 7.54 (d, 1H), 7.47 (s, 1H), 7.44-7.37 (m, 3H), 7.35 (s, 1H), 7.22 (dd, 1H), 7.18 (d, 1H), 6.45 (d, 1H), 3.83 (s, 3H), 2.61 (s, 3H).

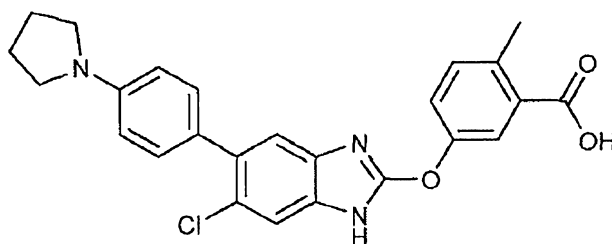
5

EXAMPLE 2305-([6-chloro-5-(4-cyclopropylphenyl)-1H-benzimidazol-2-yl]oxy)-2-methylbenzoic acid

Step A Methyl 5-([6-chloro-5-(4-cyclopropylphenyl)-1-{2-(trimethylsilyl)ethoxy}methyl]-1H-benzimidazol-2-yl)methyl]-2-methylbenzoate. A microwave vial was charged with Intermediate 11A (200 mg, 0.349 mmol), 4-cyclopropylphenylboronic acid pinacol ester (111 mg, 0.454 mmol), Pd(PPh₃)₄ (61 mg, 0.052 mmol), DMF (4.4 mL), and 1 M K₂CO₃ (1.0 mL). The reaction was sealed and microwaved at 150 °C for 8 min. The reaction was partitioned between EtOAc and water. The aqueous phase was extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na₂SO₄), filtered, and concentrated. Chromatography over silica eluting with 12% EtOAc/hexanes afforded the desired product as a viscous, yellow oil.

Step B 5-([6-chloro-5-(4-cyclopropylphenyl)-1H-benzimidazol-2-yl]oxy)-2-methylbenzoic acid. To a solution of methyl 5-([6-chloro-5-(4-cyclopropylphenyl)-1-{2-(trimethylsilyl)ethoxy}methyl]-1H-benzimidazol-2-yl)methyl]-2-methylbenzoate (160 mg, 0.284 mmol) in THF (3.0 mL) was added TBAF (1 M in THF) (1.5 mL, 1.5 mmol). The reaction was heated to 80 °C for 1 h. Additional TBAF (1 M in THF) (1.5 mL, 1.5 mmol) was added and heating continued for an additional 45 min. Volatiles were removed. The residue was dissolved in MeOH (6 mL) and treated with 2.5 N aqueous NaOH (1.1 mL, 2.75 mmol). The reaction was heated at 45 °C for 2 h. Volatiles were removed. The residue was partitioned between water and EtOAc. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with 1 M aqueous HCl, H₂O, and brine, dried (Na₂SO₄), filtered, and concentrated. Trituration of the residue with hexane and Et₂O and filtration afforded the title compound as a white solid. LC-MS: m/e 420.2 ($M + H$)⁺ (2.13 min). LC-MS: calculated for C₂₄H₁₉ClN₂O₃ 418.87, observed m/e 420.2 ($M + H$)⁺ (R_t 2.13 min). ¹H NMR (500 MHz, CD₃OD): δ 7.85 (d, 1H), 7.46 (s, 1H), 7.43-7.38 (m, 2H), 7.29-7.25 (m, 3H), 7.11 (d, 2H), 2.61 (s, 3H), 1.94 (m, 1H), 1.01-0.95 (m, 2H), 0.74-0.69 (m, 2H).

EXAMPLE 231



5-([6-chloro-5-(4-pyrrolidin-1-ylphenyl)-1H-benzimidazol-2-yl]oxy)-2-methylbenzoic acid

Step A 5-([6-chloro-5-(4-pyrrolidin-1-ylphenyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-benzimidazol-2-yl]oxy)-2-methylbenzoic acid. K_2CO_3 (2 M in water) (0.215 mL, 0.429 mmol)

5 followed by $Pd(PPh_3)_4$ (4.96 mg, 4.29 μ mol) were added to a solution of 1-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]pyrrolidine (45.0 mg, 0.165 mmol, Maybridge) and Intermediate 11A (80 mg, 0.143 mmol) in DMF (2 mL). The reaction was heated at 150°C under microwave irradiation for 10 min. Volatiles were removed to afford the desired product which was used in the next step without further purification. LC-MS: calculated for

10 $C_{29}H_{34}ClN_5O_4Si$ 577.22, observed m/e 578.06 ($M + H$)⁺ (R_t 2.41 min).

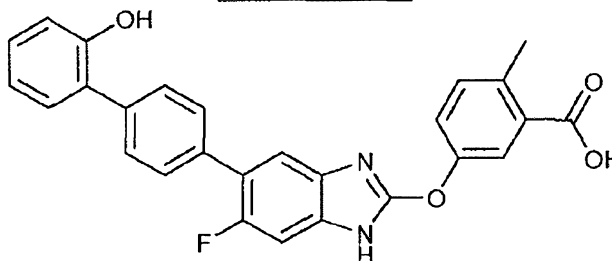
Step B 5-([6-chloro-5-(4-pyrrolidin-1-ylphenyl)-1H-benzimidazol-2-yl]oxy)-2-methylbenzoic acid. TBAF (1M in THF) (0.5 mL, 0.5 mmol) was added to a solution of 5-([6-chloro-5-(4-pyrrolidin-1-ylphenyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-benzimidazol-2-yl]oxy)-2-methylbenzoic acid in dioxane (3 mL). The reaction was heated at 80°C for 16 h. The mixture

15 was diluted with EtOAc (10 mL) and washed with 2N HCl, followed by water and concentrated.

Purification by reverse phase HPLC eluting with 10-90% MeCN:water) afforded the title compound as an off-white solid. LC-MS: calculated for $C_{25}H_{22}ClN_3O_3$ 447.13, observed m/e 448.04 ($M + H$)⁺ (R_t 1.80 min). 1H NMR (500 MHz, CD_3OD): δ 7.87 (s, 1H) 7.48 (s, 1H) 7.42 (m, 2H) 7.28 (s, 1H) 7.22 (m, 2H) 6.75 (m, 2H) 3.84 (s, 3H) 3.31 (m, 2H) 2.61 (s, 3H) 2.03 (m, 2H).

20 (m, 2H) 2.61 (s, 3H) 2.03 (m, 2H).

EXAMPLE 232



5-([6-fluoro-5-(2'-hydroxybiphenyl-4-yl)-1H-benzimidazol-2-yl]oxy)-2-methylbenzoic acid

Step A Methyl 5-([6-fluoro-5-(2'-hydroxybiphenyl-4-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-benzimidazol-2-yl]oxy)-2-methylbenzoate. Potassium phosphate (2 M in water) (270 μ L,

25 0.54 mmol) and $Pd(PPh_3)_4$ (6.3 mg, 5.4 μ mol) were added to a solution of Intermediate 11B (100mg, 0.18 mmol), and Intermediate 38 (80mg, 0.27 mmol) in dioxane (2 mL). The reaction was heated at 140°C under microwave irradiation for 20 min, then filtered through a membrane

syringe filter and concentrated. The residue was re-dissolved in 2 mL methanol, filtered and purified by HPLC eluting with 20-80% MeCN:water to afford the desired product as a white solid.

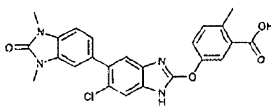
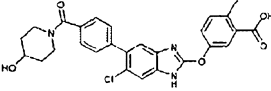
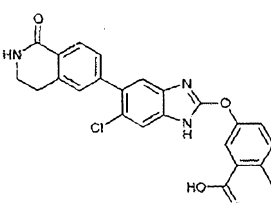
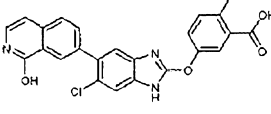
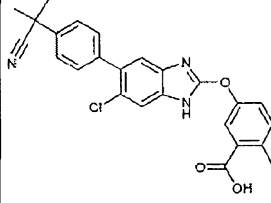
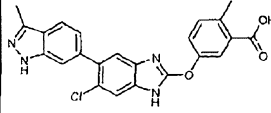
Step B 5-{[6-fluoro-5-(2'-hydroxybiphenyl-4-yl)-1*H*-benzimidazol-2-yl]oxy}-2-methylbenzoic

- 5 acid. TBAF (1 M in THF) (0.63 mL, 0.63 mmol) was added to a solution of methyl 5-[(6-fluoro-5-(2'-hydroxybiphenyl-4-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-benzimidazol-2-yl)oxy]-2-methylbenzoate (75 mg, 0.125 mmol) in THF (10 mL). The reaction was heated at 80 °C for 6 h. Volatiles were removed and the residue was purified by HPLC eluting with 20-80% MeCN:water. The resulting white solid was dissolved in MeOH (3 mL) and water (2 mL).
- 10 Aqueous 5 M NaOH (250 µl) was added. The solution was heated at 70 °C for 30 min. Volatiles were removed and the residue was re-dissolved in 10 mL water and extracted with ethyl acetate to afford the title compound as a white solid product. LC/MS: calculated for C₂₇H₁₉FN₂O₄ 454.45, observed *m/e* 455(M+H)⁺ (1.97/4 min). 1H-NMR (500MHz, D₆-acetone): 8.02-6.98 (13H, m), 2.62 (3H, s).

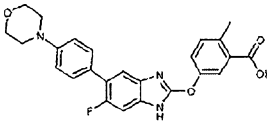
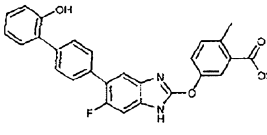
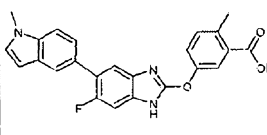
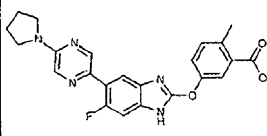
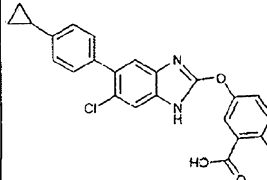
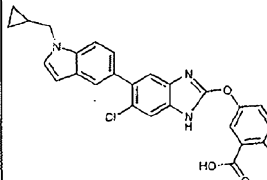
- 15 Examples 233-260 in Table 5 were prepared following the procedures described in Examples 228-232 by substituting the appropriate boronic acid, boronate ester, stannane or acetylene from the Intermediates, or from commercial sources; and by substituting the appropriate phenols from the Intermediates, or from commercial sources.

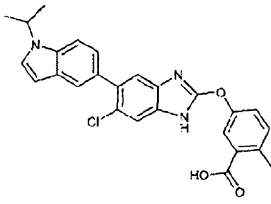
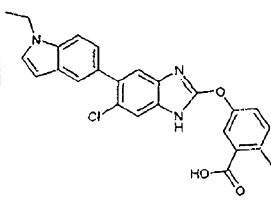
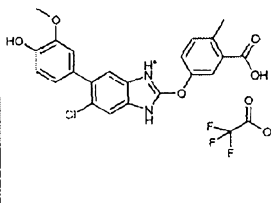
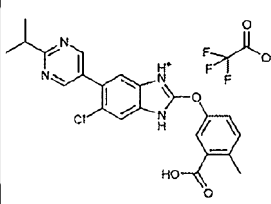
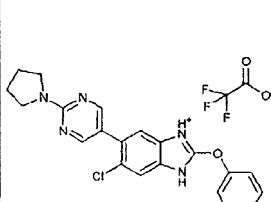
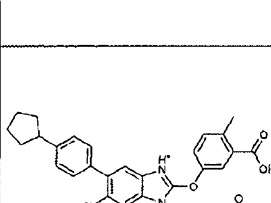
- 20 Table 5. Compounds prepared according to the methods described in Examples 228-232 and Scheme 5.

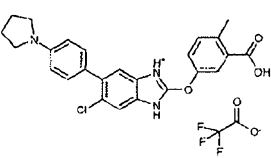
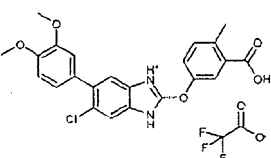
Ex. No.	Name	Structure	retention time (min)
233	5-[6-Chloro-5-(2-oxo-1,2-dihydro-quinolin-6-yl)-1 <i>H</i> -benzoimidazol-2-yl]oxy]-2-methylbenzoic acid		446
234	5-[6-Chloro-5-(1-methyl-2-oxo-1,2-dihydro-quinolin-6-yl)-1 <i>H</i> -benzoimidazol-2-yl]oxy]-2-methylbenzoic acid		460

235	5-(6-Chloro-1',3'-dimethyl-2'-oxo-2',3'-dihydro-1 <i>H</i> ,1' <i>H</i> -[5,5']bibenzoimidazolyl-2-yloxy)-2-methylbenzoic acid		463
236	5-{6-Chloro-5-[4-(4-hydroxy-piperidine-1-carbonyl)-phenyl]-1 <i>H</i> -benzoimidazol-2-yloxy}-2-methylbenzoic acid		506
237	5-[6-Chloro-5-(1-oxo-1,2,3,4-tetrahydroisoquinolin-6-yl)-1 <i>H</i> -benzoimidazol-2-yloxy]-2-methylbenzoic acid		448
238	5-[6-Chloro-5-(1-hydroxy-isoquinolin-7-yl)-1 <i>H</i> -benzoimidazol-2-yloxy]-2-methylbenzoic acid		446
239	5-{6-Chloro-5-[4-(cyano-dimethyl-methyl)-phenyl]-1 <i>H</i> -benzoimidazol-2-yloxy}-2-methylbenzoic acid		446
240	5-[6-Chloro-5-(3-methyl-1 <i>H</i> -indazol-6-yl)-1 <i>H</i> -benzoimidazol-2-yloxy]-2-methylbenzoic acid		433

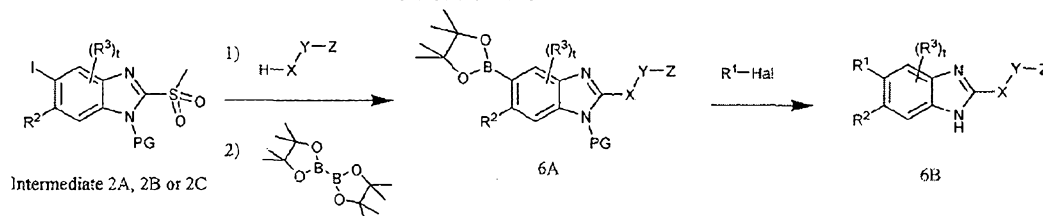
241	5-[6-Chloro-5-(4-dimethylcarbamoyl-phenyl)-1 <i>H</i> -benzoimidazol-2-yloxy]-2-methylbenzoic acid		450
242	5-[5-(4-Carbamoyl-phenyl)-6-chloro-1 <i>H</i> -benzoimidazol-2-yloxy]-2-methylbenzoic acid		422
243	{4-[6-Chloro-5-(1-methyl-1 <i>H</i> -indol-5-yl)-1 <i>H</i> -benzoimidazol-2-yloxy]-phenyl}-acetic acid		432
244	{4-[6-Chloro-5-(4-methyl-3,4-dihydro-2 <i>H</i> -benzo[1,4]oxazin-7-yl)-1 <i>H</i> -benzoimidazol-2-yloxy]-phenyl}-acetic acid		450
245	{4-[6-Chloro-5-(6-methoxy-naphthalen-2-yl)-1 <i>H</i> -benzoimidazol-2-yloxy]-phenyl}-acetic acid		459
246	5-{6-Fluoro-5-[4-(2 <i>H</i> -pyrazol-3-yl)-phenyl]-1 <i>H</i> -benzoimidazol-2-yloxy}-2-methylbenzoic acid		429.16

247	5-[6-Fluoro-5-(4-morpholin-4-yl-phenyl)-1 <i>H</i> -benzoimidazol-2-yl-oxy]-2-methyl-benzoic acid		448.16
248	5-[6-Fluoro-5-(2'-hydroxy-biphenyl-4-yl)-1 <i>H</i> -benzoimidazol-2-yl-oxy]-2-methyl-benzoic acid		455.3
249	5-[6-Fluoro-5-(1-methyl-1 <i>H</i> -indol-5-yl)-1 <i>H</i> -benzoimidazol-2-yl-oxy]-2-methyl-benzoic acid		416.22
250	5-[6-Fluoro-5-(5-pyrrolidin-1-yl-pyrazin-2-yl)-1 <i>H</i> -benzoimidazol-2-yl-oxy]-2-methyl-benzoic acid		433.51
251	L-002214273-000T 5-[6-Chloro-5-(4-cyclopropyl-phenyl)-1 <i>H</i> -benzoimidazol-2-yl-oxy]-2-methyl-benzoic acid		420.2
252	5-[6-Chloro-5-(1-cyclopropylmethyl-1 <i>H</i> -indol-5-yl)-1 <i>H</i> -benzoimidazol-2-yl-oxy]-2-methyl-benzoic acid		472.7

253	5-[6-Chloro-5-(1-isopropyl-1 <i>H</i> -indol-5-yl)-1 <i>H</i> -benzimidazol-2-yloxy]-2-methylbenzoic acid		460.7
254	5-[6-Chloro-5-(1-ethyl-1 <i>H</i> -indol-5-yl)-1 <i>H</i> -benzimidazol-2-yloxy]-2-methylbenzoic acid		447.2
255	2-(3-carboxy-4-methylphenoxy)-6-chloro-5-(4-hydroxy-3-methoxyphenyl)-1 <i>H</i> -3,1-benzimidazol-3-ium trifluoroacetate		425.01
256	2-(3-carboxy-4-methylphenoxy)-6-chloro-5-[2-(dimethylamino)pyrimidin-5-yl]-1 <i>H</i> -3,1-benzimidazol-3-ium trifluoroacetate		424.04
257	2-(3-carboxy-4-methylphenoxy)-6-chloro-5-(2-pyrrolidin-1-ylpyrimidin-5-yl)-1 <i>H</i> -3,1-benzimidazol-3-ium trifluoroacetate		450.06
258	2-(3-carboxy-4-methylphenoxy)-6-chloro-5-(4-cyclopentylphenyl)-1 <i>H</i> -3,1-benzimidazol-3-ium trifluoroacetate		447.08

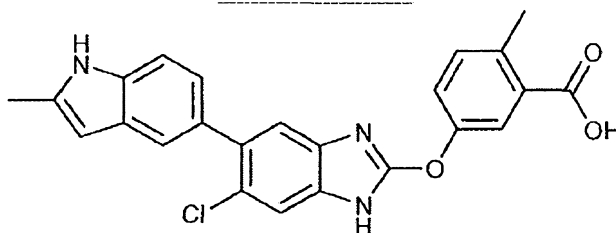
259	2-(3-carboxy-4-methylphenoxy)-6-chloro-5-(4-pyrrolidin-1-ylphenyl)-1 <i>H</i> -3,1-benzimidazol-3-ium trifluoroacetate		448.04
260	2-(3-carboxy-4-methylphenoxy)-6-chloro-5-(3,4-dimethoxyphenyl)-1 <i>H</i> -3,1-benzimidazol-3-ium trifluoroacetate		469

SCHEME 6



In Scheme 6, Intermediate 2A, 2B (protected with a suitable protecting group (PG) such as SEM or para-phenylbenzyl), or Intermediate 2C is reacted with H-X-Y-Z (where X-H is an alcohol, thiol or amine) and base followed by reaction with bis(pinacolato)diboron in the presence of palladium tetrakis(triphenyl)phosphine to afford the boronate ester 6A. Subsequent reaction of 6A with a halide, triflate or diazonium salt of R¹ (R¹-Hal) in the presence of palladium tetrakis(triphenyl)phosphine, followed by removal of the protecting group PG, and where appropriate hydrolysis of ester Z, affords the 2-substituted benzimidazole 6B.

EXAMPLE 261



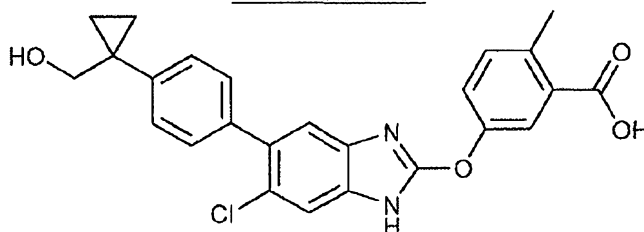
5-[[6-chloro-5-(2-methyl-1*H*-indol-5-yl)-1*H*-benzimidazol-2-yl]oxy]-2-methylbenzoic acid

Step A Methyl 5-[[6-chloro-5-(2-methyl-1*H*-indol-5-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-benzimidazol-2-yl]oxy]-2-methylbenzoate. K₂CO₃ (1M in water) (0.26 mL, 0.260 mmol)

was added to a solution of 5-bromo-2-methyl-1*H*-indole (21.5 mg, 0.096 mmol), Intermediate 13 (50 mg, 0.087 mmol) and Pd(PPh₃)₄ (8mg) in DMF (1.5 ml). The reaction was heated at 150 °C under microwave irradiation for 10 min. Volatiles were removed, and the residue was partitioned between EtOAc and water. The aqueous phase was extracted with EtOAc. Combined organic layers were washed with brine, dried (MgSO₄), filtered and concentrated *in vacuo*. Purification by HPLC eluting with 20-80% MeCN:water afforded the desired product.

Step B 5-{[6-chloro-5-(2-methyl-1*H*-indol-5-yl)-1-benzimidazol-2-yl]oxy}-2-methylbenzoic acid. TBAF (1M in THF) (0.2 mL, 0.2 mmol) was added to a solution of methyl 5-[(6-chloro-5-(2-methyl-1*H*-indol-5-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-benzimidazol-2-yl)oxy]-2-methylbenzoate (30mg, 0.052 mmol) in THF (0.5 ml). The reaction was heated at 80 °C for 4 h. Volatiles were removed *in vacuo*. The residue was diluted with MeOH (1 mL) and 2.5 N aqueous NaOH (1 ml) and heated at 50 °C for 1 h. Volatiles were removed *in vacuo* and the residue was partitioned between EtOAc and HCl (1M in water). The organic phase was washed with HCl (1M in water) dried (MgSO₄), filtered and concentrated to afford the title compound as a white solid. LC-MS: calculated for C₂₅H₂₀ClN₃O₃ 431.1, observed m/e 432.7 (M+H)⁺ (R_t: 1.95min).

EXAMPLE 262



5-[(6-chloro-5-{4-[1-(hydroxymethyl)cyclopropyl]phenyl}-1*H*-benzimidazol-2-yl)oxy]-2-methylbenzoic acid

Step A Methyl 5-[(6-chloro-5-{4-[1-(hydroxymethyl)cyclopropyl]phenyl}-1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-benzimidazol-2-yl)oxy]-2-methylbenzoate.

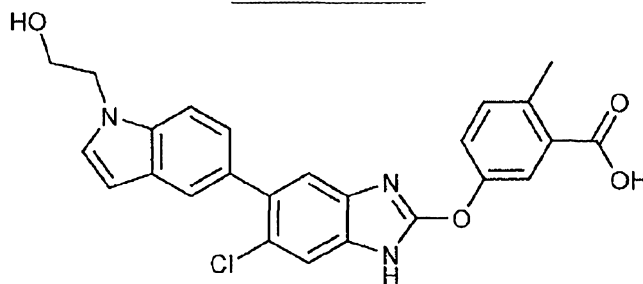
K₂CO₃ (1M in water) (2.79 ml, 2.79 mmol) was added to a solution of Intermediate 13 (800 mg, 1.396 mmol), [1-(4-bromophenyl)cyclopropyl]methanol (330 mg, 1.453 mmol, Intermediate 4), and Pd(PPh₃)₄ (129 mg, 0.112 mmol) in DMF (14 mL). The reaction was heated at 150 °C under microwave irradiation for 8 min. Volatiles were removed, and the residue was partitioned between EtOAc and water. The aqueous phase was extracted with EtOAc. Combined organic layers were washed with brine, dried (MgSO₄), filtered and concentrated *in vacuo*.

Chromatography over silica eluting with 10-60% EtOAc/Hexanes afforded the desired product.

Step B 5-[(6-chloro-5-{4-[1-(hydroxymethyl)cyclopropyl]phenyl}-1*H*-benzimidazol-2-yl)oxy]-2-methylbenzoic acid. TBAF (1M in THF) (0.35 mL, 0.35 mmol) was added to a solution of methyl 5-[(6-chloro-5-{4-[1-(hydroxymethyl)cyclopropyl]phenyl}-1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-benzimidazol-2-yl)oxy]-2-methylbenzoate (275 mg, 0.464 mmol) in dioxane (5 mL) and reaction mixture was heated at 80 °C. The volatiles were removed.

The resulting crude residue was dissolved in MeOH (2ml) and 2.5 N aqueous NaOH (2 mL) and stirred at 50 °C for 1h. Volatiles were removed and the residue was partitioned between EtOAc and water. The aqueous layer was acidified to pH=1 with 2 N aqueous HCl, and extracted with EtOAc. Combined organic layers were dried (MgSO₄), filtered and concentrated. Purification by reverse phase HPLC eluting with 10-100% acetonitrile:water afforded the title compound. LC-MS calculated for C₂₅H₂₁ClN₂O₄ 448.12, observed m/e 448.7 (M+H)⁺. Rt : 1.81/ 4min. ¹H NMR (500 MHz, CD₃OD): δ 7.85 (s, 1H), 7.50 (s, 1H), 7.40-7.45 (m, 4H), 7.35 (d, 2H), 7.30 (s, 1H), 3.65 (s, 2H), 2.61 (s, 3H), 0.85-0.95 (q, 4H).

EXAMPLE 263



5-({6-chloro-5-[1-(2-hydroxyethyl)-1H-indol-5-yl]-1H-benzimidazol-2-yl} oxy)-2-methylbenzoic acid

Step A Methyl (5-bromo-1H-indol-1-yl)acetate. A solution of 5-bromo-1H-indole (1.0 g, 5.10 mmol) in THF (10 mL) was added dropwise to a 0 °C suspension of NaH (155 mg, 6.12 mmol) in THF (10 mL). The reaction mixture was maintained at 0 °C for 15 min, then methyl bromoacetate (0.705 mL, 7.65 mmol) was added. The reaction was stirred at ambient temperature for 1 h and then partitioned between H₂O and EtOAc. The aqueous layer was extracted with EtOAc and the combined organic layers were washed with brine, dried (Na₂SO₄), filtered and concentrated. The crude product was used in the next step without purification.

Step B 2-(5-bromo-1H-indol-1-yl)ethanol. DIBAL-H (1 M in hexanes) (6.1 mL, 6.1 mmol) was added to a 0 °C solution of methyl (5-bromo-1H-indol-1-yl)acetate (660 mg, 2.46 mmol) in anhydrous THF (12 mL). The reaction was warmed to ambient temperature and maintained for 1 h. The reaction mixture was poured into saturated aqueous Rochelle's salt (25 mL) and Et₂O (25 mL). The mixture was stirred vigorously for 30 min. The layers were separated and the aqueous phase was extracted with Et₂O. The combined organic layers were washed with brine, dried (Na₂SO₄), filtered, and concentrated to afford the desired product as a yellow oil.

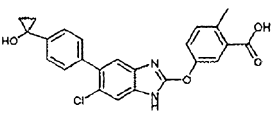
Step C Methyl 5-[(6-chloro-5-[1-(2-hydroxyethyl)-1H-indol-5-yl]-1-{2-(trimethylsilyl)ethoxy}methyl}-1H-benzimidazol-2-yl]oxy]-2-methylbenzoate. A microwave vial was charged with Intermediate 13 (170 mg, 0.297 mmol), 2-(5-bromo-1H-indol-1-yl)ethanol (100 mg, 0.415 mmol), Pd(PPh₃)₄ (51 mg, 0.045 mmol), DMF (4.3 mL), and K₂CO₃ (1 M in water) (0.89 mL). The reaction was heated at 150°C under microwave irradiation for 8 min. The reaction was partitioned between water and EtOAc. The aqueous phase was extracted with

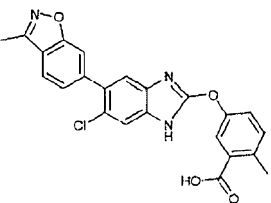
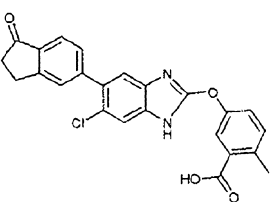
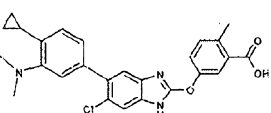
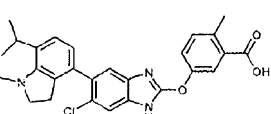
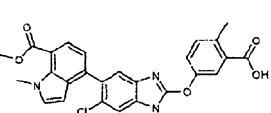
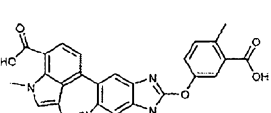
EtOAc. The combined organics were washed with brine, dried (Na₂SO₄), filtered and concentrated. Chromatography over silica eluting with 50% EtOAc/hexanes afforded the desired product as a viscous, yellow oil.

Step D 5-({6-chloro-5-[1-(2-hydroxyethyl)-1*H*-indol-5-yl]-1*H*-benzimidazol-2-yl} oxy)-2-methylbenzoic acid. TBAF (1 M in THF) (0.9 mL, 0.9 mmol) was added to a solution of methyl 5-[(6-chloro-5-[1-(2-hydroxyethyl)-1*H*-indol-5-yl]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-benzimidazol-2-yl)oxy]-2-methylbenzoate (105 mg, 0.173 mmol) in THF (2 mL). The reaction was heated at 80 °C for 1 h. TBAF (1 M in THF) (0.2 mL, 0.2 mmol) was added and heating continued for an additional 1 h. Volatiles were removed and the residue was dissolved in MeOH (3 mL) and treated with 2.5 N aqueous NaOH (1 mL). The mixture was stirred at 45 °C for 1.5 h, then at ambient temperature overnight. The reaction was diluted with EtOAc and the layers were separated. The organic layer was washed with 1 M aqueous HCl, water and brine, dried (Na₂SO₄), filtered, and concentrated. Chromatography over silica eluting with 8% MeOH/DCM containing AcOH (60 drops in 200 mL) afforded the title compound as an off-white solid. LC-MS: calculated for C₂₅H₂₀ClN₃O₄ 461.90, observed *m/e* 462.3 (M + H)⁺ (R_t 1.77 min). ¹H NMR (500 MHz, CD₃OD): δ 7.86 (d, 1H), 7.55 (s, 1H), 7.47 (s, 1H), 7.46-7.36 (m, 3H), 7.34, (s, 1H), 7.27 (d, 1H), 7.19 (dd, 1H), 6.47 (d, 1H), 4.29 (t, 2H), 3.89 (t, 2H), 2.61 (s, 3H).

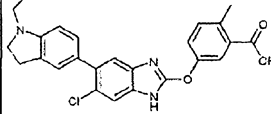
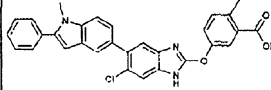
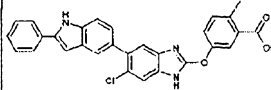
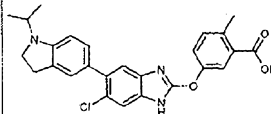
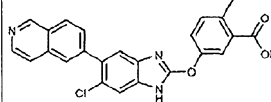
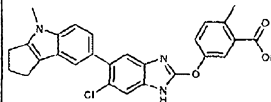
Examples 264-318 in Table 6A were prepared following the procedures described in Examples 261-262 by substituting the appropriate boronic acid, boronate ester, stannane or acetylene from the Intermediates, or from commercial sources; and by substituting the appropriate phenols from the Intermediates or from commercial sources.

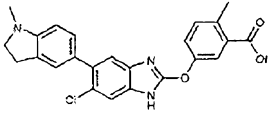
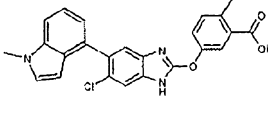
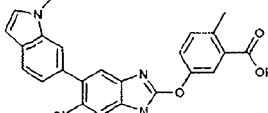
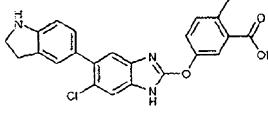
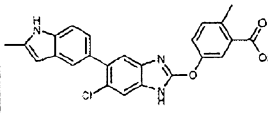
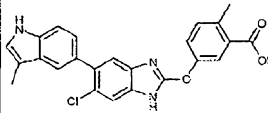
Table 6A. Compounds prepared according to the methods described in Examples 261-262 and Scheme 6.

Ex. No.	Name	Structure	HPLC-mass spectrum <i>m/e</i>
264	5-{6-Chloro-5-[4-(1-hydroxy-cyclopropyl)-phenyl]-1 <i>H</i> -benzimidazol-2-yloxy}-2-methylbenzoic acid		435

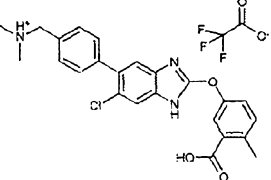
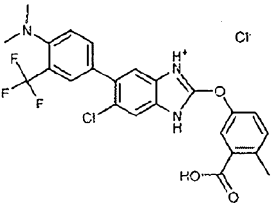
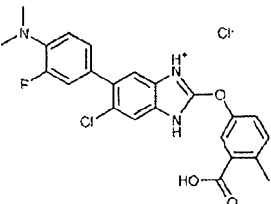
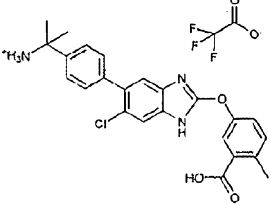
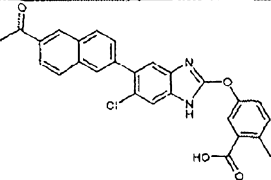
265	5-[6-Chloro-5-(3-methyl-benzo[d]isoxazol-6-yl)-1 <i>H</i> -benzoimidazol-2-yl]oxy]-2-methylbenzoic acid		433.9
266	5-[6-Chloro-5-(1-oxo-indan-5-yl)-1 <i>H</i> -benzoimidazol-2-yl]oxy]-2-methylbenzoic acid		434.0
267	5-[6-Chloro-5-(4-cyclopropyl-3-dimethylamino-phenyl)-1 <i>H</i> -benzoimidazol-2-yl]oxy]-2-methylbenzoic acid		462.9
268	5-[6-Chloro-5-(7-isopropyl-1-methyl-2,3-dihydro-1 <i>H</i> -indol-4-yl)-1 <i>H</i> -benzoimidazol-2-yl]oxy]-2-methylbenzoic acid		475.8
269	4-[2-(3-Carboxy-4-methyl-phenoxy)-6-chloro-1 <i>H</i> -benzoimidazol-5-yl]-1-methyl-1 <i>H</i> -indole-7-carboxylic acid methyl ester		490.1
270	4-[2-(3-Carboxy-4-methyl-phenoxy)-6-chloro-1 <i>H</i> -benzoimidazol-5-yl]-		490.2

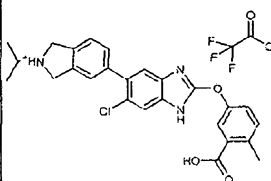
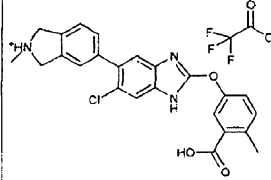
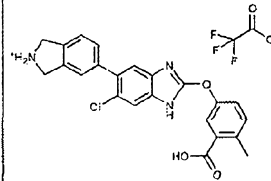
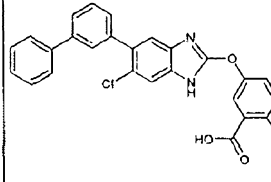
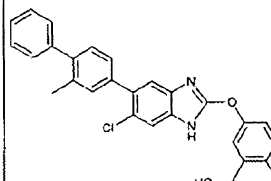
	1,3-dimethyl-1 <i>H</i> -indole-7-carboxylic acid		
271	4-[2-(3-Carboxy-4-methyl-phenoxy)-6-chloro-1 <i>H</i> -benzoimidazol-5-yl]-1-methyl-1 <i>H</i> -indole-7-carboxylic acid		476.3
272	5-[6-Chloro-5-(7-isopropyl-1-methyl-1 <i>H</i> -indol-4-yl)-1 <i>H</i> -benzoimidazol-2-yloxy]-2-methylbenzoic acid		474.3
273	5-[6-Chloro-5-(7-isopropyl-1 <i>H</i> -indol-4-yl)-1 <i>H</i> -benzoimidazol-2-yloxy]-2-methylbenzoic acid		460.3
274	5-[6-Chloro-5-(2-hydroxymethyl-1-methyl-1 <i>H</i> -indol-5-yl)-1 <i>H</i> -benzoimidazol-2-yloxy]-2-methylbenzoic acid		462.1
275	5-[2-(3-Carboxy-4-methyl-phenoxy)-6-chloro-1 <i>H</i> -benzoimidazol-5-yl]-1-methyl-1 <i>H</i> -indole-2-carboxylic acid		477.2

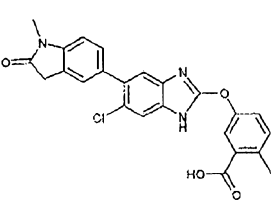
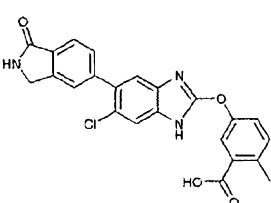
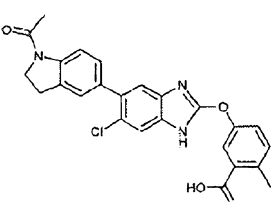
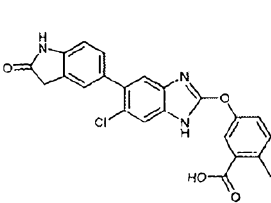
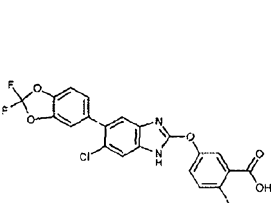
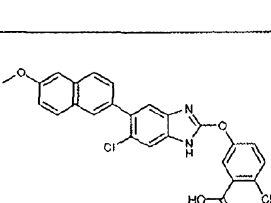
276	5-[6-Chloro-5-(1-ethyl-2,3-dihydro-1 <i>H</i> -indol-5-yl)-1 <i>H</i> -benzimidazol-2-yloxy]-2-methylbenzoic acid		448.3
277	5-[6-Chloro-5-(1-methyl-2-phenyl-1 <i>H</i> -indol-5-yl)-1 <i>H</i> -benzimidazol-2-yloxy]-2-methylbenzoic acid		508
278	5-[6-Chloro-5-(2-phenyl-1 <i>H</i> -indol-5-yl)-1 <i>H</i> -benzimidazol-2-yloxy]-2-methylbenzoic acid		494
279	5-[6-Chloro-5-(1-isopropyl-2,3-dihydro-1 <i>H</i> -indol-5-yl)-1 <i>H</i> -benzimidazol-2-yloxy]-2-methylbenzoic acid		462
280	5-(6-Chloro-5-isoquinolin-6-yl-1 <i>H</i> -benzimidazol-2-yloxy)-2-methylbenzoic acid		430.9
281	5-[6-Chloro-5-(4-methyl-1,2,3,4-tetrahydro-cyclopenta[<i>b</i>]indol-7-yl)-1 <i>H</i> -benzimidazol-2-yloxy]-2-methylbenzoic acid		472.8

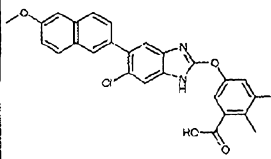
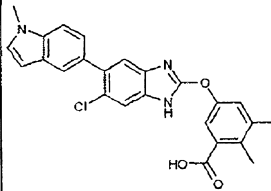
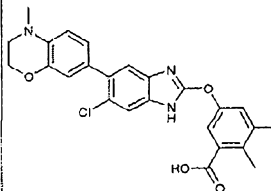
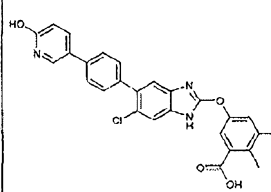
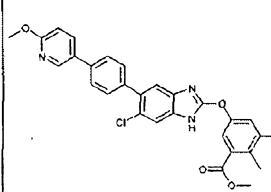
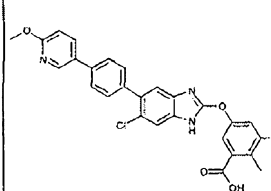
282	5-[6-Chloro-5-(1-methyl-2,3-dihydro-1 <i>H</i> -indol-5-yl)-1 <i>H</i> -benzimidazol-2-yloxy]-2-methylbenzoic acid		434.21
283	5-[6-Chloro-5-(1-methyl-1 <i>H</i> -indol-4-yl)-1 <i>H</i> -benzimidazol-2-yloxy]-2-methylbenzoic acid		432.22
284	5-[6-Chloro-5-(1-methyl-1 <i>H</i> -indol-6-yl)-1 <i>H</i> -benzimidazol-2-yloxy]-2-methylbenzoic acid		432.9
285	5-[6-Chloro-5-(2,3-dihydro-1 <i>H</i> -indol-5-yl)-1 <i>H</i> -benzimidazol-2-yloxy]-2-methylbenzoic acid		421.0
286	5-{[6-chloro-5-(2-methyl-1 <i>H</i> -indol-5-yl)-1 <i>H</i> -benzimidazol-2-yl]oxy}-2-methylbenzoic acid		432.7
287	5-[6-Chloro-5-(3-methyl-1 <i>H</i> -indol-5-yl)-1 <i>H</i> -benzimidazol-2-yloxy]-2-methylbenzoic acid		446.7

288	5-[6-Chloro-5-(1,3-dimethyl-1 <i>H</i> -indol-5-yl)-1 <i>H</i> -benzimidazol-2-yloxy]-2-methylbenzoic acid		446.9
289	5-[6-Chloro-5-(1,2-dimethyl-1 <i>H</i> -indol-5-yl)-1 <i>H</i> -benzimidazol-2-yloxy]-2-methylbenzoic acid		446.7
290	6-[2-(3-Carboxy-4-methyl-phenoxy)-6-chloro-1 <i>H</i> -benzimidazol-5-yl]-3-methyl-indole-1-carboxylic acid <i>tert</i> -butyl ester		533.7
291	5-[6-Chloro-5-(3-methyl-1 <i>H</i> -indol-6-yl)-1 <i>H</i> -benzimidazol-2-yloxy]-2-methylbenzoic acid		432.3
292	1-{4-[2-(3-carboxy-4-methylphenoxy)-6-chloro-1 <i>H</i> -benzimidazol-5-yl]phenyl}- <i>N,N</i> -dimethylethanaminium trifluoroacetate		450.08
293	1-{4-[2-(3-carboxy-4-methylphenoxy)-6-chloro-1 <i>H</i> -benzimidazol-5-yl]phenyl}ethanaminium trifluoroacetate		422.7

	um trifluoroacetate		
294	{4-[2-(3-carboxy-4-methylphenoxy)-6-chloro-1H-benzimidazol-5-yl]phenyl}-N,N-dimethylmethanaminium trifluoroacetate		436.06
295	2-(3-carboxy-4-methylphenoxy)-6-chloro-5-[4-(dimethylamino)-3-(trifluoromethyl)phenyl]-1H-3,1-benzimidazol-3-ium chloride		490.8
296	2-(3-carboxy-4-methylphenoxy)-6-chloro-5-[4-(dimethylamino)-3-fluorophenyl]-1H-3,1-benzimidazol-3-ium chloride		440.01
297	2-{4-[2-(3-carboxy-4-methylphenoxy)-6-chloro-1H-benzimidazol-5-yl]phenyl}propan-2-aminium trifluoroacetate		436.1
298	5-[5-(6-Acetylnaphthalen-2-yl)-6-chloro-1H-benzimidazol-2-		471.05

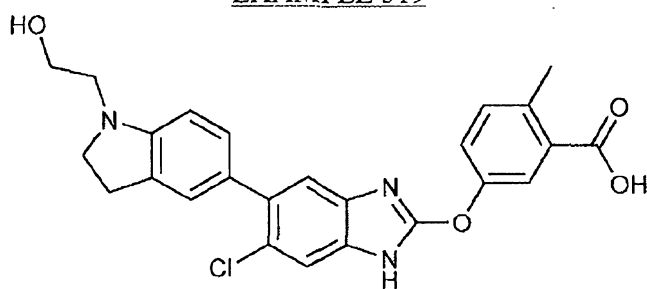
	yl-oxy]-2-methyl-benzoic acid		
299	5-[2-(3-carboxy-4-methylphenoxy)-6-chloro-1 <i>H</i> -benzimidazol-5-yl]-2-isopropyl-2,3-dihydro-1 <i>H</i> -isoindolium trifluoroacetate		463.0
300	5-[2-(3-carboxy-4-methylphenoxy)-6-chloro-1 <i>H</i> -benzimidazol-5-yl]-2-methyl-2,3-dihydro-1 <i>H</i> -isoindolium trifluoroacetate		434.05
301	5-[2-(3-carboxy-4-methylphenoxy)-6-chloro-1 <i>H</i> -benzimidazol-5-yl]-2,3-dihydro-1 <i>H</i> -isoindolium trifluoroacetate		420.05
302	5-(5-Biphenyl-3-yl-6-chloro-1 <i>H</i> -benzimidazol-2-yl-oxy)-2-methyl-benzoic acid		455.05
303	5-[6-Chloro-5-(2-methyl-biphenyl-4-yl)-1 <i>H</i> -benzimidazol-2-yl-oxy]-2-methyl-benzoic acid		469.05

304	5-[6-Chloro-5-(1-methyl-2-oxo-2,3-dihydro-1 <i>H</i> -indol-5-yl)-1 <i>H</i> -benzoimidazol-2-yloxy]-2-methylbenzoic acid		448.6
305	5-[6-Chloro-5-(1-oxo-2,3-dihydro-1 <i>H</i> -isoindol-5-yl)-1 <i>H</i> -benzoimidazol-2-yloxy]-2-methylbenzoic acid		434.5
306	5-[5-(1-Acetyl-2,3-dihydro-1 <i>H</i> -indol-5-yl)-6-chloro-1 <i>H</i> -benzoimidazol-2-yloxy]-2-methylbenzoic acid		462.2
307	5-[6-Chloro-5-(2-oxo-2,3-dihydro-1 <i>H</i> -indol-5-yl)-1 <i>H</i> -benzoimidazol-2-yloxy]-2-methylbenzoic acid		434.5
308	5-[6-Chloro-5-(2,2-difluoro-benzo[1,3]dioxol-5-yl)-1 <i>H</i> -benzoimidazol-2-yloxy]-2-methylbenzoic acid		459.01
309	2-Chloro-5-[6-chloro-5-(6-methoxy-naphthalen-2-yl)-1 <i>H</i> -benzoimidazol-2-yloxy]-benzoic acid		480

310	5-[6-Chloro-5-(6-methoxy-naphthalen-2-yl)-1 <i>H</i> -benzimidazol-2-yloxy]-2,3-dimethylbenzoic acid		473
311	5-[6-Chloro-5-(1-methyl-1 <i>H</i> -indol-5-yl)-1 <i>H</i> -benzimidazol-2-yloxy]-2,3-dimethylbenzoic acid		446
312	5-[6-Chloro-5-(4-methyl-3,4-dihydro-2 <i>H</i> -benzo[1,4]oxazin-7-yl)-1 <i>H</i> -benzimidazol-2-yloxy]-2,3-dimethylbenzoic acid		464
313	5-{6-Chloro-5-[4-(6-hydroxy-pyridin-3-yl)-phenyl]-1 <i>H</i> -benzimidazol-2-yloxy}-2,3-dimethylbenzoic acid		486
314	5-{6-Chloro-5-[4-(6-methoxy-pyridin-3-yl)-phenyl]-1 <i>H</i> -benzimidazol-2-yloxy}-2,3-dimethylbenzoic acid methyl ester		514
315	5-{6-Chloro-5-[4-(6-methoxy-pyridin-3-yl)-phenyl]-1 <i>H</i> -benzimidazol-2-yloxy}-2,3-dimethyl-		500

	benzoic acid		
316	5-{6-Chloro-5-[4-(1-hydroxy-1-methyl-ethyl)-phenyl]-1 <i>H</i> -benzimidazol-2-yl}oxy-2,3-dimethylbenzoic acid		451
317	5-[5-(4-Acetylphenyl)-6-chloro-1 <i>H</i> -benzimidazol-2-yl}oxy-2,3-dimethylbenzoic acid		435
318	2-(3-carboxy-4-methylphenoxy)-6-chloro-5-[4-(dimethylamino)phenyl]-1 <i>H</i> -benzimidazol-3-ium chloride		422.05

EXAMPLE 319



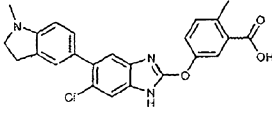
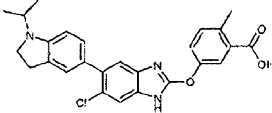
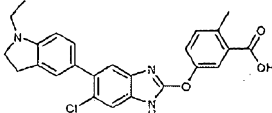
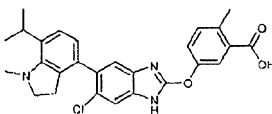
5-({6-chloro-5-[1-(2-hydroxyethyl)-2,3-dihydro-1*H*-indol-5-yl]-1*H*-benzimidazol-2-yl}oxy)-2-methylbenzoic acid. NaBH₄ (22 mg, 0.585 mmol) was added to a solution of 5-({6-chloro-5-[1-(2-hydroxyethyl)-1*H*-indol-5-yl]-1*H*-benzimidazol-2-yl}oxy)-2-methylbenzoic acid (30 mg, 0.065 mmol, Example 263) in AcOH (1mL). The reaction was maintained overnight at ambient temperature, quenched with 2 N aqueous HCl and concentrated. The residue was partitioned between EtOAc and H₂O. The aqueous phase was extracted with EtOAc. The combined organic layers were washed with brine, dried (MgSO₄), filtered and concentrated. Purification of the resulting residue by reverse phase HPLC eluting with 35-100% MeCN/water) afforded the title

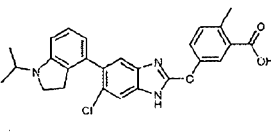
compound. LC-MS: calculated for C₂₅H₂₂ClN₃O₄ 463.91, observed m/e 464.3 (M + H)⁺ (R_t 1.60 min).

Examples 320-324 in Table 6B were prepared following the procedures described for Example 319.

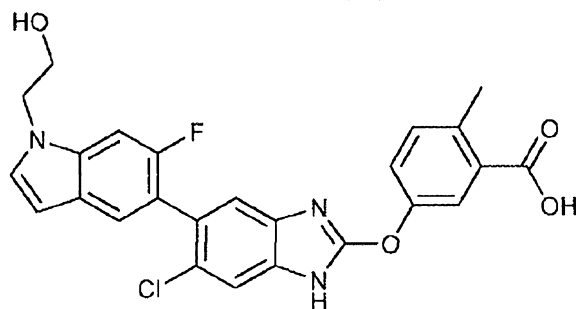
5

Table 6B. Compounds prepared according to the methods described in Example 319.

Ex. No.	Name	Structure	HPLC-mass spectrum m/e
320	5-{[6-chloro-5-(1-methyl-2,3-dihydro-1H-indol-5-yl)-1H-benzimidazol-2-yl]oxy}-2-methylbenzoic acid		434.21
321	5-{[6-chloro-5-(1-isopropyl-2,3-dihydro-1H-indol-5-yl)-1H-benzimidazol-2-yl]oxy}-2-methylbenzoic acid		462
322	5-{[6-chloro-5-(1-ethyl-2,3-dihydro-1H-indol-5-yl)-1H-benzimidazol-2-yl]oxy}-2-methylbenzoic acid		448.3
323	5-{[6-chloro-5-(7-isopropyl-1-methyl-2,3-dihydro-1H-indol-4-yl)-1H-benzimidazol-2-yl]oxy}-2-methylbenzoic acid		475.8

324	5-{{[6-chloro-5-(1-isopropyl-2,3-dihydro-1H-indol-4-yl)-1H-benzimidazol-2-yl]oxy}-2-methylbenzoic acid		462.1
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EXAMPLE 325



5-((6-chloro-5-([6-fluoro-1-(2-hydroxyethyl)-1H-indol-5-yl])-1H-benzimidazol-2-yl)oxy)-2-methylbenzoic acid

Step A 4-bromo-5-fluoro-2-iodoaniline. NIS (2.5 g, 11.1 mmol) was added to a solution of 4-bromo-5-fluoroaniline (2.0 g, 10.5 mmol) in AcOH (26 mL). The reaction was maintained at ambient temperature for 1.5 h, diluted with 20 mL toluene and concentrated. The residue was dissolved in EtOAc and washed with 2 N aqueous NaOH. The organic phase was washed with brine, dried (Na₂SO₄), filtered, and concentrated. Chromatography over silica eluting with 2-10% EtOAc/hexanes afforded the desired product as a white solid.

Step B 4-bromo-5-fluoro-2-[(trimethylsilyl)ethynyl]aniline. Triethylamine (44 mL) followed by trimethylsilylacetylene (0.737 mL, 5.32 mmol) were added dropwise to a suspension of 4-bromo-5-fluoro-2-iodoaniline (1.4 g, 4.43 mmol), Pd(PPh₃)₂Cl₂ (0.156 g, 0.222 mmol), and CuI (0.042 g, 0.222 mmol) at 0 °C. The reaction was warmed to ambient temperature and stirred for 2 h. The reaction was concentrated, diluted with Et₂O, and filtered through Celite. The filtrate was washed with brine, dried (Na₂SO₄), filtered and concentrated. Chromatography over silica eluting with 2-8% EtOAc/hexanes afforded the desired product as a yellow oil.

Step C 5-bromo-6-fluoro-1H-indole. CuI (0.932 g, 4.89 mmol) was added to a solution of 4-bromo-5-fluoro-2-[(trimethylsilyl)ethynyl]aniline (0.700 g, 2.45 mmol) in DMF (25 mL). The resulting suspension was heated at 100 °C for 1 h. The reaction mixture was partitioned between 10% aqueous Na₂S₂O₃ and Et₂O. The aqueous layer was extracted with Et₂O. The combined organic layers were washed with 5 N aqueous NaOH and brine, dried (Na₂SO₄), filtered, and concentrated. The crude product was used in the next step without further purification.

Step D Ethyl (5-bromo-6-fluoro-1H-indol-1-yl)acetate. NaH (81 mg, 3.21 mmol) was added to

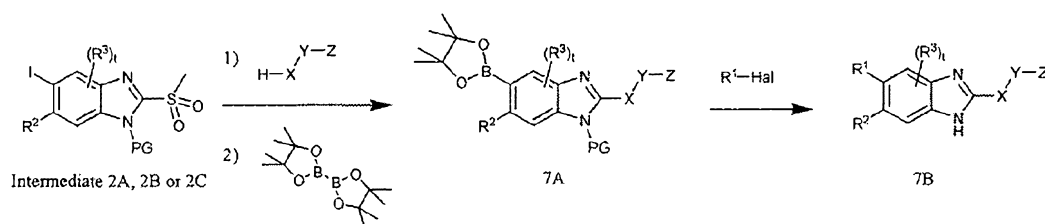
a 0 °C solution of 5-bromo-6-fluoro-1*H*-indole (0.343 g, 1.60 mmol) in THF (16 mL). The reaction mixture was stirred at 0 °C for 15 min, then ethyl bromoacetate (0.535 mL, 4.81 mmol) was added. The reaction was stirred at rt for 1 h, then partitioned between water and EtOAc. The aqueous layer was extracted with EtOAc and the combined organic layers were washed with
5 brine, dried (Na₂SO₄), filtered, and concentrated. The crude product was used in the next step without further purification.

Step E 2-(5-Bromo-6-fluoro-1*H*-indol-1-yl)ethanol. DIBAL-H (1 M in hexanes) (4 mL, 4 mmol) was added to a 0 °C solution of ethyl (5-bromo-6-fluoro-1*H*-indol-1-yl)acetate (0.480 g, 1.60 mmol) in anhydrous THF (10 mL). The reaction was stirred at rt for 1 h, then treated with
10 saturated aqueous Rochelle's salt and Et₂O. The mixture was stirred vigorously for 30 min. The layers were separated and the aqueous layer was further extracted with Et₂O. The combined organic layers were washed with brine, dried (Na₂SO₄), filtered, and concentrated. Chromatography over silica eluting with 60% EtOAc/hexanes afforded the desired compound as an oil.

Step F Methyl 5-[(6-chloro-5-[6-fluoro-1-(2-hydroxyethyl)-1*H*-indol-5-yl]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-benzimidazol-2-yl)oxy]-2-methylbenzoate. A microwave vial was charged with Intermediate 13 (200 mg, 0.349 mmol), 2-(5-bromo-6-fluoro-1*H*-indol-1-yl)ethanol (144 mg, 0.559 mmol), Pd(PPh₃)₄ (61 mg, 0.052 mmol), DMF (4.3 mL), and 1 M aqueous K₂CO₃ (0.70 mL). The reaction was heated at 150 °C under microwave irradiation for 8 min. The reaction was partitioned between water and EtOAc. The aqueous phase was extracted
15 with EtOAc. The combined organic layers were washed with brine, dried (Na₂SO₄), filtered and concentrated. Chromatography over silica eluting with 50% EtOAc/hexanes afforded the desired product as a yellow oil.

Step G 5-[(6-chloro-5-[6-fluoro-1-(2-hydroxyethyl)-1*H*-indol-5-yl]-1*H*-benzimidazol-2-yl)oxy]-2-methylbenzoic acid. TBAF (1 M in THF) (2 mL, 2 mmol) was added to a solution of methyl
25 5-[(6-chloro-5-[6-fluoro-1-(2-hydroxyethyl)-1*H*-indol-5-yl]-1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-benzimidazol-2-yl)oxy]-2-methylbenzoate in THF (2 mL). The reaction was heated at 80 °C for 3 h. Volatiles were removed and the residue was dissolved in MeOH (4 mL) and treated with 2.5 N aqueous NaOH (1.5 mL). The reaction was stirred at 45 °C for 1 h, then at
30 rt overnight. Reaction mixture was diluted with EtOAc and washed with 1 M aqueous HCl and brine. The organic layer was dried (Na₂SO₄), filtered, and concentrated. Chromatography over silica eluting with 8% MeOH/DCM afforded the title compound as a beige solid. ¹H NMR (500 MHz, CD₃OD): δ 7.86 (d, 1H), 7.48 (s, 1H), 7.44-7.37 (m, 3H), 7.33 (s, 1H), 7.27 (d, 1H), 7.23 (d, 1H), 6.46 (d, 1H), 4.25 (t, 2H), 3.88 (t, 2H), 2.61 (s, 3H). LC-MS: m/e 480.2 (M + H)⁺ (1.79 min).

SCHEME 7

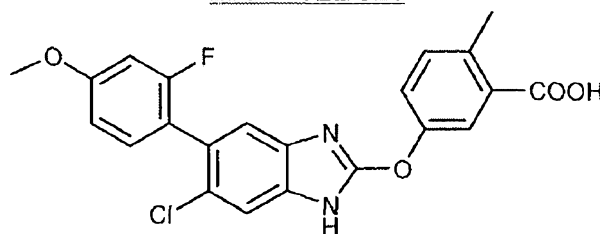


In Scheme 7, Intermediate 2A, 2B (protected with a suitable protecting group (PG) such as SEM or para-phenylbenzyl), or Intermediate 2C is reacted with H-X-Y-Z (wherein X-H is an alcohol, thiol or amine and Z is an ester) and a base, followed by reaction with

5 bis(pinacolato)diboron in the presence of palladium tetrakis(triphenyl)-phosphine to afford the boronate ester 7A. Ester Z is then hydrolyzed to the acid. The subsequent reaction of acid 7A with a halide, triflate or diazonium salt or R¹ (R¹-Hal) in the presence of palladium tetrakis(triphenyl)phosphine, followed by removal of the protecting group PG affords the 2-

10 substituted benzimidazole 7B.

EXAMPLE 326



5-[(6-chloro-5-(2-fluoro-4-methoxyphenyl)-1H-benzimidazol-2-yl)oxy]-2-methylbenzoic acid

Step A 5-[(6-chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-benzimidazol-2-yl)oxy]-2-methylbenzoic acid. A solution of

15 Intermediate 13 (5g, 8.73 mmol) in MeOH (50 mL) and 2N aqueous NaOH (20mL) was stirred at rt overnight. Volatiles were removed. The residue was partitioned between EtOAc and 2N aqueous HCl. The organic phase was washed with brine, dried (MgSO₄) and concentrated to afford the desired product as a solid, which was used in the next step without purification.

Step B 5-[(6-chloro-5-(2-fluoro-4-methoxyphenyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-benzimidazol-2-yl)oxy]-2-methylbenzoic acid. K₂CO₃ (0.293 mL, 0.585 mmol) followed by Pd(PPh₃)₄ (6.76 mg, 5.85 μmol) were added to a solution of 4-Bromo 3-fluoro anisole (0.027 mL, 0.195 mmol) and 5-[(6-chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-benzimidazol-2-yl)oxy]-2-methylbenzoic acid (122 mg, 0.219 mmol) in DMF (2 mL). The reaction was heated at 150°C under microwave irradiation for 10

25 min. Volatiles were removed to afford the desired product, which was used in the next step without further purification.

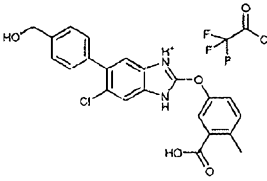
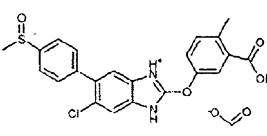
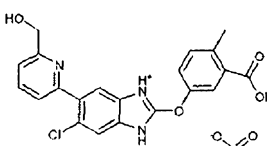
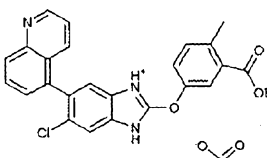
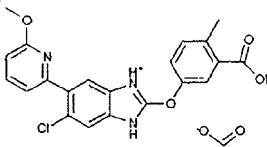
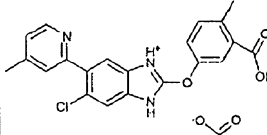
Step C 5-[(6-chloro-5-(2-fluoro-4-methoxyphenyl)-1H-benzimidazol-2-yl)oxy]-2-methylbenzoic acid. TBAF (1M in THF) (0.5 mL) was added to a solution of 5-[(6-chloro-5-(2-fluoro-4-methoxyphenyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-benzimidazol-2-yl)oxy]-2-

5 methylbenzoic acid in dioxane (3 mL). The reaction was heated at 80°C for 16 h. Volatiles were removed and the residue acidified with 2N aqueous HCl and extracted with EtOAc. The organic phase was washed with water and concentrated. Purification by reverse phase HPLC eluting with 15-90% MeCN:water afforded the title compound as a white solid. LC-MS: calculated for C₂₇H₃₆ClFN₂O₄ 426.08, observed m/e 427.00 (M + H)⁺ (R_t 1.90 min). ¹H NMR (500 MHz, CD₃OD): δ 7.87 (s, 1H) 7.48 (s, 1H) 7.42 (m, 2H) 7.28 (s, 1H) 7.20 (m, 1H) 6.80 (dd, 1H) 6.75 (dd, 1H) 3.84 (s, 3H) 2.61 (s, 3H).

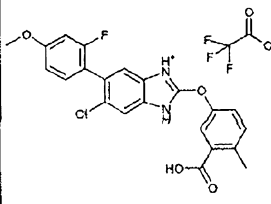
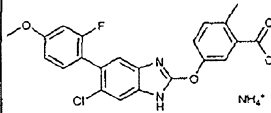
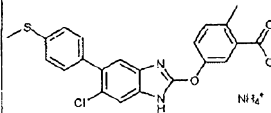
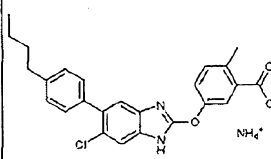
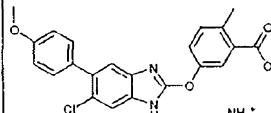
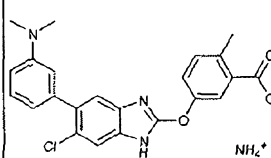
10 Examples 327-364 in Table 7 were prepared following the procedures described in Example 326 by substituting the appropriate halide or triflate from the Intermediates, or from commercial sources; and by substituting the appropriate phenols from the Intermediates, or from commercial sources.

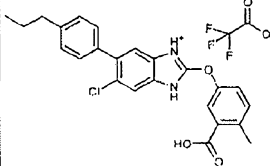
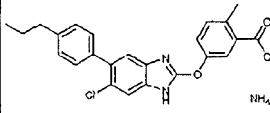
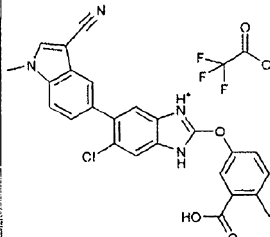
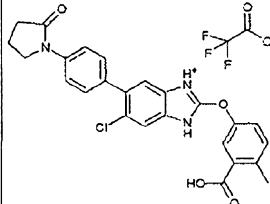
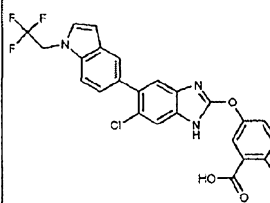
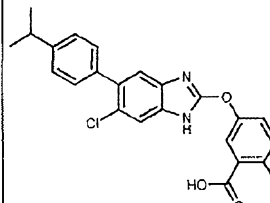
Table 7. Compounds prepared according to the methods described in Example 326 and Scheme 7.

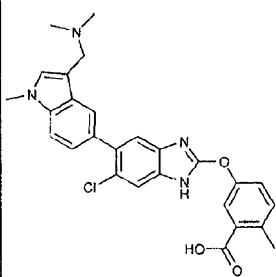
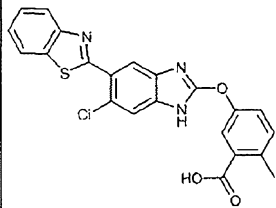
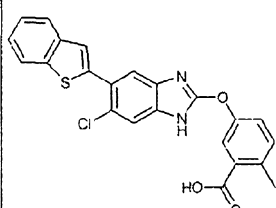
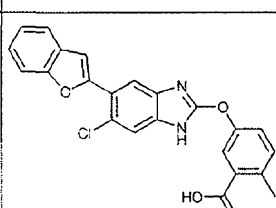
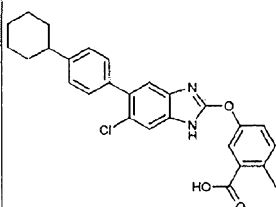
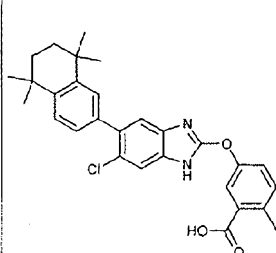
Ex. No.	Name	Structure	HPLC-mass spectrum m/e
327	2-(3-carboxy-4-methylphenoxy)-6-chloro-5-(3,4-dimethoxyphenyl)-1 <i>H</i> -3,1-benzimidazol-3-ium trifluoroacetate		438.99
328	Ammonium 5-{[6-chloro-5-(4-fluoro-3-methylphenyl)-1 <i>H</i> -benzimidazol-2-yl]oxy}-2-methylbenzoate		411.20
329	Ammonium 5-{[6-chloro-5-(2-isopropylphenyl)-1 <i>H</i> -benzimidazol-2-yl]oxy}-2-methylbenzoate		421.20

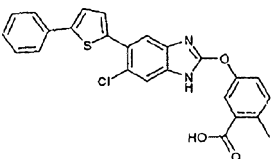
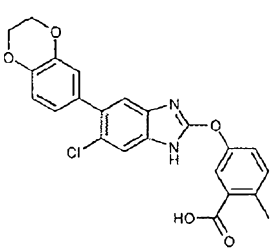
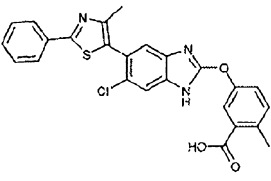
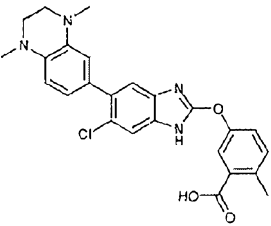
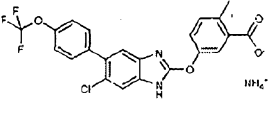
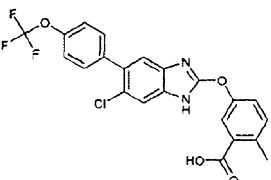
330	2-(3-carboxy-4-methylphenoxy)-6-chloro-5-[4-(hydroxymethyl)phenyl]-1 <i>H</i> -3,1-benzimidazol-3-ium trifluoroacetate		408.99
331	2-(3-carboxy-4-methylphenoxy)-6-chloro-5-[4-(methylsulfinyl)phenyl]-1 <i>H</i> -3,1-benzimidazol-3-ium formate		441.02
332	2-(3-carboxy-4-methylphenoxy)-6-chloro-5-[6-(hydroxymethyl)pyridin-2-yl]-1 <i>H</i> -3,1-benzimidazol-3-ium formate		410.05
333	2-(3-carboxy-4-methylphenoxy)-6-chloro-5-quinolin-5-yl-1 <i>H</i> -3,1-benzimidazol-3-ium formate		430.10
334	2-(3-carboxy-4-methylphenoxy)-6-chloro-5-(6-methoxypyridin-2-yl)-1 <i>H</i> -3,1-benzimidazol-3-ium formate		410.00
335	2-(3-carboxy-4-methylphenoxy)-6-chloro-5-(4-methylpyridin-2-yl)-1 <i>H</i> -3,1-benzimidazol-3-ium formate		394.2

	1 <i>H</i> -3,1-benzimidazol-3-ium formate		
336	2-(3-carboxy-4-methylphenoxy)-6-chloro-5-isoquinolin-4-yl-1 <i>H</i> -3,1-benzimidazol-3-ium formate		429.7
337	Ammonium 5-({6-chloro-5-[4-(trifluoromethyl)phenyl]-1 <i>H</i> -benzimidazol-2-yl}oxy)-2-methylbenzoate		446.96
338	Ammonium 5-{{6-chloro-5-(3-methoxyphenyl)-1 <i>H</i> -benzimidazol-2-yl}oxy}-2-methylbenzoate		409.10
339	Ammonium 5-{{6-chloro-5-(3-isopropylphenyl)-1 <i>H</i> -benzimidazol-2-yl}oxy}-2-methylbenzoate		421.02
340	L-002219698-001K Ammonium 5-{{6-chloro-5-(3,4-dimethylphenyl)-1 <i>H</i> -benzimidazol-2-yl}oxy}-2-methylbenzoate		408.99

341	2-(3-carboxy-4-methylphenoxy)-6-chloro-5-(2-fluoro-4-methoxyphenyl)-1 <i>H</i> -3,1-benzimidazol-3-ium trifluoroacetate		441.6
342	Ammonium 5-([6-chloro-5-(2-fluoro-4-methoxyphenyl)-1 <i>H</i> -benzimidazol-2-yl]oxy)-2-methylbenzoate		441.6
343	Ammonium 5-([6-chloro-5-[4-(methylthio)phenyl]-1 <i>H</i> -benzimidazol-2-yl]oxy)-2-methylbenzoate		424.97
344	Ammonium 5-([5-(4-butylphenyl)-6-chloro-1 <i>H</i> -benzimidazol-2-yl]oxy)-2-methylbenzoate		435.09
345	Ammonium 5-([6-chloro-5-(4-methoxyphenyl)-1 <i>H</i> -benzimidazol-2-yl]oxy)-2-methylbenzoate		409.00
346	Ammonium 5-([6-chloro-5-[3-(dimethylamino)phenyl]-1 <i>H</i> -benzimidazol-2-yl]oxy)-2-methylbenzoate		422.01

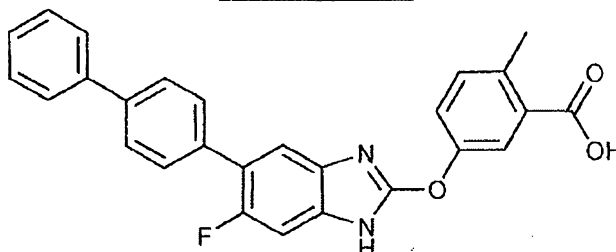
347	2-(3-carboxy-4-methylphenoxy)-6-chloro-5-(4-propylphenyl)-1 <i>H</i> -3,1-benzimidazol-3-ium trifluoroacetate		421.01
348	Ammonium 5-{[6-chloro-5-(4-propylphenyl)-1 <i>H</i> -benzimidazol-2-yl]oxy}-2-methylbenzoate		421.01
349	2-(3-carboxy-4-methylphenoxy)-6-chloro-5-(3-cyano-1-methyl-1 <i>H</i> -indol-5-yl)-1 <i>H</i> -3,1-benzimidazol-3-ium trifluoroacetate		457.06
350	2-(3-carboxy-4-methylphenoxy)-6-chloro-5-[4-(2-oxopyrrolidin-1-yl)phenyl]-1 <i>H</i> -3,1-benzimidazol-3-ium trifluoroacetate		462.03
351	5-{6-Chloro-5-[1-(2,2,2-trifluoro-ethyl)-1 <i>H</i> -indol-5-yl]-1 <i>H</i> -benzoimidazol-2-yloxy}-2-methylbenzoic acid		542.5 (+ Na ⁺ And H ₂ O)
352	5-[6-Chloro-5-(4-isopropyl-phenyl)-1 <i>H</i> -benzoimidazol-2-yloxy]-2-methylbenzoic acid		421.03

353	5-[6-Chloro-5-(3-dimethylaminomethyl-1-methyl-1 <i>H</i> -indol-5-yl)-1 <i>H</i> -benzoimidazol-2-yloxy]-2-methylbenzoic acid		471.08 (-H ₂ O)
354	5-(5-Benzothiazol-2-yl-6-chloro-1 <i>H</i> -benzoimidazol-2-yloxy)-2-methylbenzoic acid		432.1
355	5-(5-Benzo[<i>b</i>]thiophen-2-yl-6-chloro-1 <i>H</i> -benzoimidazol-2-yloxy)-2-methylbenzoic acid		435.1
356	5-(5-Benzofuran-2-yl-6-chloro-1 <i>H</i> -benzoimidazol-2-yloxy)-2-methylbenzoic acid		420.02
357	5-[6-Chloro-5-(4-cyclohexyl-phenyl)-1 <i>H</i> -benzoimidazol-2-yloxy]-2-methylbenzoic acid		461.3
358	5-[6-Chloro-5-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)-1 <i>H</i> -benzoimidazol-2-yloxy]-2-methylbenzoic acid		489.14

359	5-[6-Chloro-5-(5-phenyl-thiophen-2-yl)-1 <i>H</i> -benzimidazol-2-yl]oxy]-2-methylbenzoic acid		461.7
360	5-[6-Chloro-5-(2,3-dihydrobenzo[1,4]dioxin-6-yl)-1 <i>H</i> -benzimidazol-2-yl]oxy]-2-methylbenzoic acid		436.00
361	5-[6-Chloro-5-(4-methyl-2-phenylthiazol-5-yl)-1 <i>H</i> -benzimidazol-2-yl]oxy]-2-methylbenzoic acid		475.94
362	5-[6-Chloro-5-(1,4-dimethyl-1,2,3,4-tetrahydro-quinoxalin-6-yl)-1 <i>H</i> -benzimidazol-2-yl]oxy]-2-methylbenzoic acid		463.8
363	Ammonium 5-({6-chloro-5-[4-(trifluoromethoxy)phenyl]-1 <i>H</i> -benzimidazol-2-yl}oxy)-2-methylbenzoate		462.95
364	5-[6-Chloro-5-(4-trifluoromethoxyphenyl)-1 <i>H</i> -benzimidazol-2-yl]oxy]-2-methyl-		462.95

	benzoic acid		
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EXAMPLE 365

5-[(5-biphenyl-4-yl-6-fluoro-1H-benzimidazol-2-yl)oxy]-2-methylbenzoic acid

- 5 Step A 5-Fluoro-4-iodo-2-nitro-phenylamine (2). 5-Fluoro-2-nitroaniline (10 g, 64 mmol) was dissolved in 150 mL of acetic acid. *N*-iodosuccinimide (15.85 g, 70 mmol) was then added and the reaction mixture was heated to 70 °C for 4 h. The reaction mixture was cooled to 25 °C, then poured into 1.5 L of cold H₂O. The resulting yellow precipitate was then collected by vacuum filtration to give the title compound 2.
- 10 Step B 2-Fluoro-5-nitro-[1,1';4'1'']terphenyl-4-ylamine (3). 4-Biphenylboronic acid (737 mg, 2.4 mmol), K₂CO₃ (995 mg, 7.2 mmol), Pd(PPh₃)₄ (139 mg, 0.12 mmol) and 2 (700 mg, 2.4 mmol) in 10 mL toluene, 2 mL DMF and 2 mL H₂O were suspended in a microwave reactor vial and heated to 130 °C for 10 min in a microwave reactor. The resulting dark solution was then diluted with EtOAc (150 mL) and washed three times with 50 mL portions of saturated aqueous
- 15 NH₄Cl. The combined organic layers were dried (MgSO₄), filtered and concentrated in *vacuo*. The crude product was purified on ISCO (EtOAc/Hexanes = 6/4) to give title compound 3.
- Step C 6-Fluoro-[1,1';4'1'']terphenyl-3,4-diamine (4). To a solution of EtOH (40 mL), H₂O (10 mL) and 3 (663 mg, 2.1 mmol) was added Iron (889 mg, 16 mmol) and NH₄Cl (562 mg, 10.5 mmol). The resulting suspension was allowed to stir for 18 h at 50 °C. The crude suspension
- 20 was diluted with copious amounts of EtOAc and filtered over a pad of Celite. The resulting yellow solution was concentrated in *vacuo* then purified on ISCO (EtOAc/Hexanes = 7/3) to give title compound 4.
- Step D 5-Biphenyl-4-yl-6-fluoro-1,3-dihydro-benzimidazole-2-thione (5). To a solution of EtOH (20 mL), H₂O (4 mL) and KOH (593 mg, 11 mmol) was added 4 (2.46 g, 8.8 mmol). CS₂
- 25 (0.65 mL, 11 mmol) was then added and the suspension was heated to reflux for 2 h. The reaction mixture was cooled to 25 °C, then 40 mL of H₂O and 0.8 mL of acetic acid were added resulting in a tan precipitate. The precipitate was collected by vacuum filtration resulting in title compound 5, which required no further purification.

Step E 5-Biphenyl-4-yl-6-fluoro-2-methylsulfanyl-1H-benzoimidazole (6). To a solution of 5 (2.23g, 6.9 mmol) in 40 mL of THF was added triethylamine (2.2 mL) followed by the dropwise addition of methyl iodide (0.43 mL, 6.9 mmol). The reaction mixture was heated to 40 °C for 2 h. The solvent was then removed in *vacuo* and the residue was taken up in EtOAc and washed two times with 100 mL portions of saturated aqueous ammonium chloride and one 100 mL portion of brine. The combined organic layers were dried over MgSO₄ filtered and concentrated to dryness in *vacuo*. Then, 150 mL of CH₂Cl₂ were added and the resulting precipitate was collected by vacuum filtration to give title compound 6.

Step F 5-Biphenyl-4-yl-6-fluoro-2-methanesulfonyl-1H-benzoimidazole (7). To 32 mL of acetic acid was added 6 (2.34, 6.4 mmol) resulting in a suspension. In a separate flask KMnO₄ (2.48g, 15.7 mmol) was dissolved in 40 mL of H₂O. The KMnO₄ solution was then added to the solution of 6 in acetic acid and allowed to stir for 2 h at ambient temperature. The dark reaction mixture was diluted with EtOAc (200 mL) and washed three times with 150 mL portions of brine. The combined organic layers were dried over MgSO₄ then filtered and concentrated in *vacuo* to give title compound 7 as a pale yellow solid.

Step G 5-(5-Biphenyl-4-yl-6-fluoro-1H-benzoimidazol-2-yl-oxy)-2-methylbenzoic acid methyl ester (8). To a solution of 7 (454 mg, 1.2 mmol) in pyridine 10 mL was added 5-hydroxy-2-methylbenzoic acid methyl ester (412 mg, 2.4 mmol). The reaction mixture was heated to reflux for 5 days. Once the reaction was determined to be complete by TLC, the reaction mixture was diluted with EtOAc (100 mL) and washed two times with 100 mL portions of saturated aqueous ammonium chloride. The combined organic layers were dried over MgSO₄ filtered and concentrated in *vacuo* to give a crude brown oil. The resulting oil was purified on ISCO (EtOAc/Hexanes = 2/3) to give title compound 8 as a yellow oil.

Step H 5-[(5-biphenyl-4-yl-6-fluoro-1H-benzimidazol-2-yl)oxy]-2-methylbenzoic acid To a solution of 8 (31mg, 0.069 mmol) in 1 mL of THF was added 1 M NaOH (0.28 mL, 0.28 mmol), and the resulting solution was allowed to stir for 48 h at ambient temperature. Then 1 M HCl was added to adjust the mixture to pH to ~ 1. The solvent was removed in *vacuo* and the resulting residue was taken up in 1.3 mL of DMSO and purified by preparatory HPLC using a 30-80% CH₃CN with 0.05% trifluoroacetic acid gradient over 20 min. The pure fractions were combined and lyophilized to give the title compound as a white solid. LC-MS: calculated for C₂₇H₁₉FN₂O₃ 438.14, observed m/e 439(M + H)⁺. ¹H NMR (500 MHz, DMSO): δ 13.10 (s, 1H) 12.63 (s, 1H) 7.79-7.37 (m, 14H) 2.50 (s, 3H).

BIOLOGICAL EXAMPLE 1

AMPKSAMSF (in vitro AMPK activation assay)

The recombinant human AMPK complex 1 (containing α1β1γ1) 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, 1×10^6 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 ZnCl₂, 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 total *in vitro* AMPK activation assay volume is 50 µl in a 96-well plate. The reaction mixture contained 100 µM ATP (0.5 µCi ³³P-ATP per reaction), and 50 µM SAMS (HMRSAMSGHLVKRR) in a buffer (20 mM HEPES, pH 7.0, 5 mM MgCl₂, 0.01% Brij35). The reaction was initiated with addition of the enzyme. After 30-minute incubation at 30°C, the reaction was stopped by addition of 80 µl 1% H₃PO₄. Aliquots (100 µl) were transferred to 96-well MultiScreen plates (MAPHNOB50; Millipore Corp., Bedford, Massachusetts, USA). The plate was washed three times with 1% H₃PO₄ followed by detection in a Top-count. The counts per minute from the basal activity (the reaction without activator) was subtracted from each well and the data were expressed as % maximum AMP activation followed by EC₅₀ calculation. The % maximum AMP activation for selected compounds is provided in the table below.

The compounds of the present invention have greater than 50% maximum AMP activation of human AMPK complex 1 (containing α1β1γ1), and EC₅₀ values of less than 10 micromolar.

The compounds of Examples 1-365 were tested in the *in vitro* AMPK activation assay using recombinant human AMPK complex 1 (containing α1β1γ1) and found to have EC₅₀ values of less than 10 micromolar and greater than 80% maximum AMP activation. Preferred compounds of the present invention were found to have EC₅₀

values of less than 0.1 micromolar in the *in vitro* AMPK activation assay using recombinant human AMPK complex 1.

Maximum AMP Activation for Selected Compounds		
Example No.	% Maximum AMP Activation of human AMPK Complex 1	EC ₅₀ (nM)
1	238	8
183	207	16
230	160	9
325	181	5
229	241	3
232	187	1
67	184	3
228	159	2
326	213	10
231	203	7
184	185	8
262	162	3
68	245	7
236	206	10
151	212	22
168	161	5
365	140	9

5

BIOLOGICAL EXAMPLE 2

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

10

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pH <2 with 10 M H₂SO₄. 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 3

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 4

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 5

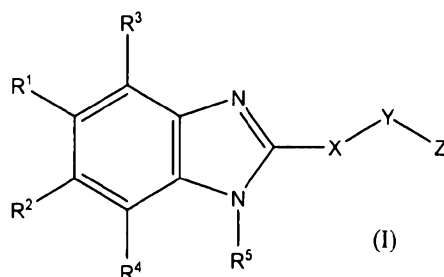
Chronic weight reduction studies in Diet Induced Obese (DIO) mice: General Procedure

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.

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 spirit and 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. It is intended, therefore, that the invention be defined by the scope of the claims which follow and that such claims be interpreted as broadly as is reasonable.

Claims:

1. A compound of structural formula I:



or a pharmaceutically acceptable salt thereof, wherein:

- 5 X is selected from:

- (1) -S-,
- (2) -O-,
- (3) -O-CH₂-, and
- (4) -NH-,

- 10 wherein CH₂ is unsubstituted or substituted with 1 or 2 substituents selected from: hydroxy, halogen, NH₂, C₁-6alkyl, CO₂H, CO₂C₁-6alkyl, COC₁-6alkyl, phenyl and -CH₂phenyl, and wherein NH is unsubstituted or substituted with 1 substituent selected from: C₁-6alkyl, CO₂H, CO₂C₁-6alkyl, COC₁-6alkyl, phenyl and -CH₂phenyl;

Y is selected from:

- 15
 - (1) -C₂-10cycloheteroalkenyl,
 - (2) aryl, and
 - (3) heteroaryl,

wherein cycloheteroalkenyl, aryl and heteroaryl are unsubstituted or substituted with 1, 2, 3 or 4 substituents selected from R^b;

- 20 Z is selected from:

- (1) oxo,
- (2) -CN,
- (3) -(CH₂)_nCO₂H,
- (4) -(CH₂)_nCO₂Rⁱ,
- 25 (5) -(CH₂)_nOH,
- (6) -(CH₂)_nC(O)NHR^g,
- (7) -(CH₂)_nNHC(O)C₁-6alkyl,

- (8) $-(CH_2)_nSO_2NHR^g$,
- (9) $-(CH_2)_nSO_2NHC(O)R^i$,
- (10) $-(CH_2)_nC(O)NHSO_2R^i$,
- (11) $-(CH_2)_nNHC(O)N(R^g)_2$,
- 5 (12) $-(CH_2)_nC_{3-10}cycloalkyl-CO_2R^e$,
- (13) heteroaryl,
- (14) $-C_{2-10}cycloheteroalkenyl$, and
- (15) $-C_{2-10}cycloheteroalkyl$,

wherein each CH_2 is unsubstituted or substituted with 1 or 2 substituents selected from
 10 $C_{1-6}alkyl$, $-OH$ and $-NH_2$, wherein each NH is unsubstituted or substituted with
 1 substituent selected from R^c , and wherein each alkyl, cycloalkyl, cycloheteroalkyl,
 cycloheteroalkenyl, aryl and heteroaryl is unsubstituted or substituted with 1, 2, 3 or
 4 substituents selected from R^c ;

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

- 15 (1) halogen,
- (2) $-CN$,
- (3) $-CF_3$,
- (4) $-C_{1-6}alkyl$,
- (5) $-(CH_2)_paryl$,
- 20 (6) biphenyl,
- (7) $-(CH_2)_pheteroaryl$,
- (8) $-C_{2-6}alkenyl-aryl$,
- (9) $-C_{2-6}alkynyl-alkyl$,
- (10) $-C_{2-6}alkynyl-aryl$,
- 25 (11) $-C_{2-6}alkynyl-heteroaryl$,
- (12) $-C_{2-6}alkynyl-C_{3-7}cycloalkyl$,
- (13) $-C_{2-6}alkynyl-C_{2-7}cycloheteroalkyl$, and
- (14) $-C_{2-6}alkynyl-C_{2-7}cycloheteroalkenyl$,

wherein each CH_2 is unsubstituted or substituted with 1 or 2 substituents selected from:
 30 halogen, CF_3 , $-OH$, $-NH_2$, $-C_{1-6}alkyl$, $-OC_{1-6}alkyl$, $-NHC_{1-6}alkyl$, and
 $-N(C_{1-6}alkyl)_2$,

wherein alkyl, alkenyl and alkynyl is unsubstituted or substituted with 1, 2 or 3 substituents selected from: halogen, CF₃, -OH, -NH₂, -C₁₋₆alkyl, -OC₁₋₆alkyl, -NHC₁₋₆alkyl, and -N(C₁₋₆alkyl)₂, and wherein each 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 R¹ and R² is selected from the group consisting of: halogen, -CN, -CF₃, and -C₁₋₆alkyl;

R³ and R⁴ are each independently selected from:

- (1) hydrogen,
- (2) halogen,
- (3) -C₁₋₆alkyl,
- (4) -CN,
- (5) -CF₃,
- (6) -OH,
- (7) -OC₁₋₆alkyl,
- (8) -SOC₁₋₆alkyl, and
- (9) -SO₂C₁₋₆alkyl;

R⁵ is selected from:

- (1) hydrogen,
- (2) -C₁₋₆alkyl,
- (3) -CH₂CO₂H, and
- (4) -CH₂CO₂C₁₋₆alkyl;

R^a is independently selected from the group consisting of:

- (1) halogen,
- (2) oxo,
- (3) -(CH₂)_mOH,
- (4) -(CH₂)_mN(R^j)₂,
- (5) -CN,
- (6) -C₁₋₆alkyl,
- (7) -(CH₂)_mCF₃,
- (8) -OCF₃,
- (9) -C(=N-OH)N(R^j)₂,
- (10) -OC₁₋₆alkyl,

- (11) -SC₁₋₆alkyl,
 (12) -S(O)C₁₋₆alkyl,
 (13) -C(O)C₁₋₆alkyl,
 (14) -C(O)C₂₋₆cycloheteroalkyl,
 5 (15) -C(O)NH₂,
 (16) -C(O)N(C₁₋₆alkyl)₂,
 (17) -CO₂H, -OC(O)H,
 (18) -CO₂C₁₋₆alkyl,
 (19) -OC(O)C₁₋₆alkyl,
 10 (20) -(CH₂)_mC₃₋₇cycloalkyl,
 (21) -C₂₋₆cycloheteroalkyl,
 (22) -C₂₋₆cycloheteroalkenyl,
 (23) aryl, and
 (24) heteroaryl,

15 wherein each CH₂ is unsubstituted or substituted with 1 or 2 substituents selected from:
 oxo, -(CH₂)₀₋₃OH, -CN, -NH₂, -NH(C₁₋₆alkyl), -N(C₁₋₆alkyl)₂, -C₁₋₆alkyl,
 -OC₁₋₆alkyl, halogen, -CH₂F, -CHF₂, -CF₃, -CO₂H, -CO₂C₁₋₆alkyl, -C₃₋₇cycloalkyl,
 phenyl, and CH₂phenyl, and wherein alkyl, cycloalkyl, cycloheteroalkyl, aryl and
 heteroaryl are unsubstituted or substituted with 1, 2, 3 or 4 substituents selected from:
 20 oxo, -(CH₂)₀₋₃OH, -CN, -NH₂, -NH(C₁₋₆alkyl), -N(C₁₋₆alkyl)₂, -C₁₋₆alkyl,
 -OC₁₋₆alkyl, halogen; -CH₂F, -CHF₂, -CF₃, -CO₂H, -CO₂C₁₋₆alkyl, -C₃₋₇cycloalkyl,
 phenyl, and CH₂phenyl;

each R^b is independently selected from:

- (1) hydrogen,
 25 (2) -C₁₋₆alkyl,
 (3) -C₃₋₆cycloalkyl,
 (4) -C₃₋₆cycloalkenyl,
 (5) -C₂₋₆cycloheteroalkyl,
 (6) aryl,
 30 (7) heteroaryl,
 (8) halogen,
 (9) -OH,
 (10) -NO₂,
 (11) -NH₂,

- (12) -NH(C₁₋₆alkyl),
 (13) -N(C₁₋₆alkyl)₂,
 (14) -OC₁₋₆alkyl,
 (15) -(CH₂)_qCO₂H,
 (16) -(CH₂)_qCO₂C₁₋₆alkyl,
 (17) -CF₃,
 (18) -CN,
 (19) -SO₂C₁₋₆alkyl, and
 (20) -(CH₂)_qCON(R^e)₂,

wherein each CH₂ is unsubstituted or substituted with 1 or 2 halogens, and wherein each alkyl, cycloalkyl, cycloalkenyl, cycloheteroalkyl, aryl and heteroaryl is unsubstituted or substituted with 1, 2 or 3 halogens;

each R^c is independently selected from:

- (1) halogen,
 (2) oxo,
 (3) -(CH₂)_rOH,
 (4) -(CH₂)_rN(R^e)₂,
 (5) -(CH₂)_rCN,
 (6) -C₁₋₆alkyl,
 (7) -CF₃,
 (8) -C₁₋₆alkyl-OH,
 (9) -OCH₂OC₁₋₆alkyl,
 (10) -(CH₂)_rOC₁₋₆alkyl,
 (11) -OCH₂aryl,
 (12) -(CH₂)_rSC₁₋₆alkyl,
 (13) -(CH₂)_rC(O)R^f,
 (14) -(CH₂)_rC(O)N(R^e)₂,
 (15) -(CH₂)_rCO₂H,
 (16) -(CH₂)_rCO₂R^f,
 (17) -(CH₂)_rC₃₋₇cycloalkyl,
 (18) -(CH₂)_rC₂₋₆cycloheteroalkyl,
 (19) -(CH₂)_raryl, and
 (20) -(CH₂)_rheteroaryl,

wherein each CH₂ is unsubstituted or substituted with 1 or 2 substituents selected from: oxo, -OH, -CN, -N(R^h)₂, -C₁₋₆alkyl, -OC₁₋₆alkyl, halogen, -CH₂F, -CHF₂, -CF₃, -CO₂H, -CO₂C₁₋₆alkyl, -C₃₋₇cycloalkyl 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, -C₁₋₆alkyl, -OC₁₋₆alkyl, halogen, -CH₂F, -CHF₂, -CF₃, -CO₂H, -CO₂C₁₋₆alkyl, -C₃₋₇cycloalkyl and heteroaryl;

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

- (1) hydrogen, and
- (2) C₁₋₆alkyl,

wherein alkyl is unsubstituted or substituted with 1, 2, 3 or 4 substituents selected from: -OH, oxo, halogen, C₁₋₆alkyl, -OC₁₋₆alkyl, -NH₂, -NH(C₁₋₆alkyl), and -N(C₁₋₆alkyl)₂; each R^j is independently selected from:

- (1) hydrogen,
- (2) C₁₋₆alkyl,
- (3) C₃₋₆cycloalkyl,
- (4) -C(O)Rⁱ, and
- (5) -SO₂Rⁱ,

wherein alkyl and cycloalkyl are unsubstituted or substituted with 1, 2, 3 or 4 substituents selected from: -OH, oxo, halogen, C₁₋₆alkyl, -OC₁₋₆alkyl, -NH₂, -NH(C₁₋₆alkyl), and -N(C₁₋₆alkyl)₂;

each R^f and Rⁱ is independently selected from:

- (1) C₁₋₆alkyl,
- (2) C₄₋₇cycloalkyl,
- (3) C₄₋₇cycloalkenyl,
- (4) C₃₋₇cycloheteroalkyl,
- (5) C₃₋₇cycloheteroalkenyl,
- (6) aryl, and
- (7) 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, -NH₂, -C₁₋₆alkyl, -OC₁₋₆alkyl, halogen, -CH₂F, -CHF₂, -CF₃, -CO₂H, -CO₂C₁₋₆alkyl, -C₃₋₇cycloalkyl, 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; and
r is 0, 1 or 2.

2. The compound according to Claim 1, wherein R¹ is selected from:

- (1) $-(CH_2)_p$ aryl,
- (2) biphenyl,
- (3) heteroaryl,
- (4) $-C_{2-6}$ alkenyl-aryl,
- (5) $-C_{2-6}$ alkynyl-alkyl,
- (6) $-C_{2-6}$ alkynyl-aryl,
- (7) $-C_{2-6}$ alkynyl-heteroaryl,
- (8) $-C_{2-6}$ alkynyl- C_{3-7} cycloalkyl,
- (9) $-C_{2-6}$ alkynyl- C_{2-7} cycloheteroalkyl, and
- (10) $-C_{2-6}$ alkynyl- C_{2-7} cycloheteroalkenyl,

wherein each CH₂ is unsubstituted or substituted with 1 or 2 substituents selected from:

halogen, CF₃, -OH, -NH₂, $-C_{1-6}$ alkyl, $-OC_{1-6}$ alkyl, $-NHC_{1-6}$ alkyl and $-N(C_{1-6}alkyl)_2$,

wherein each alkyl, alkenyl and alkynyl is unsubstituted or substituted with 1, 2 or 3 substituents selected from: halogen, CF₃, -OH, -NH₂, $-C_{1-6}$ alkyl, $-OC_{1-6}$ alkyl, $-NHC_{1-6}$ alkyl and $-N(C_{1-6}alkyl)_2$, and wherein each cycloalkyl, cycloheteroalkyl,

cycloheteroalkenyl, phenyl, aryl and heteroaryl is unsubstituted or substituted with 1, 2, 3

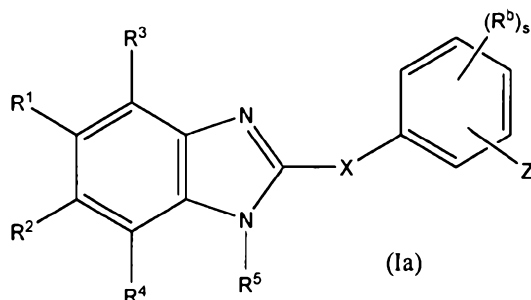
or 4 substituents independently selected from R^a, and R² is selected from the group consisting of: hydrogen, halogen, -CN, -CF₃, and $-C_{1-6}$ alkyl, and provided that if R² is hydrogen, then at least one of R³ and R⁴ is not hydrogen; or a pharmaceutically acceptable salt thereof.

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

4. The compound according to any one of Claims 1 to 3, wherein Z is $-(CH_2)_nCO_2H$, wherein each CH₂ is unsubstituted or substituted with 1 or 2 substituents selected from C_{1-6} alkyl, -OH and -NH₂; or a pharmaceutically acceptable salt thereof.

5. The compound according to any one of Claims 1 to 4, wherein R^3 is hydrogen or halogen, and R^4 is hydrogen; or a pharmaceutically acceptable salt thereof.

6. The compound according to Claim 1 of structural formula Ia:



or a pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from:

- (1) biphenyl,
- (2) aryl,
- (3) heteroaryl, and
- (4) $-C_2$ alkynyl-aryl,

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

R^2 is halogen;

R^3 is hydrogen or halogen;

R^4 and R^5 are hydrogen;

X is $-O-$;

Z is $-CO_2H$;

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

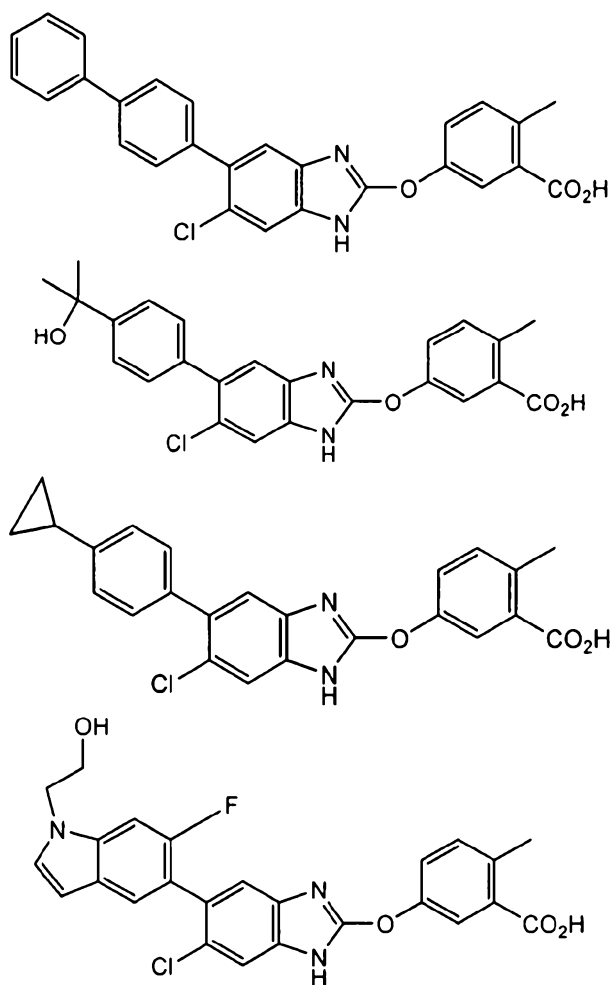
- (1) halogen,
- (2) $-(CH_2)_mOH$,
- (3) $-C_{1-6}$ alkyl,
- (4) $-OC_{1-6}$ alkyl,
- (5) $-CO_2H$,
- (6) $-C_{3-7}$ cycloalkyl,
- (7) $-C_{2-6}$ cycloheteroalkyl, and
- (8) aryl,

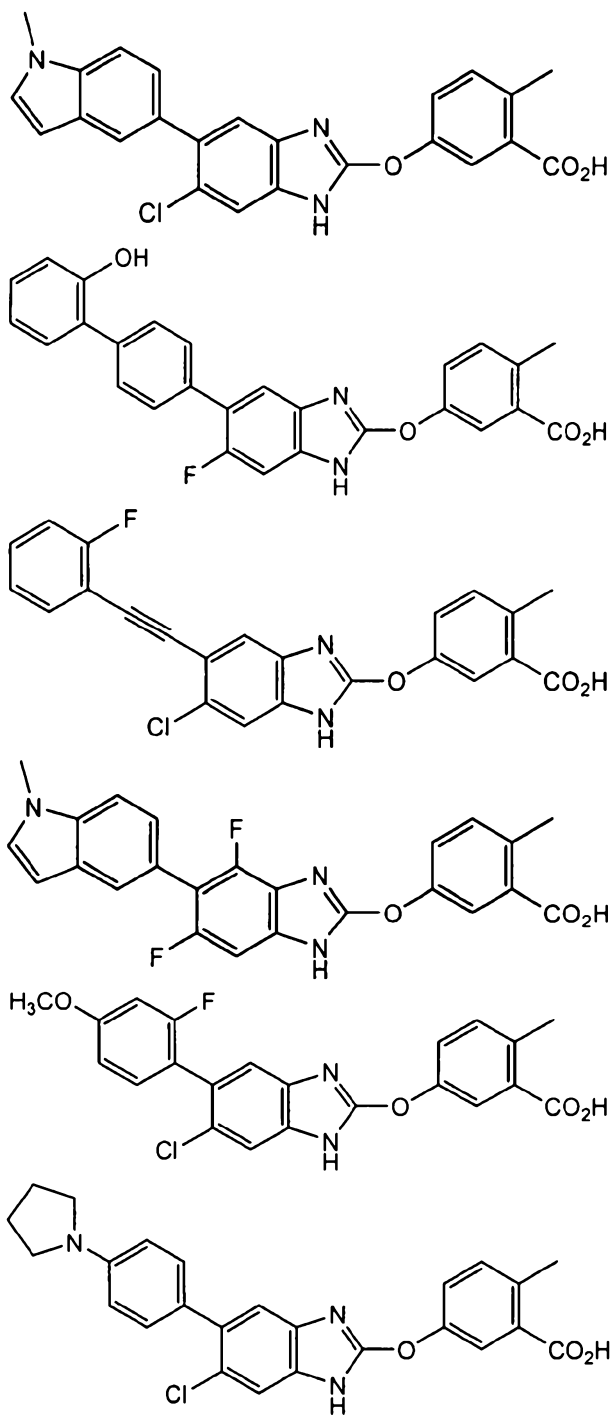
wherein each CH₂ is unsubstituted or substituted with 1 or 2 substituents selected from: oxo, -(CH₂)₀₋₃OH, -CN, -NH₂, -NH(C₁₋₆alkyl), -N(C₁₋₆alkyl)₂, -C₁₋₆alkyl, -OC₁₋₆alkyl, halogen, -CH₂F, -CHF₂, -CF₃, -CO₂H, and -CO₂C₁₋₆alkyl, and wherein alkyl, cycloalkyl, cycloheteroalkyl, and aryl are unsubstituted or substituted with 1, 2, 3 or 4 substituents selected from: oxo, -(CH₂)₀₋₃OH, -CN, -NH₂, -NH(C₁₋₆alkyl), -N(C₁₋₆alkyl)₂, -C₁₋₆alkyl, -OC₁₋₆alkyl, halogen, -CH₂F, -CHF₂, -CF₃, -CO₂H, and -CO₂C₁₋₆alkyl;

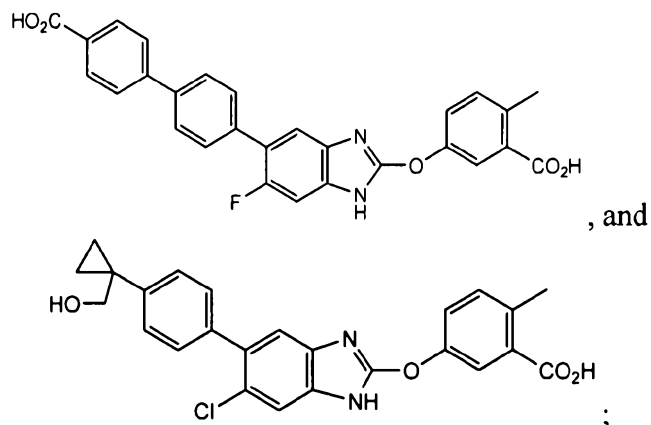
each R^b is selected from hydrogen and -C₁₋₆alkyl, unsubstituted or substituted with 1 or 2 halogens; and

s is 0, 1 or 2.

7. The compound according to Claim 6, selected from:







or a pharmaceutically acceptable salt thereof.

8. A composition comprising a compound according to any one of
 5 Claims 1 to 7, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

9. A composition comprising a compound according to any one of
 Claims 1 to 7, or a pharmaceutically acceptable salt thereof, and a compound selected
 from simvastatin, ezetimibe, taranabant and sitagliptin; and a pharmaceutically acceptable
 10 carrier.

10. The use of a compound according to any one of Claims 1 to 7, or a
 pharmaceutically acceptable salt thereof, for the preparation of a medicament useful for
 the treatment of a disorder, condition, or disease responsive to the activation of
 AMP-activated protein kinase in a mammal in need thereof.

11. The use according to Claim 10 wherein the disorder, condition, or
 15 disease is selected from the group consisting of: Type 2 diabetes, hyperglycemia,
 Metabolic Syndrome, obesity, hypercholesterolemia, and hypertension.

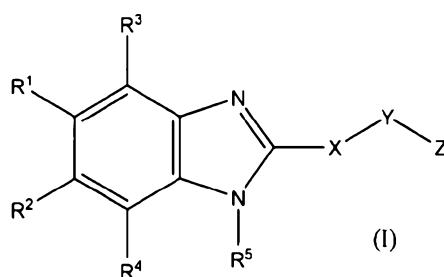
12. The use according to Claim 10 wherein the disorder, condition, or
 disease is Type 2 diabetes.

13. The use according to Claim 10 wherein the disorder, condition, or
 20 disease is obesity.

14. A method of treating a disorder, condition or disease 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 any one of Claims 1 to 7, or a pharmaceutically acceptable salt thereof, or a composition
5 according to Claim 8 or 9.

15. The method of Claim 14 wherein the disorder, condition, or disease is selected from the group consisting of: Type 2 diabetes, hyperglycemia, Metabolic Syndrome, obesity, hypercholesterolemia, hypertension, and cancer.

16. A compound of structural formula I:



as defined in Claim 1 and substantially as hereinbefore described with reference to any one of the Examples.

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Metabasis Therapeutics, Inc.**

**Patent Attorneys for the Applicant/Nominated Person
SPRUSON & FERGUSON**